Scientific Presentations and Publications

2017-2022

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SCIENTIFIC INFORMATION RESOURCE

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CEA and its subsidiaries are committed to showcasing research and scholarship in the execution of patient-centered educational programming. The use of innovative technology, study of adult learning principles, and keeping abreast of clinical gaps are the cornerstones of our research. We present the following sustained history of successful partnerships yielding pertinent white papers and presentations. This bedrock of foundational research is the template for our continued success in patient-centered healthcare professional education.

-The CEA Team

NEEDS ASSESSMENT AND CLINICAL GAPS

Gaps in Clinicians' Knowledge of MACRA, the Quality Payment Program, and the Role of CME

A CCO White Paper, September 2018

ONCOLOGY

Variance Between Experts and Community Practitioners in Treatment of Metastatic Breast Cancer

Presented at SABCS 2017

Healthcare Provider Awareness and Integration of Immunotherapy for Stage III NSCLC

Presented at ASCO-SITC 2019

Treatment of Locally Advanced or Metastatic Urothelial Carcinoma: Analysis of Expert and Community Healthcare Provider Practice Trends

Presented at ASCO GU 2019

Understanding the Educational Needs of Healthcare Providers on Emerging Treatments for HER2-Positive Advanced Breast Cancer

Published on the CCO Website

Understanding the Educational Needs of Healthcare Providers on Novel Treatments in Urothelial Carcinoma

Published on the CCO Website

Treatment Patterns for Metastatic HR-Positive Breast Cancer: Comparing Expert and Community Practice

Presented at SABCS 2019

Analysis of Practice Patterns Among Experts and Community Healthcare Providers for the Treatment of Acute Myeloid Leukemia

Published on the CCO Website

Practice Trends and Attitudes of Medical Oncologists on New Therapies in Urothelial Carcinoma

Presented at ASCO GU 2022

Practice Gaps and Barriers in Optimal Care Among Healthcare Professional Treating Patients With Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Results of a Two-Phase Qualitative/Quantitative Study

Presented at ASH 2021

Suboptimal Clinician Awareness of Appropriate NTRK Fusion Testing and TRK Inhibitor Use in Solid Tumors

Presented at ASCO 2021

Understanding the Educational Needs of Healthcare Providers on Emerging Treatments for MDS & AML

Published on the CCO Website

HEPATITIS AND IMMUNOLOGY

Provider Gaps in Key Areas of Contemporary Viral Hepatitis Management and the Value of Targeted Education

Presented at AASLD 2018

Uncovering Clinicians' Gaps and Attitudes Toward Biosimilars: Impact of a 2-Phase Educational Program

Presented at ACR/ARHP 2018

Targeting GI Nurses' Competence With Inflammatory Bowel Disease (IBD): Uncovering Regional Differences

Presented at SGNA 2019

TECHNOLOGY TO ENHANCE LEARNING AND UNDERSTAND PRACTICE GAPS

Real-World Impact of Interactive Decision Support Tools in Changing Clinical Practice at the Point of Care

A CCO White Paper, January 2018

ONCOLOGY

Clinical Impact of Internet-Based Decision Aids to Provide Expert Guidance on Clinical Management of Cancer

Presented at ACEHP 2017

Evolving Practice Patterns in Advanced NSCLC: Analysis of an Online Treatment Decision Tool

Presented at IASLC 2017

Variance From Evidence-Based Management of Immune-Related Adverse Events Among Healthcare Providers: Analysis of an Online Management Decision Tool

Presented at SITC 2017

Analysis of Online Tool to Explore Evolving Practice Patterns in Renal Cell Carcinoma

Presented at ASCO GU 2018

Consensus and Disagreement Among Experts in Treatment of Patients With HER2+ Early-Stage Breast Cancer Suggests an Unmet Need for an Online Decision Support Tool

Presented at SABCS 2018

Evolving Immunotherapy Practice Patterns in Advanced NSCLC: Analysis of an Online Treatment Decision Tool

Presented at IASLC 2018

Evolving Treatment Patterns of Healthcare Providers (HCPs) and Multiple Myeloma (MM) Experts From 2013-2017: Analysis of an Annually Updated Online Treatment Decision Tool

Presented at ASH 2017

Variability of Current Global Practice Patterns in the Management of Metastatic Colorectal Cancer

Presented at ESMO GI 2018

Variance Between Experts and Oncology Healthcare Providers in Managing Polycythemia Vera and Myelofibrosis: Analysis of an Online Treatment Decision Tool

Presented at ASH 2017

Analysis of Healthcare Provider Management of Immune-Related Adverse Events and Concordance With NCCN Guidelines®

Presented at SITC 2019

Evolution in Practice Patterns and Differences Among Experts and Community Healthcare Providers in the Treatment of Patients With Chronic Lymphocytic Leukemia

Presented at ASH 2019

Management of CAR T-cell Toxicities: Concordance and Divergence Between Healthcare Providers and Expert Consensus Recommendations

Published on the CCO Website

Treatment Trends and Variance Among Experts and Community Practitioners in Advanced Melanoma
Presented at SABCS 2019

Management of BTK Inhibitor Associated Adverse Events: Current Practice Trends Among Healthcare Providers and Concordance With Expert Recommendations
Presented at ASH 2020

Management of CAR T-Cell Toxicities: Concordance Between Healthcare Providers and Expert Consensus Recommendations in 2019 and 2020
Presented at SITC 2020

Variance Between Experts and Community Practitioners in Treating Soft Tissue Sarcomas: Analysis of an Online Decision Support Tool
Presented at CTOS 2020

Contemporary Management of Advanced Hepatocellular Carcinoma: Treatment Patterns Among HCPs and Concordance With Expert Recommendations
Presented at AASLD 2021

Variance in Practice Between Experts and Oncology Healthcare Professionals for Follicular Lymphoma: Analysis of an Online Treatment Decision Tool
Presented at ASH 2021

HEPATITIS AND HIV

Variance Between Experts and Community Clinicians in Treatment of Chronic Hepatitis B Infection
Presented at AASLD 2018

Differences Between Experts and Community Clinicians in Selecting HIV Switch Regimens for Patients With Viral Suppression
Presented at IDWeek 2019

Hep B Consult: A Point-of-Care Interactive Decision Support Tool Delivers Real-Time, Personalized, HBV Guideline-Based Teaching
Presented at AASLD 2019

Variance Between Clinicians and Guidelines in the Management of HIV/HCV Coinfection
Presented at IDWeek 2019

Variance Between Clinicians and Guidelines in the Management of HIV/HCV Infection: Results by Specialty
Presented at AASLD 2019

Point-of-Care Interactive Decision Support Tool Demonstrates Discordance Between Healthcare Practitioner Approaches and APASL Guideline Recommendations in the Management of HBV Infection
Presented at APASL 2021

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A Point-of-Care Decision Support Tool Reveals Variance Between Clinicians and Experts in Selecting Among GLP-1 RAs in Type 2 Diabetes
Presented at ENDO 2021

Diabetes Consult: Can an App Improve Healthcare Professionals' Selection of T2D Treatment for High-Risk Patients?
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Expert Advice on Managing Severe Asthma: An Interactive Decision Support Tool Provides Real-Time Expert Recommendations
Presented at AAAAI 2021

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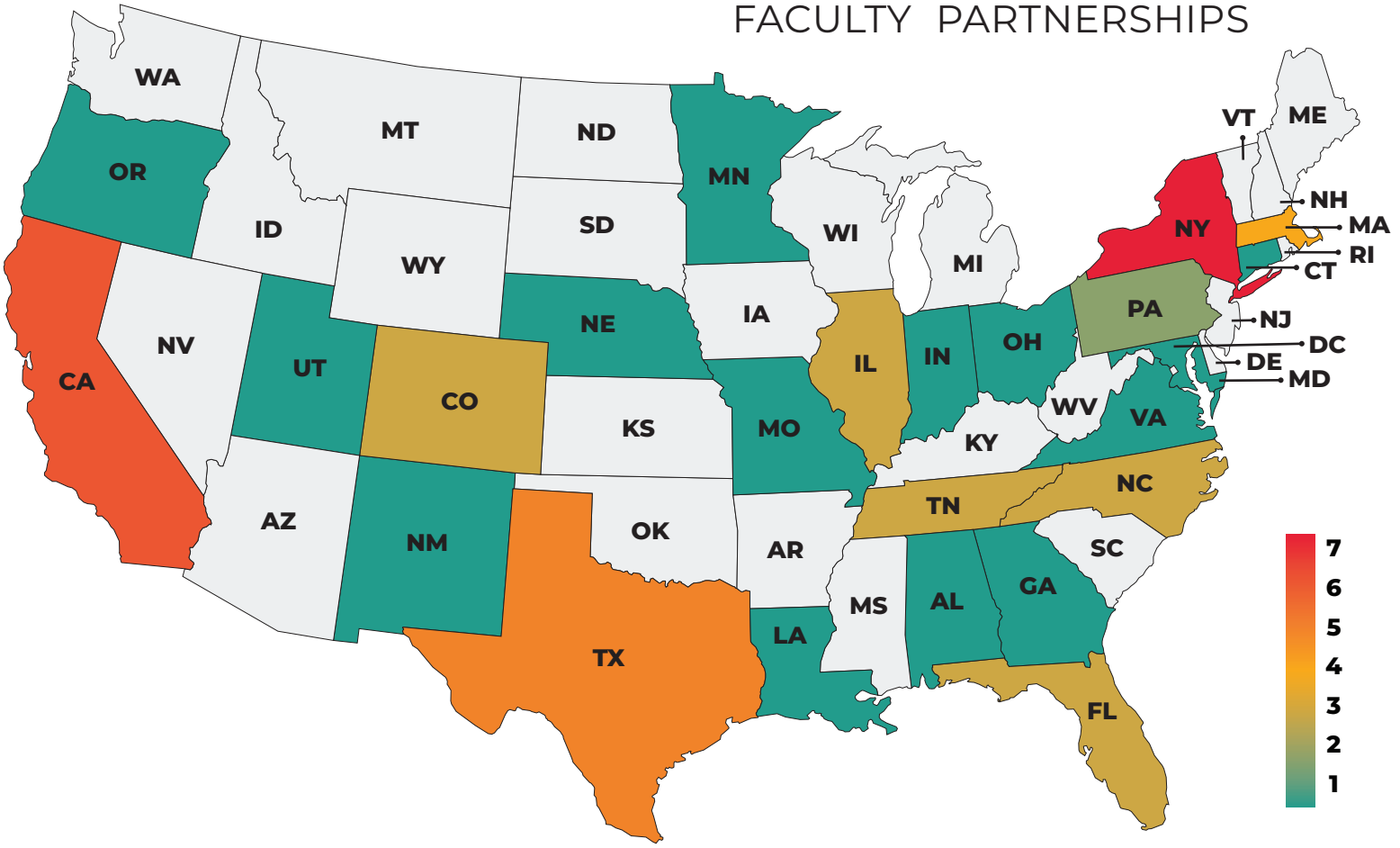
ADULT LEARNING PRINCIPLES

Educational Impact of the Flipped Classroom Model in the Setting of Hepatitis C
Presented at ACEHP 2017

Social Media Behavior and Attitudes of US Physicians: Implications for Continuing Education Providers
A CCO White Paper, January 2017

Intelligent Virtual Assistants—Think Siri and Alexa—in Medicine and Continuing Education: Small Devices With Big Concerns and Big Potential! Clinicians' Knowledge of MACRA, the Quality Payment Program, and the Role of CME
A CCO White Paper, March 2019

FACULTY PARTNERSHIPS



Baylor

Brigham and Women's Hospital

Capital Allergy and Respiratory Disease Center

Chinese University of Hong Kong

City of Hope National Medical Center

Cleveland Clinic

Columbia University

Dana-Farber Cancer Institute

Duke University

Fox Chase Cancer Center

Georgetown University

Harvard University

Hofstra/Northwell

Indiana University

Jiahui International Cancer Center

Johns Hopkins

JW Goethe University Hospital

King's College Hospital

Lee Moffitt Cancer Center

Massachusetts General Hospital

Mayo Clinic

MD Anderson Cancer Center

Memorial Sloan Kettering Cancer Center

Mount Sinai

National Jewish Hospital

New Mexico VA Health System

New York Medical College

Northside Hospital

Northwestern University

Ochner Health System

Rocky Mountain Cancer Centers

Roswell Park Comprehensive Cancer Center

Rush University

Sarah Cannon Research Institute

Stanford University

Sylvester Comprehensive Cancer Center

Tennessee Oncology

Texas Oncology

Texas Tech University

Tish Cancer Institute

Toronto Centre for Liver Disease

University of Alabama

University of California Los Angeles

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University of Chicago

University of Colorado

University of Nebraska

University of North Carolina

University of Pennsylvania

University of Southern California

University of Texas

University of Toronto

University of Utah

Vanderbilt-Ingram Cancer Center

Virginia Cancer Specialists

Washington University

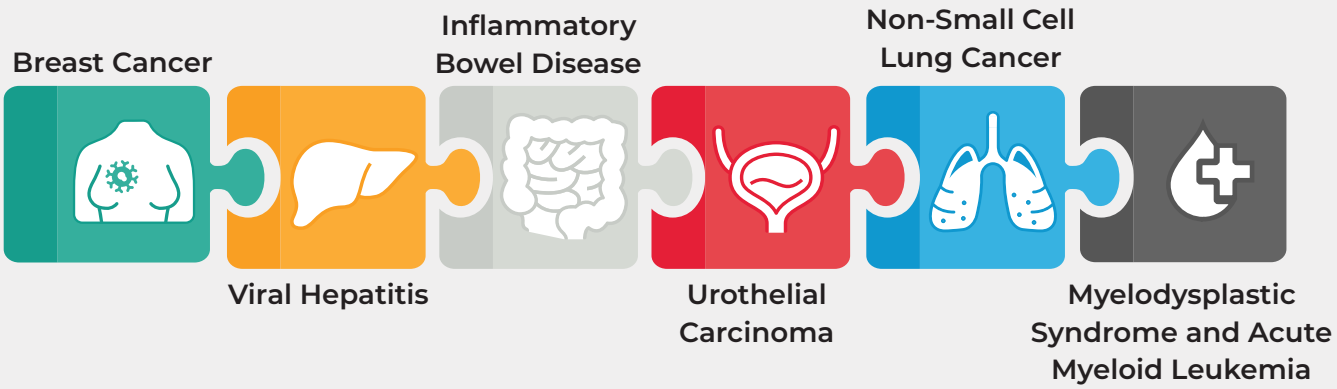
Weill Cornell Medicine

Willamette Valley Cancer Institute

Yale University

NEEDS ASSESSMENT AND CLINICAL GAPS

Clinical gaps research has identified much needed education in:



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Gaps in Clinicians' Knowledge of MACRA, the Quality Payment Program, and the Role of CME

September 2018

A Clinical Care Options (CCO) White Paper

In 2015, Congress passed the Medicare Access and CHIP Reauthorization Act (MACRA), ushering in one of the largest changes in healthcare reimbursement from the federal government, the largest single payer in the United States. For the estimated 600,000 eligible clinicians providing care under Medicare Part B, MACRA has significant implications for their reimbursement. This White Paper summarizes the changes and presents new CCO survey data that illuminate clinicians' challenges in understanding how these complex changes may affect their practice as well as the role of continuing medical education (CME) in meeting the new requirements that MACRA introduces.

MACRA Overview

In 2015, MACRA replaced the Medicare Sustainable Growth Rate approach that was enacted under the Balanced Budget Act of 1997 as a means of providing fee-for-service payments based on the *volume* of healthcare services delivered. Under MACRA, these payments were replaced by new Quality Payment Program (QPP) models that link Medicare reimbursement payments to the *quality* of care provided, with the goal of achieving improvements in health outcomes and cost efficiency by rewarding clinicians for providing better care.

Not all clinicians are eligible to participate in the QPP. In 2017, more than 800,000 clinicians were exempted, including those whose practices care for fewer than 100 Medicare Part B beneficiaries as well as those whose practices incur less than $30,000 in Medicare charges per year. In 2018, the exemption has been modified to exclude clinicians with fewer than 200 Medicare Part B beneficiaries and those who billed less than $90,000 in Medicare charges per year.[1]

As of January 2017, the remaining eligible clinicians must participate successfully in the QPP or face a negative payment adjustment to their Medicare reimbursements. Eligible clinicians include physicians, physician assistants, nurse practitioners, clinical nurse specialists, and certified registered nurse anesthetists. For these clinicians, the QPP offers 2 program options:

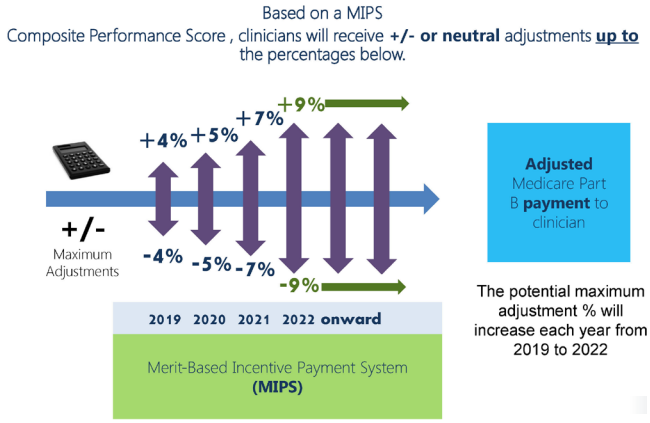
1. The Merit-Based Incentive Payment System (MIPS), discussed in more detail below, or
2. The Advanced Alternative Payment Models (APMs), through which eligible clinicians can earn additional compensation as an incentive for achieving defined thresholds of high-quality and cost-efficient care. To learn more about APMs, visit https://qpp.cms.gov/apms/overview

For eligible clinicians participating in MIPS, the Centers for Medicare & Medicaid Services (CMS) have created a scoring system that includes measures in 4 performance categories (Figure 1) to generate a composite score on a scale of 0-100.

Figure 1. MIPS performance categories for 2018.[2]

Clinicians' individual performance scores are compared with prespecified performance thresholds to determine if they should receive a positive, negative, or neutral payment adjustment to their future Medicare reimbursements. Data collected in 2017 are being analyzed and scored in 2018 and will result in payment adjustments in 2019 that will range from -4% to +4%. By 2022, the adjustments will increase to between -9% and +9% (Figure 2).

Figure 2. Medicare reimbursement adjustments based on MIPS performance score.[3]



In 2018, CMS ruled that eligible clinicians can report their participation in appropriate continuing education activities as examples of their engagement in Improvement Activities (which represent up to 15 points toward the final score).

CMS has provided the following criteria that CME activities must meet to qualify as Improvement Activities:

- The activity must address a quality or safety gap that is supported by a needs assessment or problem analysis or must support the completion of such a needs assessment as part of the activity
- The activity must have specific, measurable aim(s) for improvement
- The activity must include interventions intended to result in improvement
- The activity must include data collection and analysis of performance data to assess the impact of the interventions
- The accredited program must define meaningful clinician participation in their activity, describe the mechanism for identifying clinicians who meet the requirements, and provide participant completion information

CCO Survey of US Clinicians

To assess the extent to which clinicians understand the process associated with MACRA and the implications on their practice, a nationwide survey was undertaken among CCO's clinician membership. The results demonstrate profound gaps in clinicians' general knowledge of the changes introduced by MACRA and, particularly, a lack of awareness that participating in appropriate CME activities not only can help them improve the quality of care they provide, but also can help them gain points toward the Improvement Activity component of their overall performance score, which in turn determines the rate of Medicare reimbursement payments they will receive.

The 227 survey respondents comprised clinicians, system administrators, and system leaders, with the vast majority (93%) being clinicians in various practice types (Figure 3) and settings (Figure 4). Respondents reported a wide range of 20 specialties, reflecting the diversity of the CCO membership.

Figure 3. Survey respondents by practice type.

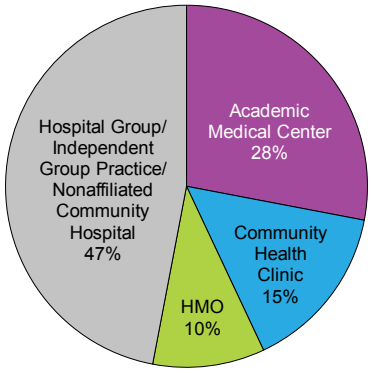
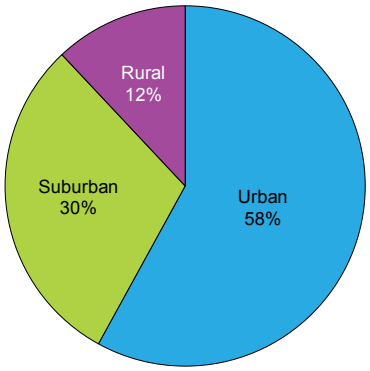


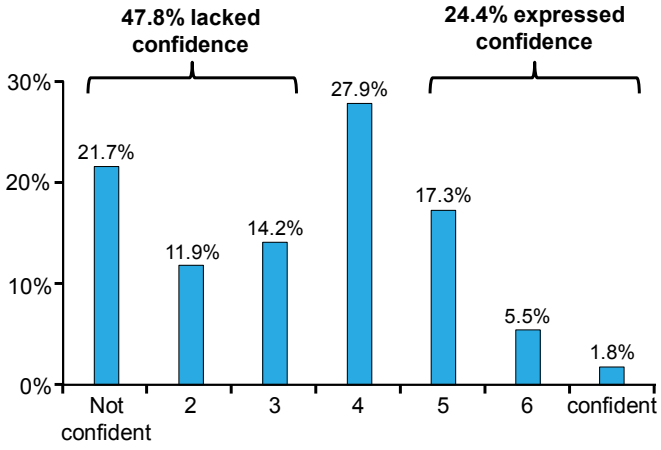
Figure 4. Survey respondents by practice setting.



Participants' Understanding of the QPP

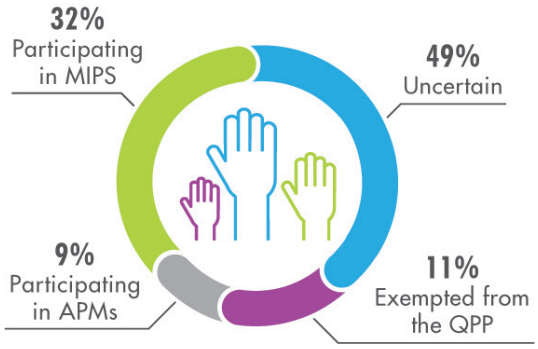
Participants were asked to assess their confidence in their understanding of the QPP on a 7-point scale. Almost one half indicated they were less than confident in their understanding of QPP (Figure 5).

Figure 5. Respondents' confidence in their understanding of the QPP



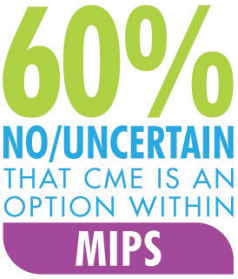
In addition, 32% of respondents indicated they are participating in MIPS, 9% are participating in the APMs, and 11% have been exempted from the QPP (Figure 6). However, 49% were uncertain whether they are participating or not—a remarkably high proportion, given that the survey was conducted months after the CMS had already sent notifications about whether clinicians were exempt from being evaluated under MIPS in the first half of 2017. Among this subgroup, 70% had classified their understanding of the QPP as less than confident (1-3 on the scale) in the previous question.

Figure 6. Respondents' current engagement with MACRA-defined reimbursement systems



Certified CME Activities Included as Improvement Activities Within the QPP

Only 40% of respondents were aware that certified CME activities can be included as Improvement Activities within the QPP, as confirmed by CMS in early 2018. However, when asked if they would be interested in participating in appropriate CME activities as part of MIPS, 63% indicated that they would.



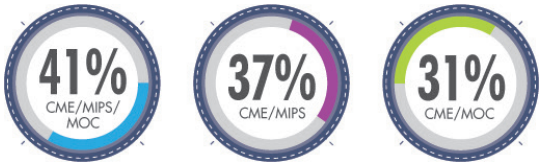
These data indicate that a great deal of work needs to be done to improve clinicians' awareness that appropriate CME activities can help them meet the MIPS requirements for participating in Improvement Activities. At the same time, it is reassuring to see that large majorities of respondents were interested in participating in CME, suggesting that awareness is the key barrier to the uptake of CME to satisfy the requirement.

Educational Activities Offering Multiple Forms of Certification

Additional questions helped to characterize respondents' preferences for being informed about the availability of CME that can be counted toward their MIPS needs and the attractiveness of educational activities that offer multiple forms of certification.

Most clinicians reported that they currently (61%) or would in the future (20%) seek out educational activities that offer Maintenance of Certification (MOC) points that are required for board-certified physicians.

Additional questions helped to characterize respondents' interest in accessing education that offered combinations of CME credits, MOC points, and/or MIPS recognition. Thirty-seven percent would be likely to participate in education that offered both CME credit plus MIPS Improvement Activity designation, 31% in education that offered both CME credit and MOC points, and 41% in education that offered all 3 categories.



What Can the CME Community Do to Help Clinicians Through the Transition?

After 2 years during which CMS has been communicating the MACRA changes, it is clear more clinician education is needed to ensure a successful transition from fee-for-service to merit-based reimbursement. New in 2018, clinicians can use CME activities to meet the requirement for participating in Improvement Activities within MIPS. There is a clear opportunity for participation in appropriate CME activities, already a trusted resource used by hundreds of thousands of clinicians, to play a significant role in enabling clinicians to demonstrate their commitment to enhancing patient outcomes and the quality of care.

> *"Accredited CME providers are ideally placed to support their clinicians' engagement in MIPS through building activities for individuals and teams to improve performance, quality, and safety. As outlined in more detail on our Web site (accme.org), accredited CME providers have great flexibility in offering education that will count as Improvement Activities, and can also help clinicians understand how to identify Improvement Activities, assist them in attesting to their participation in MIPS, and directly issue CME and MOC credits."*
>
> *Graham McMahon, MD, MMSc*
> *President and CEO of the Accreditation Council for Continuing Medical Education (ACCME)*

Many existing or currently planned CME activities are likely to already qualify as Improvement Activities for MIPS. CME planners can review the requirements in a step-by-step implementation guide by the ACCME, available at https://tinyurl.com/ycsz6dn7.

Clinicians also need to be aware of the process to document their participation in such activities. Currently, eligible clinicians may submit their Improvement Activities by attestation by any of the following options:

- CMS QPP Web site
- Qualified clinical data registry
- Qualified registry
- Electronic health record system

Practice groups of 25 or more clinicians may choose to use the CMS Web interface. Eligible clinicians and groups only need to attest, via the QPP Web site, that they completed the Improvement Activities they selected or should work with their organization to determine the best way to submit their activities via a qualified clinical data registry, a qualified registry, or their electronic health record system. Eligible clinicians are encouraged to retain documentation for 6 years as required by the CMS document retention policy.[4]

CME Companies Can Actively Help to Eliminate the Confusion In Support of the Physician Community

The reporting of activities is the responsibility of the eligible clinicians, but CME providers can help them by providing clear instruction to learners on how to attest to having completed appropriate activities. CCO has already noted that some clinicians are proactively asking questions about whether and how they can report their participation in CME activities to help them meet their QPP requirements. Within the CME industry, discussions have begun about potentially creating a taskforce of various stakeholders such as providers, supporters, accredited societies, and medical societies, with the goal of creating a unified awareness campaign to educate clinicians on how participation in CME can be used to demonstrate their engagement in Improvement Activities.

> *"Stakeholders, including the CME Coalition, have committed to developing easy-to-recognize, uniform language that CME providers can share with learners to indicate that an activity meets the CMS requirements and is, thus, essentially 'MIPS approved'."*
>
> *Andy Rosenberg, JD*
> *Senior Advisor to the CME Coalition*

In the CCO survey, participants responded favorably (93%) to various suggested ways in which CME programs that qualify as Improvement Activities could be brought to their attention, including a dedicated page listing such activities, a clear logo or label on qualifying activities, or an email announcement.

In addition, a taskforce might analyze the reporting process and determine ways in which the CME industry could reduce barriers to clinicians' reporting of qualifying participation—perhaps, for example, using the ACCME's Program and Activity Reporting System (PARS).

In conclusion, the intersection of continuing education activities with the QPP provides the CME community a wonderful opportunity to further our mission to educate clinicians while also helping to reduce their current confusion about the changes to the healthcare system, allowing them to continue to focus on improving patient outcomes.

About Clinical Care Options

CCO, a leader in the development of innovative, interactive, online, and live CME/CE-certified programs and proprietary medical education technologies, creates and publishes original CME/CE and information resources that are designed specifically for healthcare professionals. CCO's educational programs are developed not only to provide the latest scientific information, but also to support the understanding, confidence, application, and competence of healthcare professional learners. In addition to the point-of-care resource—*in*Practice®—CCO provides a spectrum of live and online educational programs and formats.

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Additional Resources

Accreditation Council for Continuing Medical Education. Step-by-Step Guide to Implementing Accredited CME Improvement Activities. Available at: http://www.accme.org/sites/default/files/2018-06/777_20180618_Step-by-Step_Guide_to_Implementing_Accredited_CME_Improvement_Activities_0.pdf. Accessed September 6, 2018.

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Variance Between Experts and Community Practitioners in Treatment of Metastatic Breast Cancer

Timothy A. Quill, PhD[1]; Kimberly L. Blackwell, MD[2]; Sara Hurvitz, MD, FACP[3]; Kathy D. Miller, MD[4]; Nicholas J. Robert, MD[5]; Kevin Obholz, PhD[1]; and Mohammad Jahanzeb, MD[6]

1. Clinical Care Options, LLC; 2. Duke University School of Medicine; 3. David Geffen School of Medicine at UCLA;
4. Indiana University Melvin and Bren Simon Cancer Center; 5. Virginia Cancer Specialists; 6. Sylvester Comprehensive Cancer Center

San Antonio Breast Cancer Symposium
December 5-9, 2017

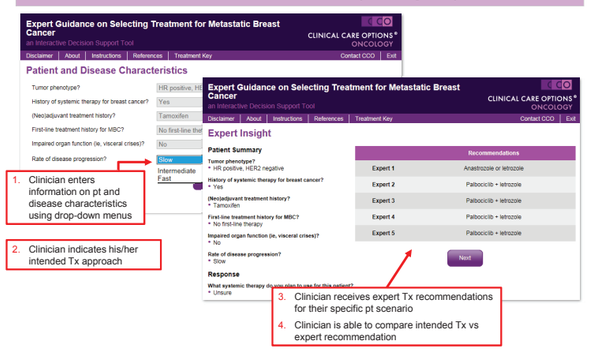
Background

- Practice guidelines in metastatic breast cancer (MBC) are an important resource to help guide management of patients (pts) but can be difficult to apply to individual pts, particularly when there are 2 or more treatment (Tx) options with similar levels of evidence
- To provide healthcare providers (HCPs) with expert guidance and feedback on choice of Tx for specific case scenarios, we implemented an **interactive Web-based decision support tool**, in which HCPs input specific pt and tumor characteristics along with their planned Tx approach and then receive expert recommendations
- Here we analyze data from this tool capturing recent Tx trends in the evolving therapeutic landscape for MBC, variance in HCP planned Tx vs expert recommendations, and the impact of this online tool on practice

Study Components

- Online decision support tool published in December 2016
  - Each expert provided Tx recommendations in October 2016
- The tool included **492 different MBC case variations** based on specific pt/tumor characteristics, including disease phenotype, previous therapy, visceral crisis, and rate of disease progression
- HCPs are prompted to enter pt/tumor characteristics and indicate their intended clinical approach
  - Recommendations from the 5 experts are displayed
  - Users are asked whether the experts' recommendation confirmed or changed their intended clinical approach
- **The tool is online at: clinicaloptions.com/MBCtool**

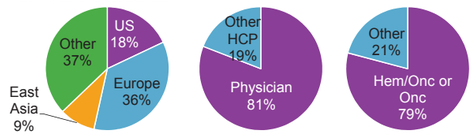
MBC Tool Screenshots (Examples)



Results

Tool Participant Demographics

- 793 HCPs entered 1470 different pt cases between December 2016 and October 2017



Phenotype of Cases Entered and Practice Impact

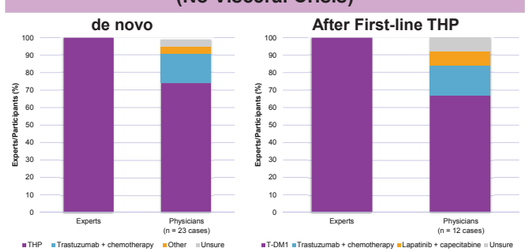
HR+/HER2-, %	HR-/HER2+, %	HR+/HER2+, %	HR-/HER2-, %
54	10	14	21

Intended Use of Tool (n = 388 cases)	Cases, %
Hypothetical pt case (educational resource)	51
Actual pt case (virtual consultation)	49

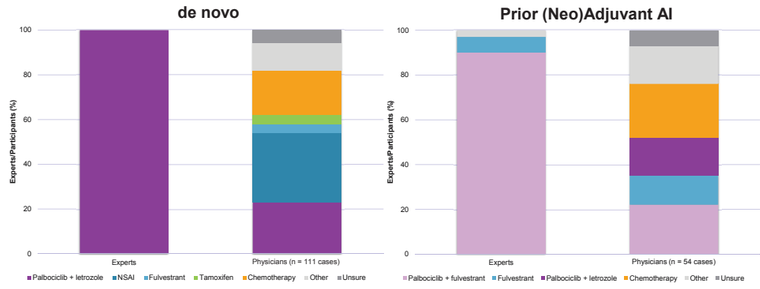
Self-Identified Impact (n = 388 cases)	Cases, %
Changed treatment plan to match experts ***(among those who initially differed from experts)***	62
Confirmed treatment plan	35

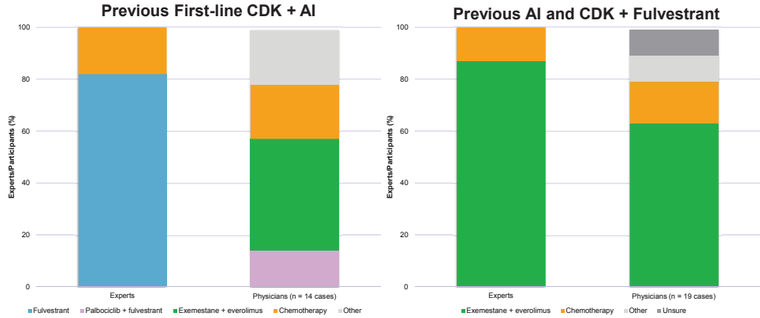
All subsequent presented data analyses limited to 973 cases entered by 523 physicians with an indicated specialty of oncology or hem/onc

Treatment Choice for HR-/HER2+ MBC (No Visceral Crisis)

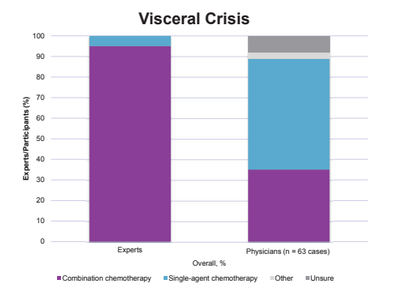


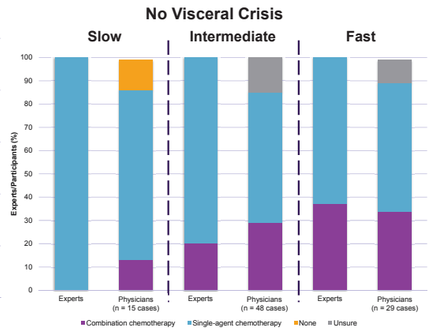
Treatment Choice for HR+/HER2- MBC (No Visceral Crisis)





Treatment Choice for mTNBC





Conclusions

- The majority of cases entered by HCPs were HR+/HER2- MBC
- Substantial variation was evident between oncologists' planned Tx and expert recommendations for each MBC subtype
  - For HR+/HER2- MBC, in the de novo or post-(neo)adjuvant AI therapy disease settings, experts frequently chose a regimen with a CDK4/6 inhibitor vs approximately 1 in 5 oncologists
  - For HR-/HER2+ MBC, approximately 1 in 4 (de novo) or 1 in 3 (post-THP therapy) oncologists' planned Tx differed from expert consensus
  - For HR-/HER2- MBC, in the setting of a visceral crisis, experts frequently chose combination chemotherapy vs approximately 1 in 3 oncologists
- Expert recommendations from this tool led to a change in intended treatment for 62% of cases where HCPs initially chose a Tx plan different from the expert panel indicating this tool can have an impact on patient care

 The online tool is part of an educational program supported by a grant from Genentech.

Healthcare Provider Awareness and Integration of Immunotherapy for Stage III NSCLC

Rachael M. Andrie, PhD; Timothy A. Quill, PhD; Angelique Vinther, CHCP; Tina B. Stacy, PharmD, BCOP, CHCP; Kevin Obholz, PhD
Clinical Care Options, LLC

CLINICAL CARE OPTIONS® ONCOLOGY

Abstract #123

Background

- Phase III PACIFIC trial: Anti–PD-L1 inhibitor, durvalumab, demonstrated survival benefit vs placebo[1,2]
  - Median PFS: 16.8 vs 5.6 months (HR: 0.52; *P* < .001)
  - Median OS: NR vs 28.7 months (HR: 0.68; *P* = .0025)
- In February 2018, durvalumab approved for unresectable stage III NSCLC without progression after concurrent chemoradiotherapy (cCRT)[3]
- Checkpoint inhibition is now considered by most experts to be standard of care in this setting

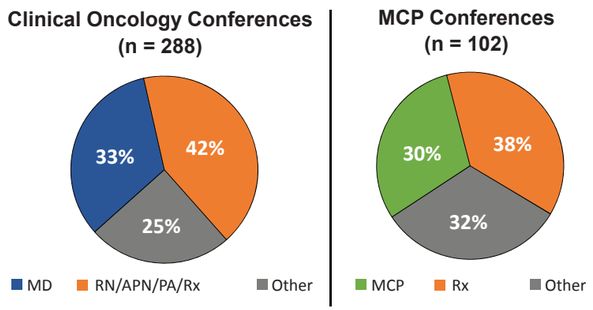
Methods

- 6 CME/CE-certified symposia conducted following the approval of durvalumab to provide healthcare providers (HCPs) with education on this new treatment option for unresectable stage III NSCLC
- 4 major clinical oncology conferences: NCCN, AACR, ASCO, SITC
- 2 managed care pharmacy (MCP) conferences: AMCP Annual, AMCP Nexus
- Self-identified practice trends obtained through case-based polling questions, which were asked before and then again after completion of the education
  - Identical questions repeated at each symposium

Symposia Timeline

Results

Symposia Participant Demographics



Pre-Education HCP Knowledge & Practice Trends

- An average of 44% of HCPs recommended durvalumab consolidation for an ideal patient candidate with stage III NSCLC after cCRT
- An average of 31% of HCPs would recommended durvalumab for a duration of 1 year
- Physicians (77%) selected the optimal management of immune-related pulmonary toxicity more often than other HCPs (32% for RN/APN/PA/Rx,11% for MCPs)
- Of interest, individual pre-education data sets across symposia and over time failed to show a clear trend in an increased utilization of durvalumab since its approval (data not shown)

Post-Education HCP Knowledge & Practice Trends

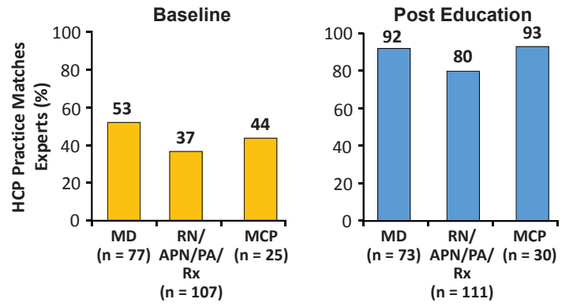
- HCP competence significantly improved (*P* < .0001) in regard to selecting optimal immune checkpoint inhibitor (ICI) therapy and managing pulmonary toxicity

Additional Resources: Treatment Decision Tools

- Expert Insight on Therapy Selection for Unresectable Stage III and Metastatic NSCLC
  www.clinicaloptions.com/LungTool
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Managing Immune Checkpoint Inhibitor–Related Toxicities:
  www.clinicaloptions.com/immuneAETool

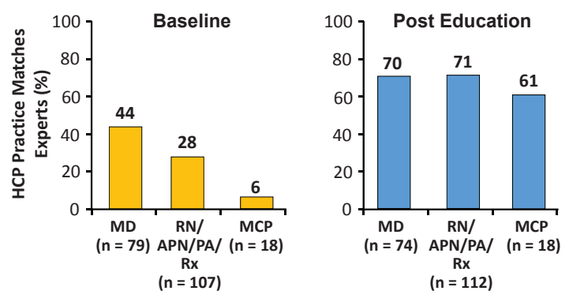
HCP Knowledge & Practice Trends by Specialty

Q1: ICI Consolidation for Stage III NSCLC After cCRT*

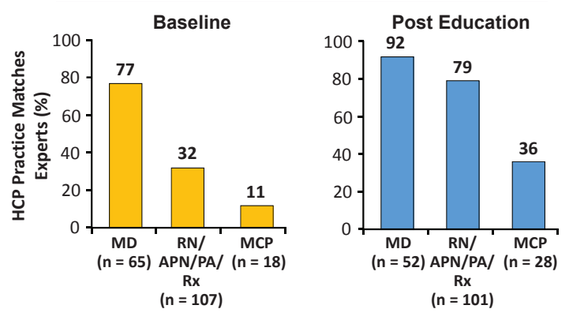


*CCO NSCLC treatment decision tool shows consensus among 5 experts to give ICI for stage III NSCLC after cCRT

Q2: Optimal Duration of ICI Therapy After cCRT



Q3: Management of Pulmonary Toxicity From ICI



Audience FAQs

- Are you checking PD-L1 status after cCRT? Would you give durvalumab to a patient with < 1% PD-L1 expression?
- Are there any comorbidities that would preclude a patient from receiving durvalumab? Is there any patient with stage III NSCLC who should not get durvalumab?
- How quickly do you typically get patients on durvalumab? Is it possible to start it within 14 days?
- Does synergy of CRT with durvalumab persist 4 months out?
- Would you treat a patient with stage II unresectable lung cancer who received cCRT? How about a stage III patient who received sequential CRT?
- What therapeutic options would you consider for stage III patients that progress on durvalumab consolidation?

Conclusions

- Prior to attending CME/CE-certified symposia in 2018, most HCPs were not optimally treating unresectable stage III NSCLC
- These data were consistent over time and, with the FAQs, suggest there is a persistent challenge and educational need on this new treatment modality in this setting
- Posteducation data suggest that HCPs are willing to modify their practice in this setting after receiving expert led education and guidance

References

1. Antonia SJ, et al. N Engl J Med. 2017;377:1919-1929.
2. Antonia SJ, et al. N Engl J Med. 2018;379:2342-2350.
3. Durvalumab PI. Wilmington, DE: AstraZeneca; 2018.

For correspondence regarding this poster, please contact Rachael M. Andrie, PhD (randrie@clinicaloptions.com).

Treatment of Locally Advanced or Metastatic Urothelial Carcinoma: Analysis of Expert and Community Healthcare Provider Practice Trends

Kristen M. Rosenthal, PhD[1]; Matthew Galsky, MD[2]; Matthew I. Milowsky, MD[3]; Daniel P. Petrylak, MD[4]; Jonathan E. Rosenberg, MD[5]; Kevin L. Obholz, PhD[1]; and Elizabeth R. Plimack, MD, MS[6]

[1]Clinical Care Options, LLC; [2]Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute; [3]UNC School of Medicine; [4]Yale Cancer Center; [5]Memorial Sloan Kettering Cancer Center; [6]Fox Chase Cancer Center.

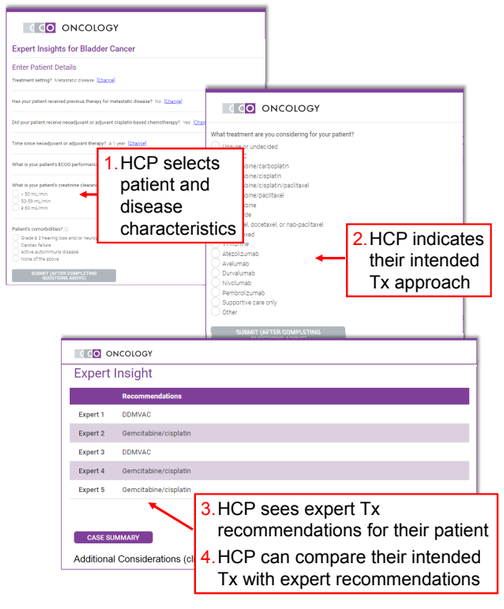
Background

With new indications for immune checkpoint inhibitors (ICIs), treatment decisions for patients with locally advanced (LA) and metastatic urothelial carcinoma (mUC) are becoming increasingly complex. The aim of this analysis was to assess real-world practice patterns for LA or mUC and compare them with recommendations from US experts based on patient cases entered by healthcare providers (HCPs) into an online decision support tool designed to provide specific, individualized expert recommendations.

Methods

- 5 experts provided treatment recommendations in Jan 2018 for 318 unique LA or mUC case scenarios based on key factors defined by those experts
- This analysis compared intended treatment of HCPs vs expert recommendations for 398 cases entered in the tool **from Feb 1, 2018, through Aug 15, 2018**
  - **Data cut-off due to updated FDA ICI indications to require PD-L1 testing for cisplatin-ineligible patients**
- To use the tool, HCPs entered their patients' information and their intended treatment plan. Expert recommendations for that specific patient are then provided to the HCP
- Tool online at **clinicaloptions.com/BladderTool**

Tool Screenshots (Examples)



This activity was supported by an educational grant from Merck & Co., Inc.

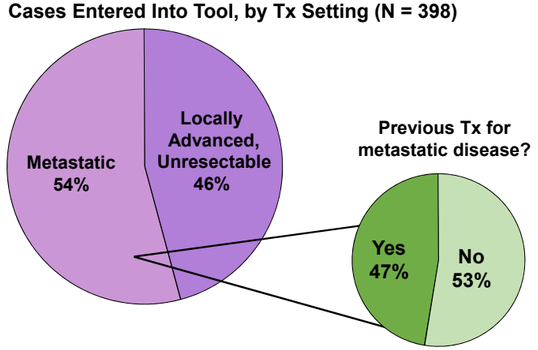
Results

Tool Participant (HCPs) Demographics

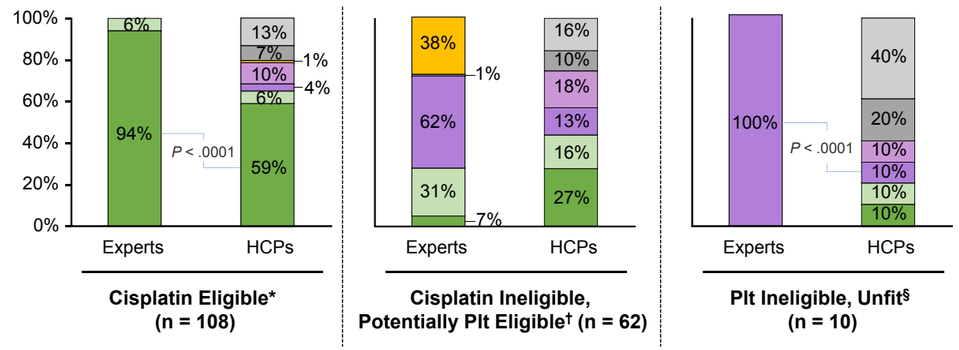
- Analyzed 398 patient cases entered by 251 HCPs
- 67% of users were medical oncologists
- 29% of users were US based and 71% were outside the US
  - US (n = 73), Europe (n = 88), Asia (n = 49), Other (n = 43)

Case Demographics

Cases Entered Into Tool, by Tx Setting (N = 398)



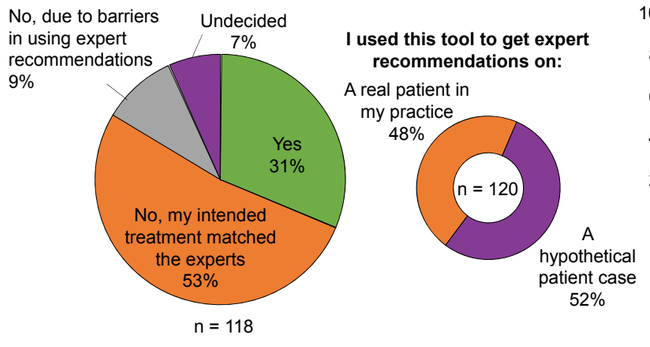
Locally Advanced, Unresectable



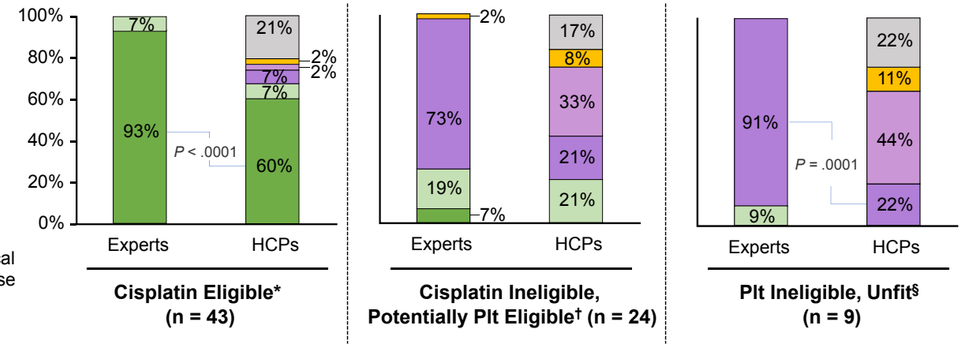
- Cisplatin-based chemo
- Carboplatin-based chemo
- Pembrolizumab
- Nivolumab, atezolizumab, durvalumab, or avelumab
- Supportive care
- Single-agent chemo or other
- Undecided

*Cisplatin eligible: pts with ECOG PS 0/1, CrCl of 50-59 mL/min or > 60 mL/min and no listed comorbidities. †Cisplatin ineligible but potentially plt eligible: pts with ECOG PS ≥ 2 and CrCl of 50-59 mL/min or > 60 mL/min and no listed comorbidities or those with ECOG PS 0/1 and either CrCl of < 50 mL/min, grade 2+ hearing loss or neuropathy, and/or cardiac failure. §Plt ineligible: pts with ECOG ≥ 2 and either CrCl of < 50 mL/min, grade 2+ hearing loss or neuropathy, and/or cardiac failure.

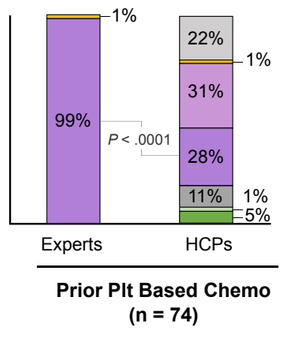
Did Expert Recommendation Change Your Tx Choice?



Metastatic, No Prior Tx for Metastatic Disease



Metastatic, After Prior Tx



Conclusions

- Treatment patterns between experts and HCPs differed significantly for UC across multiple settings, particularly with integration of ICIs into clinical practice
- There were similar treatment patterns in patients with LA, unresectable UC and those with mUC and no prior treatment
  - Cisplatin-eligible cases had the least variance between experts and HCPs; but 35% of HCPs intended to prescribe treatments not recommended by the experts
  - In patients who were ineligible for cisplatin-based chemo but potentially eligible for carboplatin-based chemo, the majority of experts recommended pembrolizumab prior to the updated ICI indications to require PD-L1 testing for cisplatin-ineligible patients (LA UC: 62%; mUC: 73%) but fewer HCPs selected pembrolizumab (LA UC: 13%; mUC: 21%) or other ICIs (LA UC: 18%; mUC: 33%)
  - Experts recommended pembrolizumab for patients ineligible for any platinum treatment (LA UC: 100%; mUC: 91%), but few HCPs selected pembrolizumab (LA UC: 10%; mUC: 22%) or other ICIs (LA UC: 10%; mUC: 44%) in this setting
- For patients who progressed after previous platinum-based chemo, experts recommend pembrolizumab in 99% of cases; however, only 28% of HCPs selected this option, 31% selected other ICIs, and 22% were unsure of the best treatment choice
- This online tool revealed significant and clinically relevant gaps between expert consensus and Tx decisions made by HCPs. Expert recommendations often reinforced or changed HCPs' treatment plans, highlighting the need for ongoing education and the potential of an online tool to improve clinical outcomes for patients with advanced UC

Understanding the Educational Needs of Healthcare Providers on Emerging Treatments for HER2-Positive Advanced Breast Cancer

Supported by an educational grant from Seattle Genetics.

Table of Contents

EXECUTIVE SUMMARY

Background

The management of and the prognosis for patients with HER2-positive breast cancer (BC) drastically improved after the introduction of the HER2-targeted monoclonal antibody trastuzumab. More recently, the approvals of a second HER2-targeted monoclonal antibody, pertuzumab, and an antibody-drug conjugate, ado-trastuzumab emtansine (T-DM1), have further improved the prognosis of patients with HER2-positive breast cancer. However, many patients with HER2-positive metastatic breast cancer (MBC) continue to receive suboptimal care when compared with expert consensus recommendations. Moreover, the advent of new and next-generation HER2-targeted agents in late-stage clinical development such as the tyrosine kinase inhibitors (TKIs) tucatinib and neratinib, as well as the antibody–drug conjugates trastuzumab deruxtecan and trastuzumab duocarmazine, will likely increase the challenges faced by healthcare providers who care for patients with HER2-positive MBC.

Study Goal

The goal of this comprehensive needs assessment was to understand current practice patterns in managing patients with HER2-positive MBC as well as clinician knowledge of emerging therapeutic options for these patients in order to identify the current educational needs of healthcare providers across the United States. Clinical Care Options (CCO) and Thistle Editorial, LLC, strategically designed a multi-methods assessment involving an in-depth qualitative exploration and a quantitative survey of current approaches to practice, knowledge of emerging therapy options, and specific challenges faced by US healthcare providers responsible for treatment decisions for patients with HER2-positive MBC.

Design and Methodology

This two-phase, mixed-methods needs assessment study consisted of qualitative telephone interviews (Phase 1) and an online survey (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of US medical oncologists, radiation oncologists, and advanced practice providers responsible for the treatment decisions for patients with HER2-positive MBC. Phase 2 (quantitative) examined practice trends among clinicians within the United States.

Key Clinical Practice Gaps

Practice Gap #1: Disparities in Using a Multidisciplinary Approach to Decision-Making and Treatment Planning

A multidisciplinary approach to cancer care that relies on the expertise of all relevant disciplines to discuss optimal disease management is recommended by experts and clinical practice guidelines. Clinicians with access to tumor boards are more likely to describe treatment planning as a collaborative or multidisciplinary process. Clinicians without access to multidisciplinary planning or other clinical decision support resources are more likely to view themselves as primary decision-makers when it comes to treatment planning for patients with advanced HER2-positive BC.

Practice Gap #2: Deficits in Clinical Trial Referral

Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with cancer and to promote discovery of new therapies. Although clinicians say they discuss clinical trials with patients, they vary in the timing of such discussion and the estimated percentage of patients that clinicians said they were able to refer for clinical trials is low.

Practice Gap #3: Deficits in Selecting Optimal First-line Therapy for Patients With de novo HER2-Positive MBC

Many clinicians appropriately chose THP (docetaxel plus trastuzumab and pertuzumab) and HP (trastuzumab and pertuzumab) maintenance as initial therapy for de novo HER2-positive MBC; however, overtreatment in the de novo setting is evident, with approximately one half of clinicians reporting they would also add local therapy (surgery or radiation) to the treatment regimen.

Practice Gap #4: Challenges in Selecting First-line Therapy for Patients With Newly Diagnosed MBC Who Were Previously Treated for Early BC

Many clinicians are unsure which first-line therapy is appropriate for patients who received TCHP (docetaxel/carboplatin plus trastuzumab, and pertuzumab) and T-DM1 for early-stage BC. Clinicians also vary in how they define a treatment-free interval, which is an important factor in choosing subsequent therapy at the time of progression to metastatic disease. Clinician uncertainty about therapy selection is noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 or for patients whose disease recurs after a longer treatment-free interval, which some clinicians defined as after more than 6 months while others defined it as after more than 12 months.

Practice Gap #5: Challenges in Managing Patients With CNS Disease

A majority of clinicians would switch systemic therapy in a patient with brain-only progression in contrast to the expert recommendation to continue with the same systemic therapy and treat central nervous system (CNS) metastases with local therapy. Managing patients with leptomeningeal disease and identifying radiation necrosis after radiation therapy are significant challenges in the management of CNS disease for clinicians in all specialties, including radiation oncology. Most clinicians are imaging symptomatic patients when they present with metastatic disease vs at baseline. Few clinicians, even radiation oncologists, are aware of investigational therapies that have shown activity in patients with CNS metastases after treatment with available standard of care options.

Practice Gap #6: Challenges in Selecting Optimal Therapy for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies

Clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1 for HER2-positive MBC and are unfamiliar with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Practice Gap #7: Challenges in Treating Patients With Low HER2 Expression
There was broad consensus among interviewed clinicians that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies and low awareness that there are emerging therapeutic options for patients with low HER2 expression.

Practice Gap #8: Deficits in Familiarity With Novel Agents
Clinicians are largely unfamiliar with novel agents being developed for the treatment of HER2-positive MBC or their associated toxicity profiles, and in interviews, their mechanisms of action. A majority consider only FDA approval based on phase III clinical data as sufficient evidence to incorporate a new agent or regimen into their practice for patients with advanced HER2-positive BC.

Practice Gap #9: Inconsistencies in Defining Quality of Life and Palliative Care
Although quality of life factors into discussions about goal and expectation setting, there is little consensus among clinicians about how best to define quality of life. Similarly, clinicians view palliative care as an important component of addressing quality of life but vary in how they define palliative care and when they initiate discussions about palliative care with their patients.

Key Recommendations

This study highlights a global need for education and resource exposure across professional role, specialty, and practice setting in the following areas of clinical knowledge and practice in the treatment of patients with HER2-positive MBC:

Recommendation #1: Promote Use of a Multidisciplinary Approach to Decision-Making and Treatment Planning
Develop resources to support multidisciplinary pathways in HER2-positive MBC treatment planning that reinforce the importance of team-based approaches to patient care.

Recommendation #2: Enhance Clinical Trial Referral
Direct clinicians to resources that increase awareness of and ability to access available clinical trials as part of their routine approach to managing patients with HER2-positive MBC.

Recommendation #3: Optimize Therapy Selection for Patients With de novo HER2-Positive MBC
Clinicians need access to expert perspectives on the appropriate therapeutic strategy for patients with de novo HER2-positive MBC. Clinicians also need expert guidance on how to integrate clinical and nonclinical criteria into their decision-making, and exposure to strategies that enable patients to remain engaged in their care over the long-term.

Recommendation #4: Optimize Therapy Selection for Patients With Newly Diagnosed HER2-Positive MBC Who Were Previously Treated for Early BC
Clinicians need access to expert perspectives on the appropriate selection of therapies for patients who received TCHP and T-DM1 for early stage BC, including guidance on how best to define a treatment-free interval, and how to integrate novel agents into clinical practice.

Recommendation #5: Optimize CNS Disease Management
Clinicians need guidance on how best to define “low threshold” for performing diagnostic MRI in the setting of neurologic symptoms suggestive of brain involvement to ensure timely access to investigational and/or newly approved agents with potential benefit for CNS disease. Clinicians also need exposure to expert guidance on the optimal management of patients with brain-only progression as well as strategies for identifying radiation necrosis after radiation therapy and managing patients with leptomeningeal disease. Finally, education on emerging treatment options that have shown activity in patients with CNS metastases is also needed.

Recommendation #6: Optimize Therapy Selection for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies
Clinicians need exposure to expert perspectives on the appropriate selection of therapies for patients who progress following previous treatment of first- and second-line standard of care regimens THP and T-DM1, respectively, and education that will help them build familiarity with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Recommendation #7: Optimize Therapy Selection for Patients With Low HER2 Expression
Clinicians need exposure to expert guidance on accurate strategies to define HER2 status and emerging therapeutic options for patients with low HER2 expression.

Recommendation #8: Increase Familiarity With Novel Agents

Clinicians need education on novel agents being developed for the treatment of HER2-positive MBC, including their toxicity profiles and mechanisms of action. An increase in familiarity with investigational agents could help to increase clinician comfort with and confidence in using agents sooner after regulatory approval.

Recommendation #9: Define and Initiate Palliative Care Discussions

Patients with HER2-positive MBC have complex needs that require support to minimize distress and deterioration in quality of life. Clinicians need guidance on the breadth and availability of oncology-led or palliative specialist–led palliative care options, the timing of palliative care discussions, and the impact of palliative care on quality of life.

Study Design and Methodology

Background

The management of and prognosis for patients with HER2-positive BC drastically improved after the introduction of the HER2-targeted monoclonal antibody trastuzumab. Thankfully, the field is still advancing rapidly, and new HER2-targeted options have improved the survival and quality of life of patients with advanced or MBC. The CLEOPATRA and EMILIA studies established THP and T-DM1 as new standards of care for first-line and second-line therapies, respectively. However, analyses of cases entered into the CCO MBC Interactive Decision Support Tool suggest that many patients with HER2-positive MBC are still not being treated optimally when compared with expert consensus recommendations (**Figures 1 and 2**).[1]

Figure 1. First-line treatment choice for de novo disease.

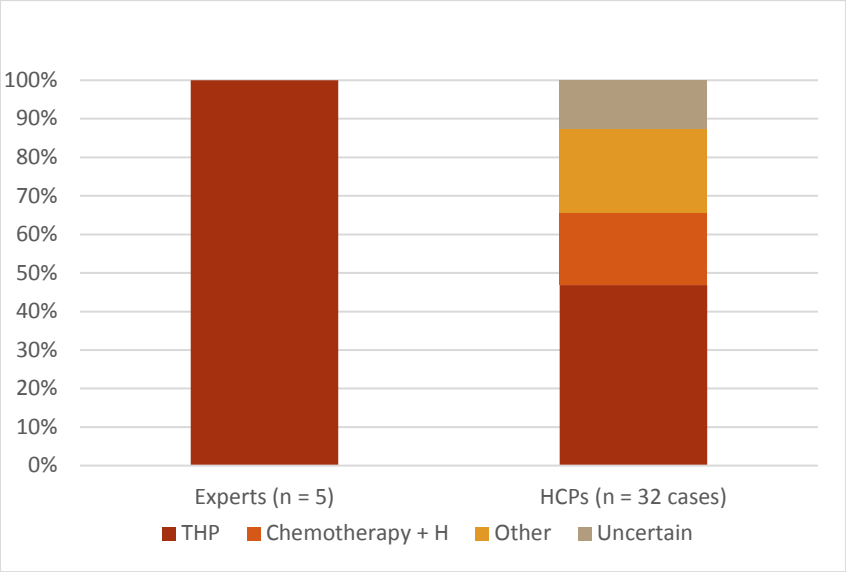
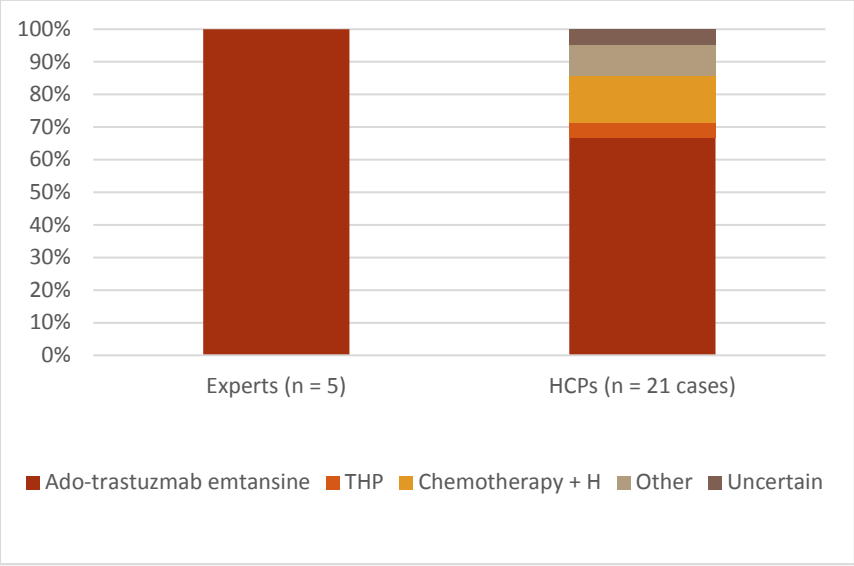


Figure 2. Second-line treatment choice after THP.



With new and next-generation HER2-targeted agents such as the TKIs tucatinib and neratinib along with antibody–drug conjugates in late-stage clinical development, the optimal choice and sequencing of HER2 therapies in MBC is highly likely to become even more challenging for healthcare providers. In addition, approximately 30% to 50% of patients with advanced HER2-positive BC will develop CNS metastases.[2] The limited penetration of trastuzumab and pertuzumab into the CNS can substantially hinder their efficacy in these patients. However, TKIs such as tucatinib and neratinib have established activity in HER2-positive BC brain metastases (BCBM).[3,4] Sara A. Hurvitz, MD, FACP, wrote in a recent editorial that "*patients with BCBM have a worse quality of life, reduced [PFS], and shorter [OS] compared with those without CNS involvement. Identifying regimens to improve outcomes for this poor prognostic subset of patients remains a considerable unmet need in [BC]*."

Clinicians will soon be challenged to understand and integrate emerging research into clinical practice. It will be critical to assess their understanding of the mechanisms of action and the role of novel HER2-targeted therapies in clinical investigations for patients with HER2-positive advanced BC. The HER2-targeted agents pertuzumab and T-DM1 currently approved in this setting, as well as neratinib and tucatinib, are being investigated in combination with each other, immunotherapies, and endocrine therapies in patients with HER2-positive and/or hormone receptor–positive MBC. Among heavily pretreated patients with HER2-positive MBC with and without brain metastases, tucatinib in combination with T-DM1 appeared to have an acceptable toxicity and promising efficacy.[5] Tucatinib is also being investigated in combination with capecitabine and trastuzumab, which has demonstrated acceptable toxicity and preliminary antitumor activity[3] and is being further studied in the double-blinded, randomized, multi-center HER2CLIMB trial (NCT02614794). In addition, ongoing clinical investigations of next-generation, novel HER2-targeted agents as monotherapy or in combination, along with novel antibody–drug conjugates, such as trastuzumab deruxtecan[6,7] and trastuzumab duocarmazine,[8] have shown the promise of relevant clinical activity in pretreated patients, with some of the agents/combinations showing preliminary activity in BCBM and/or low HER2-expressing tumors. Other well-tolerated and promising HER2-targeted agents include margetuximab[9] and DHES0815A.

To provide targeted education that adequately prepares clinicians to confidently and safely use these emerging HER2-targeted agents, a clear understanding of the current educational needs of healthcare providers is needed.

Study Design

Following a review of the literature and CCO internal data, this two-phase, mixed-methods needs assessment study was designed to include qualitative telephone interviews (Phase 1) and an online survey (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of US-based healthcare providers responsible for treatment decisions for patients with HER2-positive MBC. Phase 2 examined practice trends among clinicians within the United States. The study design included informed consent and measures to ensure protection and confidentiality for participants. Participants were offered an ethically acceptable level of compensation (ie, fair market value, but not enough to create coercion) to increase the number of participants and improve the statistical power as well as the likelihood that our study cohort is representative of the general US oncology specialist healthcare provider population.

Qualitative Phase

Semi-structured interviews were designed to explore intuitive decision-making factors influencing clinical reasoning.[10] We conducted a series of confidential, 30- to 45-minute telephone interviews, directed by an interview topic guide based on literature review, faculty input, and synthesis. Interviews were transcribed verbatim and imported into NVivo 12 for Mac (*QSR International*), a software package designed to support the systematic analysis of unstructured textual data. Analysis was based on grounded theory and an open-ended process of constant comparison that generates themes, descriptive patterns, and hypotheses as an ongoing, iterative process.[11] This approach included 4 components:

1. Data immersion and familiarization
2. Descriptive coding and node generation
3. Thematic coding and analysis
4. Subgroup analysis by demographic and other relevant attributes

The transcript content was coded into descriptive categories, or “nodes,” that were tagged to sections of text. Following descriptive node generation, a second round of coding identified potential themes of relevance until we achieved thematic saturation. Indicators of themes included words, phrases or segments of text that were used in a similar fashion by respondents across or within interviews, and that pointed to an emerging idea or concept. Qualitative findings were also examined for educationally significant differences among subgroups (ie, practice setting, specialty, designation) and reported where relevant. The conclusions for the overall group are, for the most part, relevant across all subgroups.

Quantitative Phase

We fielded an in-depth quantitative survey to identify practice trends concerning integrating new agents and therapeutic advances in the care of patients with HER2-positive MBC, sources of information consulted for best practices and/or education, gaps in knowledge, competence, and performance, and barriers to the adoption of new treatment options.

Oncology clinicians treating HER2-positive MBC were recruited to complete a 10- to 15-minute online survey. Sara A. Hurvitz, MD, FACP, Director, Breast Cancer Oncology Program, Associate Professor of Medicine, Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine

at UCLA and Sara M. Tolaney, MD, MPH, Assistant Professor of Medicine, Harvard Medical School, Associate Director, Susan F. Smith Center for Women's Cancers, and Director, Clinical Research, Breast Oncology, Dana-Farber Cancer Institute—both nationally recognized experts in HER2-positive MBC—worked with educational and survey design/assessment experts to develop case scenarios and clinical questions to assess gaps in optimal patient management, trends in care, knowledge of clinical trials and investigational agents, and self-identified barriers to optimal care.

Recruitment

Invitations to participate in both phases of the study were sent through email to a list of CCO members as well as lists specific to radiation oncologists, neuro-oncologists, and midlevel providers. CCO Oncology membership includes more than 163,000 clinicians worldwide, including more than 26,000 physicians in the United States, of whom more than 16,000 define themselves as having a specialized interest in medical oncology or hematology/oncology. The lists for radiation oncologists, neuro-oncologists, and midlevel providers included 4245, 3783, and 3184 clinicians, respectively. Multiple targeted emails were sent to each group in an effort to maximize participation.

Participant Characteristics

Demographic Characteristics of Participants

We conducted qualitative interviews between June 25 and August 20, 2019. For the qualitative phase, we recruited 30 clinicians who described themselves as practicing in US academic centers, community cancer centers, private practice, or community-based settings (**Table 1**). A majority of interview participants were physicians with a decision-making role with regards to treatment; 7 participants were Advanced Practice Providers (Advanced Practice Nurses or Physician Assistants) and 1 was a nurse practitioner (NP). Many of the community-based clinicians were affiliated with a community or academic hospital. The quantitative survey was conducted between July and August 2019 and yielded 347 US-based participants (**Table 1**).

Table 1. Demographic Characteristics of Participants

	Qualitative (n = 30)		Quantitative (n = 347)	
Position	**n**	**%**	**n**	**%**
Physician	22	73.33	128	36.89
Nurse Practitioner	1	3.33	15	4.32
Physician Assistant	1	3.33	13	3.75
Advanced Practice Nurse	6	20	28	8.07
Nurse Navigator	--	--	19	5.48
Pharmacist	--	--	63	18.16
Nurses	--	--	81	23.34
Specialty	**n**	**%**	**n**	**%**
Medical oncology	14	46.66	94	29.75
Hematology/oncology	11	33.33	109	34.49
Radiation oncology	5	16.66	28	8.86
Surgical oncology	--	--	7	2.22
Neuro-oncology	--	--	0	0
Neurosurgery	--	--	1	0.32
Primary care	--	--	17	5.38
Pharmacy	--	--	46	14.56
Other	--	--	14	4.43
Years of practice	**n**	**%**	**n**	**%**
< 5	NA	NA	70	22.15
5-10	NA	NA	67	21.20
11-15	NA	NA	35	11.08
16-20	NA	NA	35	11.08
21-30	NA	NA	59	18.67
> 30	NA	NA	50	15.82
Practice setting	**n**	**%**	**n**	**%**
Academic	8	26.66	66	20.89
Community/hospital/ health system owned	13	43.33	150	47.47
Physician owned	7	23.33	57	18.04

Federal government owned	--	--	5	1.58
Other	2	6.66	38	12.03
BC patients/month	**n**	**%**	**n**	**%**
< 5	NA	NA	76	24.05
5-10	NA	NA	48	15.19
11-15	NA	NA	52	16.46
16-20	NA	NA	27	8.54
21-30	NA	NA	42	13.29
> 30	NA	NA	71	22.47

Roles and Responsibilities

One half of the interview participants saw patients with a range of solid tumors and one half specialized in or mainly saw patients with BC. The roles of interview participants in managing patients with HER2-positive MBC differed by degree/professional qualification (**Table 2**).

Table 2. Self-Reported Role by Degree/Professional Qualification

MD	APN/MSN/PA	NP
Treatment determination	Initial evaluation	Infusion administration
Collaboration lead	Patient education	Patient education
Clinical trial identification	Symptom management	Symptom management
	Navigation	

Practice Gap #1: Disparities in Using a Multidisciplinary Approach to Decision-Making and Treatment Planning

A multidisciplinary approach to cancer care that relies on the expertise of all relevant disciplines to discuss optimal disease management is recommended by experts and clinical practice guidelines. Clinicians with access to tumor boards are more likely to describe treatment planning as a collaborative or multidisciplinary process. Clinicians without access to multidisciplinary planning or other clinical decision support resources are more likely to view themselves as primary decision-makers when it comes to treatment planning for patients with advanced HER2-positive BC.

Treatment Planning as a Collaborative Process

Almost one half of interview participants (n = 14) participated in tumor boards. Although some of these participants also described themselves as primary decision-makers, overall, this group was more likely to describe treatment planning as collaborative or multidisciplinary, and used words such as "team" and "consensus" to describe the process.

> *We have a **multidisciplinary breast tumor board**, so usually we run the patient through that and/or we discuss them on the phone between ourselves.* [provider 16, MD, oncology, community]

> *A lot of those patients are presented at the breast tumor board. So, whatever the treatment we are doing or we'd recommend to the patient is **usually a consensus or at least most oncologists agreed upon** at that meeting.* [provider 18, MD, radiation oncology, community]

> *It's quite comprehensive. Our physicians sit at our weekly tumor board meetings that are located at the hospital and you have a dynamic team of physicians that are part of patient care, from surgeons to pathologists and **all of the care team members that are involved in making diagnoses for patients** based on what their findings are, with radiologists. And so those decisions are made together, as a team.* [provider 15, APN, hematology/oncology, community]

Participants viewed the tumor board as an especially pertinent clinical decision support resource in the setting of early HER2-positive BC but also emphasized how important and necessary the tumor board is becoming as a resource to support decision-making in advanced disease. A discussion of metastatic cases at a tumor board provides an opportunity to review pathology, imaging, and evolving standards of care for patients with complex disease as well as to clarify metastatic biopsy sites and identify potential clinical trials. One academic interview participant described a weekly tumor board initiative that concentrates solely on patients with metastatic disease.

> *We're probably unique in that, in the last year, **we've actually formed a metastatic tumor board** where we only discuss metastatic cases, so we do that once a week. It's partially to get everybody's idea **because the care of metastatic patients is becoming so complicated and it's also helped us a lot with clinical trial screening and enrollment.*** [provider 26, MD, oncology, academic]

Primary Decision-Makers in Treatment Planning

Most interview participants said they collaborated with other clinicians and specialists in treatment planning, which typically included breast surgeons or general surgeons focused on BC, radiation oncologists, and pathologists. However, more than one half (n = 16) described themselves as primary decision-makers in treatment planning for patients with HER2-positive BC ("the oncologist is the main quarterback"). Radiation oncology clinicians also described the medical oncologist as "in charge of systemic therapy."

> *[My] primary role is the administration and management of systemic treatment around HER2-positive breast cancer. So* ***choosing therapy, ordering therapy, administering therapy, managing toxicity, managing expectations****…*[provider 14, MD, hematology/oncology, community]

> *I'm a physician, so* ***I'm the decision maker from diagnosis to the treatment*** *and all the journey through the treatment.* [provider 6, MD, hematology/oncology, private practice]

> *I'm the doctor.* ***I'm the primary decision-maker****. I make all the recommendations*. [provider 12, MD, hematology/oncology, private practice]

> ***It's mainly up to the medical oncologist to assign the treatment****. That's how [decisions are made] for the care of their patient.* [provider 1, APN, oncology, community]

Communication Among Clinicians

Interview participants who had access to tumor boards noted that communications among specialists about treatment for patients with advanced disease usually occurred in person at the tumor board itself. In the absence of a tumor board discussion (eg, if a decision were made before the tumor board occurred), communications among team members most commonly occurred via telephone calls, as well as secure text message platforms or electronic medical records. Community clinicians or clinicians in private practice were more likely to communicate with other specialists on a case-by-case basis rather than using a multidisciplinary approach as a rule of thumb, and described having access to specialists in radiation oncology or neurosurgery via hospital affiliation or through their specialist network.

> *If they have something wrong with them that will need the services of a radiation-oncologist, I just pick up the phone and call them. It depends.* [provider 12, MD, hematology/oncology, private practice]

> *It depends on the situation—if we need a neurosurgeon, if we need a thoracic surgeon, if we need pain specialists, so it depends on a case-by-case basis.* [provider 7, MD, hematology/oncology, private practice]

Treatment Planning

The medical oncologists we interviewed acknowledged that "while each case is different" there is a common range of clinical factors that they (and colleagues, if participating in tumor boards) consider when determining treatment for patients with advanced HER2-positive BC. These factors included:

- Expected response
- Duration of disease control
- PFS
- OS
- Types of adverse events
- Frequency of adverse events
- Hormone receptor–positive status
- Comorbidities
- De novo metastatic disease
- Previous adjuvant/neo-adjuvant therapy
- Performance status
- Disease stage
- Extent of metastatic disease

Radiation oncology clinicians had less to say about the initial treatment for patients with de novo or previously treated metastatic disease. One physician noted the following:

> *Their HER2-positive status doesn't really affect the radiation decision as far as whether it's a curative treatment or a palliative treatment. We know that HER2-positive patients generally have more aggressive disease, so that's something to think about when thinking about recommending or not recommending treatment. But the type of treatment that's recommended is not that drastically different than somebody that's HER negative, as, you know, HER2 positivity is not really a predictor of outcome with radiation*. [provider 21, MD, radiation oncology, community]

Communication With Patients

Clinicians with access to tumor boards noted that following tumor board discussion, they would typically have a treatment planning discussion with the patient that reflected the extent of the patient's disease as well as team consensus about treatment. Medical oncologists reported that they typically met with patients in person to offer treatment recommendations based on either tumor board consensus or, for medical oncologists with no access to tumor boards, to offer their own recommendations based on patient history, disease characteristics, and previous treatment.

APNs and NPs described their role in communication with patients as "*reinforcing*" what the medical oncologist has already discussed as based on information and orders documented in and available via electronic medical records. Some interview participants also pointed to the increasing role of nurse navigators to coordinate care and help patients navigate through the treatment process.

> *The oncologist will directly communicate that with the nurse navigator and if the patient is going to receive an infusion, the nurse navigator is going to talk with our precertification department,*

making sure everything is covered and the patient will be set up and scheduled and that the nurse navigator will call the infusion team after the patient is scheduled and the patient will come to the department. [provider 10, APN, oncology, community]

Setting Expectations

Medical oncologists described in considerable detail their approach to discussing treatment recommendations and setting expectations for patients (**Table 3**).

Table 3. Examples of How Medical Oncologists Set Patient Expectations in Treatment Planning
In the first meeting when I see somebody with metastatic breast cancer, I tell them that, unfortunately, at this point, their disease is not curable, meaning that there will never be a time where I can tell them that their breast cancer's not going to come back and that there will never be a time that I can recommend that they go off treatment. With that being said, I do say that metastatic breast cancer is very treatable and we are getting more and more drugs to treat this disease every year and it's sort of something that we manage as a chronic disease for as long as we can and as best as we can. And then I say something like, "The goals of your care at this point are to prolong your life and give you the best quality of life for as long as possible." [provider 26, MD, hematology/oncology, academia]
We lay down all the treatment options and from the beginning very well plan what is a prognosis going to be, what they should look for the outcome in the future. [provider 6, MD, hematology/oncology, private practice]
Well, the first thing we say is that the median overall survival of these patients has more than quadrupled in the last decade or two, so nowadays patients are living, on average, 5 years. So we say that to the patient that, "We think we're going to change your disease into a chronic disease." We don't say, "We're going to cure you," but we'll say, "This disease can be treated for many, many years and some patients may go 10 years." [provider 7, MD, hematology/oncology, private practice]
You want to initially establish with them that this is an incurable condition and whether it's chemotherapy plus or minus targeted therapy, they'd likely be on something for the rest of their life. [provider 8, MD, oncology, private practice]

While oncologists generally told patients upfront that HER2-positive MBC is incurable ("*we're honest from the beginning*") most viewed metastatic disease as a chronic, treatable disease and described "*laying out all the options to help patients make a decision they're comfortable with*."

Clinicians ranged in how they specifically addressed the prognosis, from telling patients at the time of diagnosis of metastatic disease, *"there is no cure,*" to quantifying the prognosis, as described here by a physician:

> *I am discussing their prognosis on a few data points. One is what are the chances of response—60%, 80%—based on the data that has been accumulated and is readily available to me…*[provider 14, MD, hematology/oncology, community]).

A radiation oncologist also noted that he discussed treatment success with patients in terms of "*the percentage of control of their cancer*" and with consideration of risk vs benefit:

> *You know, we talk about side effects and complications and the percentage of severe complications and all of those things and then we come to a conclusion about whether the patient wants to proceed.* [provider 21, MD, radiation oncology, community]

In contrast, for some clinicians, there was a general sense that most patients are not looking for quantifiable data on prognosis, but rather, a "*general sense of kind of a vague concept of 'how long have I got*?'" As such, 1 clinician noted "*you have your clichéd phrases that you help pacify the patient and then you hope for the best*." [provider 24, MD, oncology, academia]

APNs and NPs were less likely to have conversations with patients about prognosis and generally ceded such discussions to the medical oncologist. However, APNs and NPs emphasized the importance of setting immediate goals with patients before initiating systemic therapy and 1 APN described a tool her practice uses to gauge how patients want to handle challenging information.

> *In our practice, we have a sheet, a wishes sheet (My Wishes), and then we read the wishes**, what they would like and how comfortable they feel about being told that they are dying**. We do this, you know. We discuss that with every patient now regardless if they're metastatic or not.* [provider 1, APN, oncology, community]

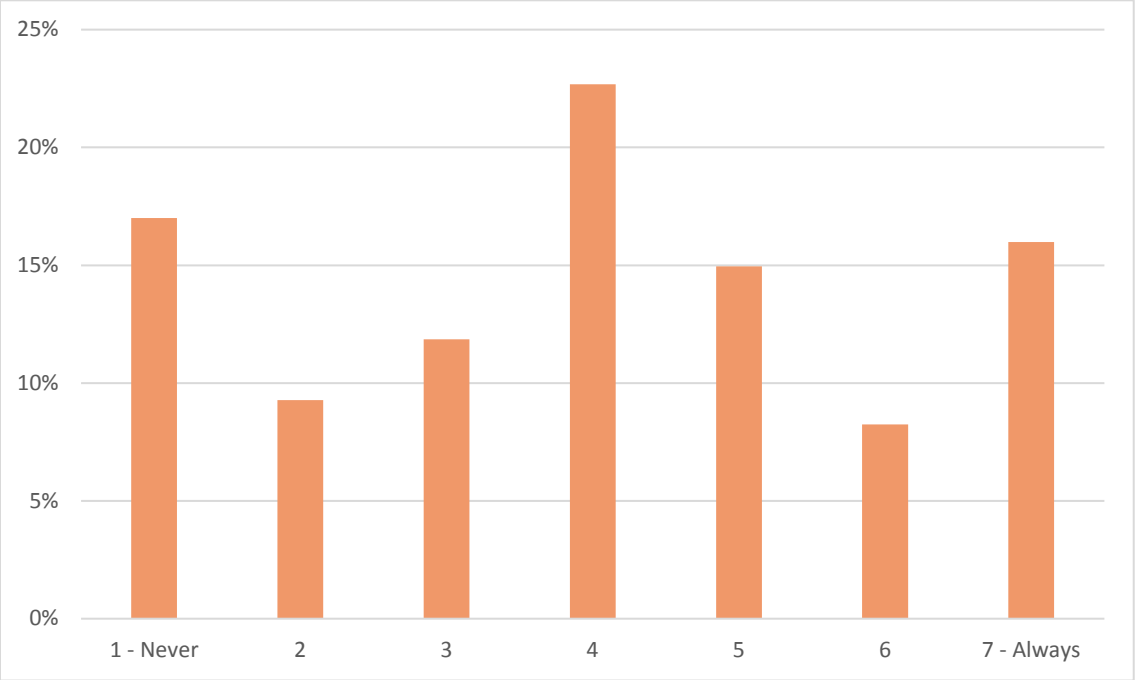
Practice Gap #2: Deficits in Clinical Trial Referral

Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with cancer and to promote discovery of new therapies. Although clinicians say they discuss clinical trials with patients, they vary in the timing of such discussions, and the estimated percentage of patients that clinicians said they were able to refer for clinical trial is low.

Clinical Trials in Treatment Planning

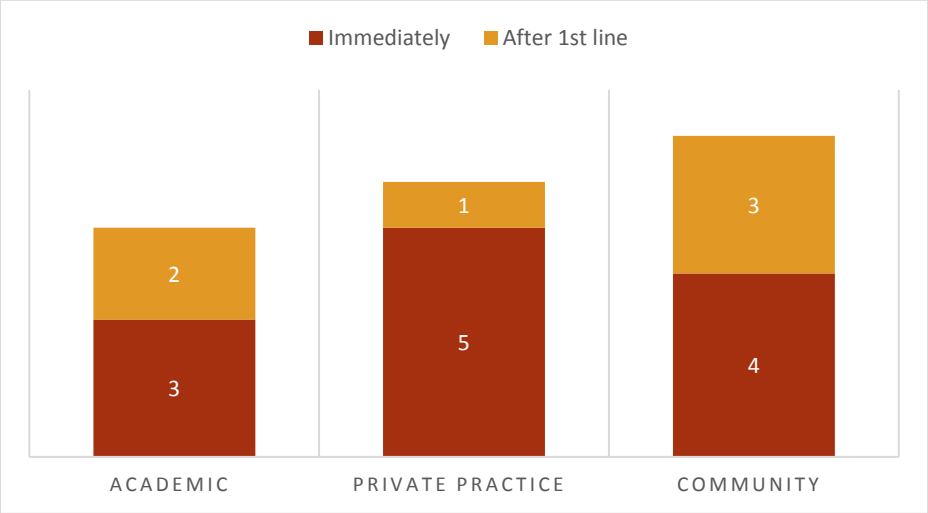
Survey data show that only 1 in 6 clinicians said they always discuss clinical trials with their patients and approximately 25% indicated that they rarely or never discuss clinical trials (**Figure 3**).

Figure 3. Percentage of clinicians discussing clinical trials with patients (n = 194).



In interviews, more than one half of the medical oncology clinicians said they usually discussed clinical trials with their patients as an option early in treatment planning and revisited the potential for trial enrollment at progression (**Figure 4**). The remaining medical oncology clinicians we interviewed said they typically discussed clinical trials following failure of first-line therapy in the metastatic setting (**Figure 2**).

Figure 4. Timing of clinical trial discussion by medical oncology clinicians (n = 18).



APNs/NPs and clinicians working in radiation oncology were unaware if their radiation oncology physicians or medical oncology colleagues discussed clinical trials with patients at any point in treatment planning.

While only one of the radiation oncology clinicians we interviewed indicated that the potential for clinical trial referral was an option for their patients (this provider had participated in a national hippocampus-sparing trial), survey data suggest that approximately one half (55%) of radiation oncology specialists recommend trials to their medical oncology colleagues.

Clinicians broadly agreed that with few exceptions, patients rarely asked them about clinical trials.

Clinical Trials in Initial Treatment Planning

Clinicians who said they usually discussed clinical trials with their patients as an option early in treatment planning and revisited the potential for trial enrollment at progression appeared to feel a responsibility to consider clinical trials for their patients with HER2-positive MBC in an effort to improve patient care.

> *I tend to think about clinical trials as early on as possible.* ***At basically every treatment decision, I will be looking to see if there's a clinical trial that makes more sense*** *than what I might be offering. I'm pretty proactive about looking at clinical trials and seeing where something might be more beneficial than what I currently have available.* [provider 11, MD, hematology/oncology, private practice]

> ***The clinician has a responsibility to know what clinical trials are available at their institution****, so that you kind of broach the topic having one in mind, because that is, I think, a difficult concept for patients to wrap their head around if they're just kind of wrapping their head around the diagnosis. I introduce the concept of clinical trials and let them know that we have an interesting trial for them, but probably go more so into detail about the specific trial when they come back, after their staging studies.* [provider 24, MD, oncology, academic]

If there is a clinical trial available, ***then the first option would be to enroll****. Definitely something that I encourage.* [provider 2, MD, hematology/oncology, academic]

However, the estimated percentage of patients that interviewed clinicians said they were able to refer for clinical trial was low (approximate range: 1% to 20%). In practice, even among those who said they discussed clinical trials at the initial treatment planning visit, clinical trial referral was more likely to occur at the second or third line of therapy.

You know, as we go down the line and ***we're exhausting standard treatments, then people are much more receptive to seeking out clinical trials,*** *but I do try to have that conversation right at the beginning if I feel like the person is going to be receptive.* [provider 4, MD, hematology/oncology, community]

Private practice and community clinicians offered the additional caveat that although some of their patients might be eligible for clinical trial referral at a tertiary center, distance would likely pose a barrier to participation.

We know how these ***patients are living far away from big cities and they don't want to travel****, many of them don't have cars, so you have to put things in perspective and if I have a standard of care that can give you 60 months of survival, I don't think clinical trials are feasible.* [provider 7, MD, hematology/oncology, private practice]

Clinical Trials After First-line Treatment Failure

Clinicians who waited to discuss clinical trials until later lines of therapy felt that the current standard approaches (dual-HER2 trastuzumab/pertuzumab-containing therapy, T-DM1–containing therapy, and neratinib- or lapatinib-containing therapy) were effective for most patients, depending on disease and patient characteristics.

I would say that I'm usually not bringing up clinical trials at the first or second meeting in metastatic HER2-positive breast cancer, because ***we have a very clear cut sort of first-line regimen that provides an overall survival benefit and there's rarely any trials in the first-line setting*** *and most patients are going on the standard of care best therapy in the first line.* [provider 26, MD, hematology/oncology, academic]

I always discuss clinical trials, to be very open to, in the metastatic HER2 setting. I'm a little reluctant to talk about it, you know, in the first couple of months, because we have such good upfront drug therapy right now and I don't have a great first-line trial right now. So, personally, I ***tend to talk about trials as we go forth in the subsequent months and so forth****. I typically am not a big fan of doing it right away in this particular disease. I typically wait in this setting, just because so much is going on and I think you have to do it****. It's a marathon journey****, I tend to not just sprint and do everything at once.* [provider 25, DO, oncology, community]

Oftentimes, ***the discussion for clinical trial usually happens much later****, because we have such great effective treatments today that it's possible that the patient continues to have a beneficial effect for a very, very long time on current therapy before we are in the clinical trial world. So it*

depends on how the disease in the patient is behaving. [provider 14, MD, hematology/oncology, community]

Practice Gap #3: Deficits in Selecting Optimal First-line Therapy for Patients With de novo HER2-Positive MBC

Many clinicians appropriately chose THP and HP maintenance as initial therapy for de novo HER2-positive MBC; however, potential overtreatment in the de novo setting is evident, with approximately one half reporting they would also add local therapy (surgery or radiation) to the treatment regimen.

Current Standard of Care for de novo HER2-Positive MBC

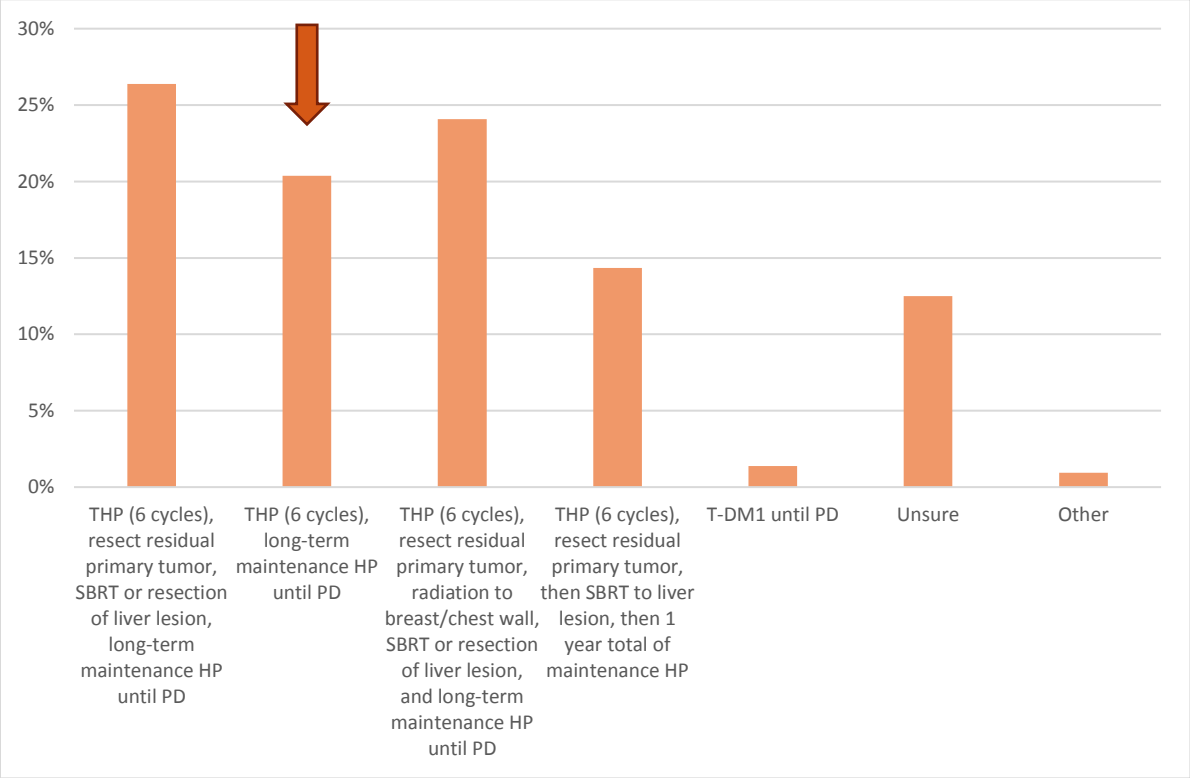
Based on the positive results of the phase III CLEOPATRA trial, the current standard of care for patients diagnosed with de novo HER2-positive MBC is initial therapy with THP followed maintenance HP until progression or intolerance.[11] Experts indicated that, although reasonable in some cases, additional local therapy might represent overtreatment. Upon disease progression following THP plus HP, the standard of care is the antibody–drug conjugate T-DM1 based on positive results of the phase III EMILIA trial.[12]

Case #1: Newly Diagnosed de novo HER2-Positive MBC

A 54-year-old woman presented to her primary care doctor with a 4-cm breast mass and a palpable ipsilateral axillary lymph node. Biopsy of the breast mass demonstrated an ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma and fine-needle aspiration of the lymph node was positive for carcinoma. Staging studies revealed a 2-cm liver lesion, the biopsy of which was ER negative, PgR negative, and HER2 positive (3+), consistent with her BC.

Which of the following treatment approaches would be most appropriate for this patient?

Figure 5. Selection of optimal therapy for newly diagnosed de novo HER2-positive MBC (n = 216).



Expert preference for this newly diagnosed patient with HER2-positive MBC is THP for 6 cycles followed by long-term HP maintenance (**Figure 5, indicated by arrow**). Experts indicated that although THP for 6 cycles followed by surgical resection and/or radiation therapy and long-term HP maintenance therapy would be reasonable in some cases, additional local therapy might represent overtreatment placing the patient at increased risk of complications from their treatment. Breast cancer expert Sara Tolaney, MD, MPH, was "*surprised that so many were doing local therapy for patients with de novo metastatic disease that was more than just oligometastatic.*"

Clinician Rationale for de novo Therapy Selections

In interviews, most clinicians similarly identified THP (a taxane, paclitaxel or docetaxel, plus trastuzumab and pertuzumab) as their preferred therapy for patients presenting with de novo metastatic disease. Clinicians pointed to performance status, functional status, extent of disease, symptoms, tolerability of the THP regimen, age, and preexisting neuropathy as being rationale for this choice, as well as patient desire for systemic therapy. Many clinicians viewed de novo therapy as "*pretty standard*" and echoed the sentiment of one oncologist who noted "*there's not a whole lot that's going to affect what I give them in the first line*."

Although the THP regimen was frequently mentioned, other chemotherapy agents that clinicians cited included navelbine (hair loss–sparing), nab-paclitaxel (on the grounds that there are some data showing equivalence to taxanes), and carboplatin.

> *Everybody kind of agrees that dual blockade is the best option with chemotherapy. We can discuss sometimes which is the best partner for the dual blockade, which chemotherapy will be the best partner, paclitaxel, docetaxel, or sometimes we use vinorelbine.* [provider 5, MD, oncology, academic]

Three APNs identified dual HER2 blockade as standard in the de novo metastatic setting but were less clear about which specific combinations oncologists were likely to recommend. In patients whose disease was also hormone receptor positive, the approach that clinicians most frequently mentioned was to introduce hormone-based therapy following completion of chemotherapy, alongside dual HER2 blockade.

Nonclinical Factors

Clinicians reported that they collected a range of information from patients to support decision-making via medical history, review of systems, and, in some cases, patient preference questionnaires. Most of this information pertained to clinical issues such as symptoms and comorbidities. However, few of the clinicians we interviewed described how they used nonclinical factors in their decision-making for de novo metastatic patients. Typical responses to this question include this remark from an oncologist, who said:

> *Nonclinical factors, not a whole lot**. I can't think of anything nonclinical, so to speak**. I mean, one can say the desire of the patient to receive therapy, and so on.* [provider 14, MD, hematology/oncology, community]

The nonclinical factors most frequently cited were convenience for the patient, patient willingness to go through treatment, psychosocial issues, social issues (eg, transport, family support), and insurance coverage. Clinicians who factored nonclinical information into their decision-making provided the following rationales:

> *So, depending on **how old a patient is, is she still working and wants to continue working, if she has young kids,** other relationship issues, I think all that information is very important to have.* [provider 23, MD, oncology, private practice]

> ***We always take the patient's consideration into effect**. The family's a little bit, but the patient comes first. So that's really it: trying to make sure that the patient is comfortable with what we do. And I mean, we have some that go, "No, I'm not going to do it," and that's their choice.* [provider 9, APN, oncology, academic]

> *If people have a hard time getting to and from our center or if they're going to not have good family support during therapy, **we might consider less aggressive therapies or more convenient therapies**.* [provider 16, MD, oncology, community]

Therapy Selection in HER2-Positive MBC That Is Also Hormone Receptor Positive

Current Standard of Care for de novo Hormone Receptor–Positive/HER2-Positive MBC

In patients with hormone receptor–positive, HER2-positive MBC, clinical guidelines recommend treatment with dual HER2 blockade plus chemotherapy followed by the introduction of hormone-based therapy after chemotherapy is completed.

The most common practice described by the clinicians we interviewed concerning the treatment of hormone receptor–positive, HER2-positive advanced BC involved adding endocrine therapy to HER2 blockade and/or introducing hormone-based therapy to dual HER2 blockade following completion of chemotherapy. This approach (typically fulvestrant/trastuzumab or aromatase inhibitor/trastuzumab) was considered standard by clinicians for patients with small disease burden, no visceral crisis, and who might not desire chemotherapy. CDK4/6 inhibitors were also mentioned by a small group of private practice and community-based clinicians.

> *If the patient is tolerating Taxotere, **I will continue to use it as long as I can use it**. **At that point, I'll switch over to hormone plus dual HER2** if the disease is under control and continue with that until disease progression and then switch out altogether to Kadcyla. So the only difference is utilization of hormones at some point, either before progression or after progression.* [provider 14, MD, hematology/oncology, community]

> ***Usually these patients will get a hormonal therapy in the maintenance phase**, more or less, not as the primary treatment, because the data has been limited. We have a few studies here and there using an AI plus anti-HER2, more in the elderly who didn't want chemotherapy or were not eligible for chemotherapy. The responses certainly were inferior to chemotherapy, but you can certainly use it in the situation where you cannot use or the patient doesn't want chemotherapy.* [provider 7, MD, hematology/oncology, private practice]

After induction treatment, when the response has been the maximum, we change chemotherapy for endocrine therapy plus blockade*. But if the patient is kind of old, she's been pre-treated, or she's not willing to go through chemo side effects, and if there is a high expression of hormone receptors, we go for endocrine therapy plus doing a blockade but plus anti-HER2 therapy.* [provider 5, MD, oncology, academic]

Practice Gap #4: Challenges in Selecting First-line Therapy for Newly Diagnosed MBC in Patients Previously Treated for Early BC

Many clinicians are unsure which first-line therapy is appropriate for patients who received TCHP (docetaxel/carboplatin plus trastuzumab, and pertuzumab) and T-DM1 for early-stage BC. Clinicians also vary in how they define a treatment-free interval, which is an important factor in choosing subsequent therapy at the time of progression to metastatic disease. Clinician uncertainty about therapy selection is noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 or for patients whose disease recurs after a longer treatment-free interval, which some clinicians defined as after more than 6 months while others defined it as after more than 12 months.

Standard of Care for Early HER2-Positive BC and Impact on Management of Newly Diagnosed MBC

Many patients are diagnosed with earlier stages of HER2-positive BC and may be treated with neoadjuvant or adjuvant trastuzumab/pertuzumab in combination with chemotherapy, as well as extended adjuvant therapy with neratinib in some high-risk patients.[13,14] More recently, the FDA also approved T-DM1 (May 2019) as adjuvant therapy for these patients.[15] Thus, clinicians are increasingly encountering patients with newly diagnosed HER2-positive MBC with previous exposure to trastuzumab, pertuzumab, T-DM1, and neratinib, and are facing the challenge of deciding how to treat these patients upon recurrence with metastatic disease in the absence of a standard-of-care treatment. Current approved treatment options for patients who progress to metastatic disease following treatment for early stage HER2-positive breast cancer include rechallenge with a previous treatment regimen in some select cases, lapatinib plus capecitabine, trastuzumab plus chemotherapy, or chemotherapy. However, most patients eventually experience disease progression with these treatment regimens, thus new options are clearly needed.[16]

New Therapies in Clinical Development for Pretreated HER2-Positive MBC

Therapies under development that have shown promise in the setting of pretreated HER2-positive MBC, whether for early BC or MBC, include improved HER2-targeted TKIs, monoclonal antibodies, and antibody–drug conjugates. In the phase III NALA trial, neratinib, an irreversible pan-HER TKI, in combination with capecitabine significantly improved PFS vs lapatinib plus capecitabine in patients who had received at least 2 regimens targeting HER2 (HR: 0.76; P = .0059, with 12-month PFS rates of 29% vs 15%, respectively).[17] Tucatinib, an oral, selective HER2-targeted TKI, has also demonstrated early phase activity in this setting, achieving an ORR of 48% and PFS of 8.2 months in combination with T-DM1, and an ORR of 61% and PFS of 7.8 months in combination with capecitabine and trastuzumab.[5,18] Furthermore, because of its selectivity for HER2, tucatinib has demonstrated fewer EGFR-related toxicities than many of the other HER2-targeted TKIs.[16] The combination of tucatinib plus capecitabine and trastuzumab is being evaluated in the ongoing randomized phase II HER2CLIMB trial.[19]

Clinician Rationale for Therapy Selection for Newly Diagnosed MBC Following Treatment for Early BC

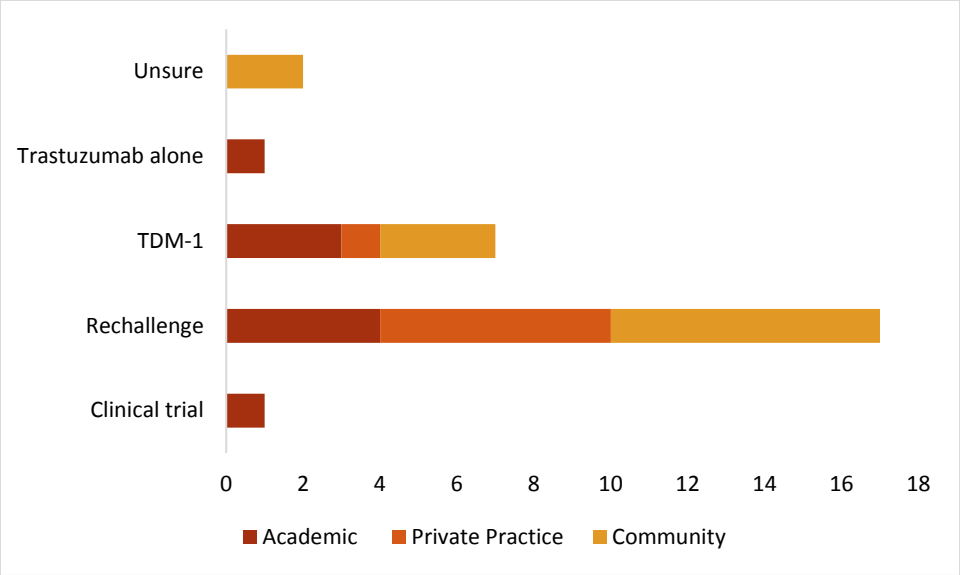
We asked clinicians to explain their rationales for choosing therapy for patients with newly diagnosed MBC who were previously treated for early BC. **Table 4** describes the range of responses that clinicians provided.

Table 4. Clinician Rationales for Therapy Selection Following Treatment for Early BC
The rationale is what you think is the best option based on the level of response, the type of therapy that she had, the receptor status, the level of response, the duration of therapy, the level of side effect. All of that would play a role. So the idea is to maximize and use something that most likely the patient will respond to, whether they have previously responded to it, whether they have achieved a tremendous response, minimal response, near complete response. All of that stuff will play a role. [provider 14, MD, hematology/oncology, community]
The rationale is, if the treatment-free interval is longer, then still, there is a likelihood of responding to the same treatment. And that tells me the prognosis is probably better. If treatment field is shorter, that tells me it's excessive disease. That helps me to prepare the patient also. Say you have a bad disease—the likelihood of treatment for longer time is small, possibly. [provider 6, MD, hematology/oncology, private practice]
All what we decide is based on large phase III trials, and that didn't come from 1 or 2 years, over many, many years of research that we have these milestone phase III trials that set in stone what I'm talking about. [provider 7, MD, hematology/oncology, private practice]
Things like patients' clinical factors, performance status or comorbidities or volume in extended disease, impact treatment decisions…as far as burden of disease in HER2-positive breast cancer, that does not affect my treatment decisions as much as it does in, say, estrogen receptor-positive breast cancer. Because the first, second, and third lines all have efficacy that is not based on volume of disease. [provider 26, MD, hematology/oncology, academic]
When you have someone who's been already treated, then you have to see what their time to progression was, what their treatment-free interval was. That is very important and plus what they had already been treated with. So a lot of times patients, if they've had taxanes before, they may come in already with some treatment-related symptoms from taxanes, such as neuropathies. If they have gotten any anthracyclines or Herceptin in the past, they may have already some cardiac issues. So, yeah, I think you have to be very careful when you're then treating patients with metastatic disease what kind of symptoms may be related to their treatment before. [provider 23, MD, oncology, private practice]

Therapy Following Adjuvant/Neoadjuvant HP

The general consensus following neoadjuvant or adjuvant treatment with trastuzumab or pertuzumab among medical oncologists we interviewed was that "if it's been a while" a rechallenge with HP was feasible for patients with metastatic disease (**Figure 6**). Medical oncology APNs and radiation oncology clinicians were unsure of available options, said they would use trastuzumab alone or T-DM1, or look for a clinical trial.

Figure 6. Therapy following neoadjuvant/adjuvant trastuzumab/pertuzumab (n = 28).

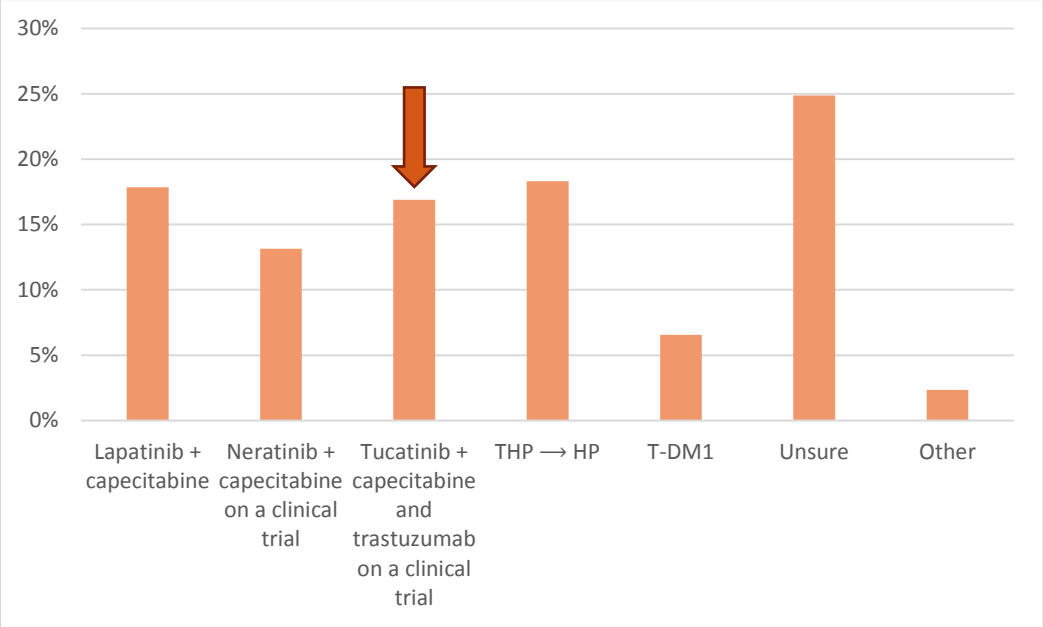


Case #2: Therapy Following Adjuvant T-DM1 for Early BC

A 58-year-old woman who was treated for T2N1 ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma received preoperative TCHP and was found to have residual disease in the breast and lymph node. She subsequently received adjuvant T-DM1 for 14 cycles. Two years later, she presented with right upper quadrant discomfort and was found to have liver metastases. Biopsy confirmed the liver metastasis was ER negative, PgR negative, HER2 positive (3+).

Which of the following treatment regimens would be most appropriate for this patient?

Figure 7. Appropriate therapy selection for patient newly diagnosed with HER2-positive MBC who previously received TCHP and T-DM1 for early-stage disease (n = 213).



Expert preference for this newly diagnosed patient with HER2-positive MBC who previously received TCHP and T-DM1 for early stage disease would be to enroll them on a clinical trial of tucatinib plus capecitabine and trastuzumab (**Figure 7, indicated by arrow**). Experts indicated that other reasonable options include lapatinib/capecitabine, neratinib/capecitabine on a clinical trial, or THP followed by maintenance HP.

Rationale for Therapy Selection After T-DM1 for Early BC

Clinician uncertainty was noticeably greater concerning treatment for metastatic disease following therapy with adjuvant T-DM1 for early BC. While a small group of interviewed clinicians said they might circle back to HP, rechallenge with T-DM1, or make a switch to lapatinib, the majority of clinicians expressed uncertainty about next steps (**Table 5**). In fact, less than one half of interviewed clinicians said their practice is even to use T-DM1 in the adjuvant setting for patients with early BC who were treated with neoadjuvant HER2-targeted therapy and then had residual disease. Most interviewed radiation oncology clinicians were unfamiliar with T-DM1 and APNs were unaware of options in this setting.

Table 5. Uncertainty Concerning Approach to Therapy Following T-DM1 for Early BC
We'd look at could we do another anti-HER2-neu—I mean, again, it would depend on how long ago they had it and how well they responded to it. So we could, you know, consider doing some endocrine manipulation or CDK inhibitor if they're ER/PR positive, or ***trying a different anti-HER2-neu agent****. So I think those would all be on the table for consideration, but which one we would pick I think would just depend on the patient's individual clinical situation*. [provider 16, MD, oncology, community]
*If they progressed on T-DM1 then, yeah****, it becomes questionable what you should use****. I'd probably try to use Perjeta triplet in those patients and if they progressed on Perjeta then I think I'm going to go to T-DM1*. [provider 11, MD, oncology, private practice]
*That's a really tough question and I haven't even seen that yet. If they have residual disease and they've already had Herceptin and Perjeta and then they've already had T-DM1 and then if they progress****, it would really depend on what the treatment-free interval was, how long after they progressed, what their repeat receptors look like****. Again, I would biopsy them again, I would repeat the receptors and go from there.* [provider 26, MD, hematology/oncology, academia]
*Now, we do know that T-DM1 can be used as part of consolidation therapy after initial Herceptin-Perjeta neo-adjuvant treatment, that there may be T-DM1 consolidation after their breast surgery and then they may, at some point, develop stage IV disease****. Nobody is quite sure yet whether they should be restarted on Herceptin-Perjeta, whether they should be restarted on T-DM1****. Nobody is quite sure what to do with that woman. I would be influenced by the cardiac status. I would be interested by how long the free interval was. So, for example, if someone had consolidated T-DM1 and maybe they had stage IV disease 9 months later, I'd say they're done with Herceptin, Perjeta, and T-DM1. They may just be refractory to those agents. So another very unlikely possibility is lapatinib with capecitabine, particularly if the relapse occurred in the brain—but again, that's an extremely unlikely scenario for us.* [provider 12, MD, hematology/oncology, private practice]

Sara Tolaney, MD, MPH, was "*not surprised by the confusion in the approach for patients who have had adjuvant HP and/or T-DM1, given the lack of data in this setting and unclear optimal disease-free interval for re-exposure to these agents.*"

Defining Treatment-Free Interval With HER2-Targeted Therapy for Early BC

The duration of a treatment-free interval factors into clinical decision-making when determining therapy for patients previously treated with trastuzumab/pertuzumab in the (neo)adjuvant setting. **Although the FDA currently defines this interval as 6 months, many experts adopt a treatment-free interval of either 6 or 12 months.** Interviewed clinicians varied in how they defined "treatment-free interval," a definition that included 1 month, 6 months, 12 months, or 2 years (**Table 6**).

Table 6. Rationales for Therapy for Newly Diagnosed MBC Following Adjuvant/Neoadjuvant HP	
Rechallenge With HP	**Switch to T-DM1**
If it's been a while, we would generally re-give it or re-challenge—I mean, give it again, if it's been many years. [provider 16, MD, oncology, community]	*If you develop metastatic disease at a later date, then we don't go back to that regimen, we start—we usually use Kadcyla or a clinical trial. We're going to get Kadcyla, we're not using Herceptin. Well, the Herceptin is in the Kadcyla because it's a conjugate; it's got Herceptin and a chemo helper*

	drug in it but it's just 1 medication. [provider 19, NP, oncology, private practice]
If it is more than a year, usually we go back. Remember, they are going to be on anti-HER2 for a year anyway, either Herceptin or Herceptin plus Perjeta and now we have even neratinib approved for extended adjuvant, so when you say "adjuvant therapy," that can go on for 2 years. So I'm talking about from the end of the adjuvant therapy. If it's been more than a year, you can certainly go back to Herceptin and chemo again and do it with Perjeta. [provider 7, MD, hematology/oncology, private practice]	*If it is a short recurrence, then I probably would do T-DM1. If it is a longer duration recurrence, then I would probably—I don't think I would revisit pertuzumab if they've already seen it, but certainly trastuzumab and any other cytotoxic therapy I think would be appropriate.* [provider 24, MD, oncology, academic]
It would depend on what they progressed on. You know, primarily, if they had progressed on, like, Herceptin alone, I would maybe consider using Perjeta in combination or perhaps T-DM1 if they progressed. [provider 11, MD, oncology, private practice]	*Generally, if someone has received pertuzumab and trastuzumab both in adjuvant and neoadjuvant settings then I'll go to T-DM1 as the first-line therapy in the metastatic setting.* [provider 13, MD, hematology/oncology, community]
This is an area that we just don't really have any answers to right now. It's become a real problem. However, depending on what their treatment-free interval was—so, say that they had been treated and they progressed 2 years after having their treatment, that's a patient that I may retreat again with Taxotere, Perjeta, and Herceptin. [provider 23, MD, oncology, private practice]	*If the patient has not had a duration or less than a year's worth of remission duration, I would consider using Kadcyla in those patients*. [provider 14, MD, hematology/oncology, community]
	It would depend how long ago their adjuvant therapy was. I mean, more than 6 months or less than 6 months, then you would go to second line vs try to re-challenge them with Herceptin. [provider 2, MD, hematology/oncology, academic]

Therapy at Recurrence Within 6 Months Following Initial Treatment

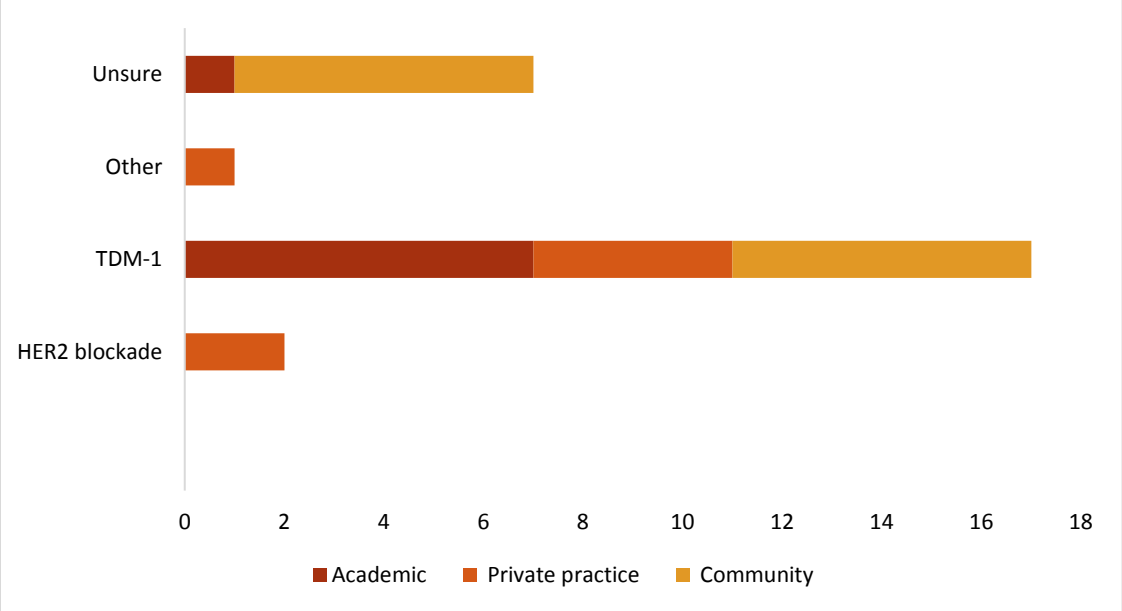
Clinicians expressed greater certainty in their likely treatment selections for patients whose disease recurs within a short treatment-free interval (which, as mentioned above, some clinicians defined as within 6 months while others defined it as within 12 months) following any previous treatment (**Table 7**). In this scenario, T-DM1 was the clear choice for oncologists and 1 radiation oncologist (**Figure 8**). Nonphysicians were unsure about potential options in this scenario.

Table 7. Rationale for Therapy Selection at Recurrence Within 6 Months After HER2-Targeted (Neo)Adjuvant Therapy for Early BC

Dual HER2 Blockade
Probably if they are HER2-positive, if they have received only Herceptin as an adjuvant therapy, did not see Perjeta, I may add Perjeta. [provider 6, MD, hematology/oncology, private practice]

It would depend on what they progressed on. You know, primarily, if they had progressed on, like, Herceptin alone, I would maybe consider using Perjeta in combination. [provider 11, MD, oncology, private practice]
T-DM1
If they are less than 6 months, I would probably use an alternative agent—Kadcyla or otherwise—again, depending on what they have received previously. If they have received Kadcyla and it's less than 6 months since completion, I would be looking at lapatinib or neratinib. [provider 14, MD, hematology/oncology, community]
Kadcyla, that would be my first-line option for someone if it's been less than 6 months. [provider 2, MD, hematology/oncology, academic]
So then it becomes harder because I feel like they're going to progress really soon. So if they were getting Herceptin-pertuzumab, then I would move on to Kadcyla. But if it's a patient who's kind of looking well, feeling well, and it's just scans that are beginning to look scary, then sometimes I'll just reuse what we did before. [provider 4, MD, hematology/oncology, community]
Well, it depends on what was the free interval between the cessation of their adjuvant/neo-adjuvant treatment and the demonstration of stage IV disease. If it's less than a year, then I'm typically not going to use Herceptin and Perjeta again. I might go right to T-DM1. [provider 12, MD, hematology/oncology, private practice]
Other
Less than 6 months, then we get concerned about resistant mechanisms. So what I was starting to say is that's when I may look at their estrogen receptor. That's going to be really important in assessing these patients, because now that neratinib has finally finished the NALA study and has shown some benefit in metastatic disease, that might be the scenario that I would consider. [provider 23, MD, oncology, private practice]

Figure 8. Therapy selection at recurrence within 6 months (n = 27).

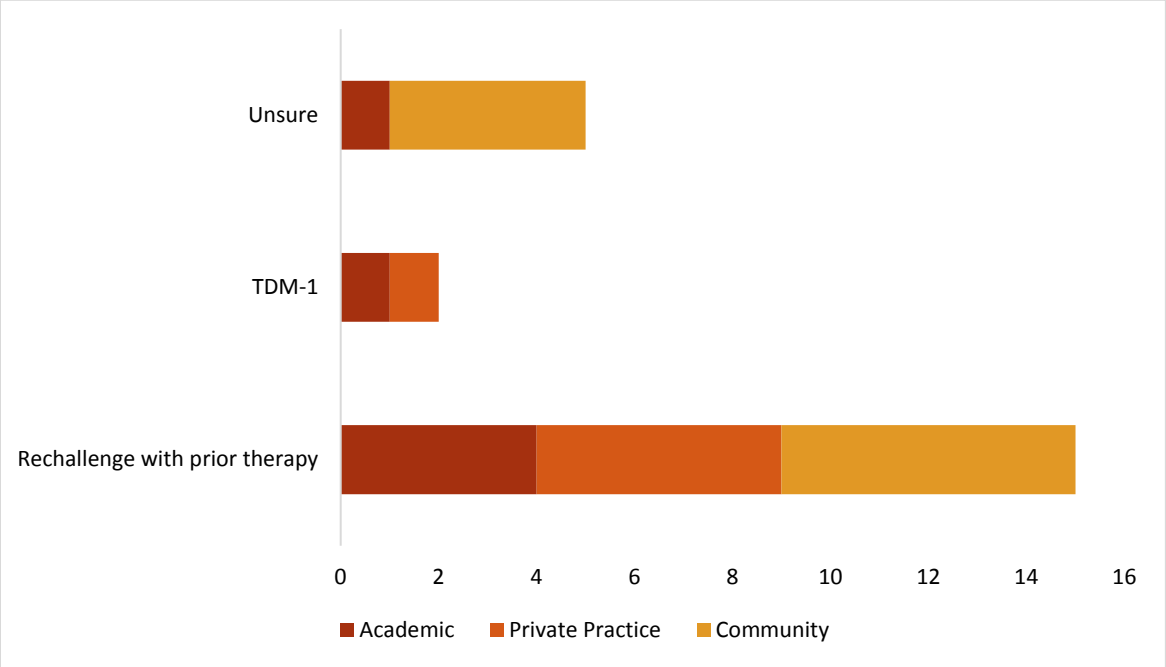


Therapy at Recurrence More Than 6 Months Following Initial Treatment

Interviewed clinicians were mixed in their views on which therapy they would likely select for patients whose disease recurs after a longer treatment-free interval following any previous treatment (which, as mentioned above, some clinicians defined as after more than 6 months while others defined it as after more than 12 months) (**Table 8; Figure 9**). Nonphysicians and radiation oncology clinicians were unsure about potential options in this scenario.

Table 8. Rationale for Therapy Selection at Recurrence More Than 6 Months Following Initial Treatment
Rechallenge with Previous Therapy
So, depending on if it's greater than 6 months, I will go back to the same treatment which we have done before. [provider 6, MD, hematology/oncology, private practice]
I often re-use whatever regimen I was on. A common scenario is they're on the 4-drug regimen, their scans are really good and I take off the chemotherapy and they're just on Herceptin-pertuzumab or just on Herceptin and if I'm able to get many months out of this, if I start seeing growth of lesions or whatever on a CAT scan, then I just reintroduce that chemotherapy and that way I can just get a year or more out of the same drugs without exhausting my first line of drugs. But if I do, then sometimes I just switch out my chemotherapy without moving on to Kadcyla, so I might switch from taxane to something else, like a Xeloda or a Navelbine or something without changing the Herceptin-Pejeta, especially if it's sort of a small recur, small progression, or not a major progression, just to try to get more mileage out of the medication. [provider 4, MD, hematology/oncology, community]
I think if they've been on treatment for 12 months and they had a good response to the prior option, meaning while they were on that option they tolerated the treatment well, I'll likely give it a shot with that same option again, especially if there's not rip-roaring disease causing a lot of visceral crisis and things like that. [provider 11, MD, oncology, private practice]
The only thing that really matters and the only thing that should matter is how long they relapsed after their last receipt of Herceptin. I believe in the CLEOPATRA trial you could go on if you had relapsed at least after 12 months after your last dose of Herceptin. So if they had adjuvant Herceptin and relapsed more than a year later, I would still give them the CLEOPATRA regimen. [provider 26, MD, hematology/oncology, academic]
Oftentimes we'll give chemo plus either Herceptin and/or pertuzumab. [provider 13, MD, hematology/oncology, community]
I would definitely do trastuzumab, pertuzumab, docetaxel. [provider 25, DO, oncology, community]
T-DM1
So the HER2 that we were using before, we may not—even whether it's 6 months or 1 year—I tried to not use the same drug again. We would like to change to some other lines of conjugate monoclonal antibodies and then again, looking at chemo, what they've got, whether they've got hormonal chemotherapy, what type, and then what type of options we have—but I would've mostly changed the HER2-neu treatment that the patient got the first time and then change it to a different one. [provider 20, MD, oncology, academic]
I would try Kadcyla, maybe—try to see if I can use that then. [provider 2, MD, hematology/oncology, academic]

Figure 9. Therapy selection at recurrence more than 6 months after initial therapy (n = 22).



Practice Gap #5: Challenges in Managing Patients With HER2-Positive MBC and CNS Disease

A majority of clinicians would switch systemic therapy in a patient with brain-only progression, in contrast to the expert recommendation to continue with the same systemic therapy and treat CNS metastases with local therapy. Managing patients with leptomeningeal disease and identifying radiation necrosis after radiation therapy are significant challenges in the management of CNS disease for clinicians in all specialties, including radiation oncology. Most clinicians are imaging symptomatic patients when they present with metastatic disease vs at baseline. Few clinicians, even radiation oncologists, are aware of investigational therapies that have shown activity in patients with CNS metastases after available standard-of-care options.

Standard of Care for Patients With HER2-Positive MBC and CNS Disease

Upwards of 40% to 50% of patients with HER2-positive disease eventually develop CNS metastases during their disease course.[16] Because of this high incidence, it is recommended that clinicians have a low threshold for brain MRI screening if CNS disease is suspected.[23] Patients who do develop brain metastases should receive appropriate local therapy, whether surgery, whole-brain radiotherapy, or stereotactic radiosurgery, and if indicated, systemic therapy. However, patients whose systemic disease is controlled should remain on their current systemic therapy while receiving local therapy for their CNS disease.

Investigational HER2-Targeted Therapies With Promising CNS Activity

With such a high incidence of CNS metastases and because current standard-of-care therapies for HER2-positive MBC are not CNS penetrant, better options for the prevention and treatment of brain metastases are needed in this setting.[16] Due to their small size and improved ability to penetrate through the blood–brain barrier compared with current standard-of-care therapies and other investigational agents, HER2-targeted TKIs are the most promising candidates for this purpose. In fact, both neratinib and tucatinib have demonstrated CNS activity in patients with pretreated HER2-positive MBC. Most recently, neratinib plus capecitabine was shown to reduce time to intervention for CNS metastases vs lapatinib plus capecitabine in the phase III NALA trial (22.8% vs 29.2%, respectively; P = .043), suggesting that neratinib is more effective in the CNS than lapatinib.[17] Tucatinib in combination with capecitabine and trastuzumab showed a promising ORR of 42% (5/12) in patients with measurable brain metastases in a phase I study. In combination with T-DM1, it showed a brain-specific ORR of 36% in patients with measurable disease and a median PFS of 6.7 months among the 30 patients with brain metastases.[5,18]

Baseline Screening for CNS Disease

As per the updated American Society of Clinical Oncology guidelines,[23] most of the clinicians we interviewed, including radiation oncology clinicians, said that patients typically receive an MRI scan when they begin to exhibit symptoms indicative of CNS disease (eg, changes in vision, falls, headaches, coordination changes).

> *I would say most of the time the medical oncologists that are seeing the patient hear about certain complaints—let's say headaches, nausea, neurologic deficit—and then they order an MRI and then, if they find something that's suggestive of metastatic disease, then they get referred to us for palliative radiation.* [provider 21, MD, radiation oncology, community]

A small group (n = 8) of clinicians across practice settings prefer to screen patients at baseline when they present with metastatic disease as part of the typical workup (**Table 9**).

Table 9. Rationale for Baseline CNS Disease Screening
My typical workup would include usually a CAT scan of the chest, abdomen, and pelvis and a bone scan. I, personally, do do a brain MRI on every patient with metastatic HER2 breast cancer. I think the rate is high for brain metastases, and I always get a heart echocardiogram as well on the patient, for cardiac clearance for their therapy. [provider 25, DO, oncology, community]
If they're metastatic, they're scanned from head to toe. PET scan to see how active the tumor is. CAT scan, MRI, not all of them, but one of the other—just scan the brain, a whole-body scan to see where all the tumor has travelled to. [provider 1, APN, oncology, community]
Most of the time I would start with CAT scan chest, abdomen, pelvis, and bone scan. Sometimes when they are found to have some concern from metastatic disease, they may have already come to me with some imaging, CT, and then we may obtain a PET scan and then proceed with the biopsy. If they can tolerate MRI, then I usually prefer the MRI with and without contrast. If they can't tolerate MRI, then I try to do CT of the head with contrast. [provider 8, MD, oncology, private practice]

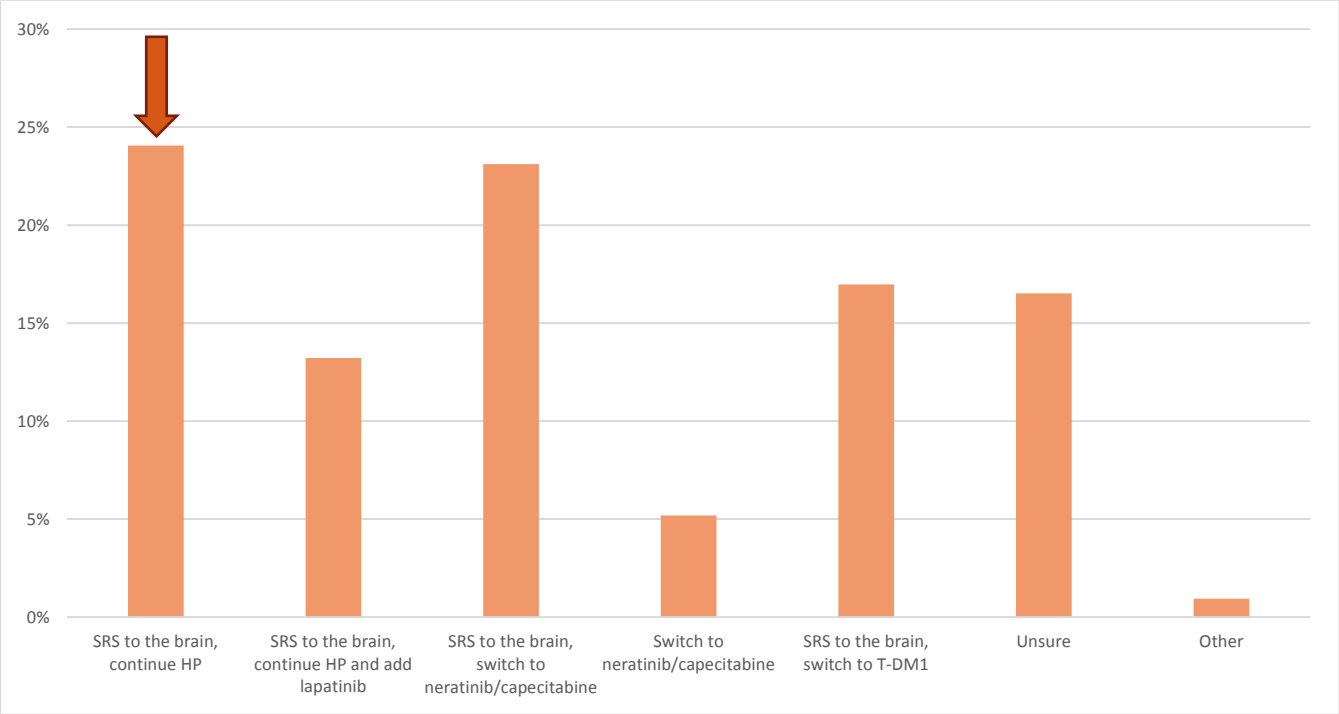
A majority of interviewed clinicians say they monitor patients for CNS disease symptoms and have a low threshold for suspicion of brain metastases ("*at the slightest hint of any concern of CNS disease we'll get an MRI brain*"). Once patients are symptomatic, they liaise with radiation oncology and schedule imaging every 3-6 months throughout the treatment duration.

Case #3: Therapy Selection for Patients With CNS Disease

A 63-year-old woman is treated for hormone receptor–positive, HER2-positive MBC to liver/lungs with THP ⟶ HP. After 18 months, her disease progresses with 3 new lesions in the brain, each approximately 1 cm. There is no evidence of disease outside of the CNS.

Which of the following treatment options would be most appropriate for this patient?

Figure 10. Appropriate therapy selection for patients with CNS progression but stable systemic disease (n = 212).



Experts indicated that local therapy to brain metastases while continuing the current systemic therapy was optimal for this patient with CNS progression but stable systemic disease (**Figure 10**). A majority of survey respondents chose to combine local therapy and a switch of systemic therapy in contrast to the expert recommendation to continue with the same systemic therapy and treat with local therapy. Sara Tolaney, MD, MPH, was "*surprised that so many were switching [systemic] therapy with CNS only progression.*"

The clinicians we interviewed said that they collaborate with radiation oncologists and/or neurosurgeons to manage patients with CNS disease and determine the appropriate primary management modality. Localized radiation, whole brain radiation, and surgery (gamma knife) were the main approaches to primary management described by clinicians across setting and specialty. In line with survey data, interviewed clinicians varied in whether they would continue anti-HER2 therapy, stop systemic therapy, or switch agents during radiation therapy (**Table 10**).

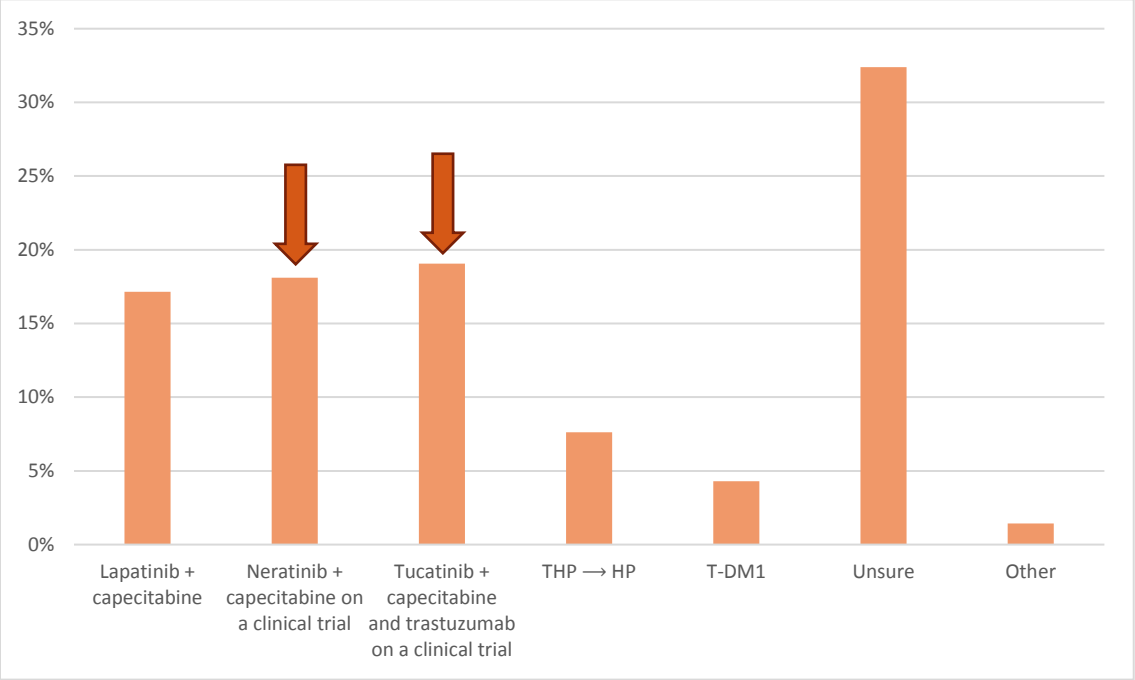
Table 10. Perspectives on Systemic Therapy During Radiation
Continuing Anti-HER2 Therapy
If we can radiate it without causing too much neurotoxicity, I would recommend radiation and then try to continue—if they have systemic disease too, then continue with the treatment. If not, we've also sometimes done Herceptin directed therapy to lepto-meningeal disease. [provider 2, MD, hematology/oncology, academic]
We would just typically treat them, you know, the same way, so the brain mets really wouldn't influence very much what we did. You know, in most cases we still would give the same type of chemotherapy regardless of if they have brain mets or not. [provider 16, MD, oncology, community]
The role of systemic therapies are relatively—systemic therapy for—just for the brain mets, it's not a great option. The reason is all the therapies, they don't go into the brain. So the main treatment is still radiation. [provider 6, MD, hematology/oncology, private practice]
They send the referral to us, we see the patient and I tell them—well, I tell the patient what I recommend and I also send a note to the medical oncologist about what the treatment plan is for the treatment of the brain mets. And then we coordinate as far as whether they're going to continue systemic therapy simultaneously or there might be a break during their treatment. That decision is usually made mostly by medical oncologists, although I don't necessarily discourage continuing systemic therapy, especially HER2 -directed, single -agent therapy during radiation treatment. [provider 21, MD, radiation oncology, community]
Switch Systemic Therapy
Depending on how much disease there is, we follow up with targeted radiation or whole-brain radiation. And then, systemically, I mean, those are the patients that you would like to use a small TKI and that's where neratinib may have more of a benefit, or perhaps using different chemotherapy that I know will cross the blood-brain barrier. [provider 23, MD, oncology, private practice]
So let's say a woman was on Herceptin-Perjeta and they develop brain mets that get treated with resection or radiation or both. Should we switch to Kadcyla, should we think about lapatinib, which we know has brain penetration? I would probably stop the Herceptin and Perjeta. I'm not sure they get into the brain as well as the other 2 drugs. But I have to tell the truth, I would have to review the literature on whether or not continued Herceptin-Perjeta is worthwhile in a person who had resected brain mets. [provider 12, MD, hematology/oncology, private practice]

Case #4: Investigational Therapies With Activity in Patients With CNS Metastases

A 58-year-old woman who was treated for T2N1 ER-negative, PgR-negative, HER2-positive (3+) invasive ductal carcinoma received preoperative TCHP and was found to have residual disease in the breast and lymph node. She subsequently received adjuvant T-DM1 for 14 cycles. Two years later, she presented with right upper quadrant discomfort and was found to have liver and CNS metastases. Biopsy confirmed the liver metastasis was ER negative, PgR negative, and HER2 positive (3+).

Which of the following treatment regimens would be most appropriate for this patient if CNS lesions were treated with local therapy as appropriate?

Figure 11. Clinician awareness of investigational therapies in patients with CNS disease (n = 210).



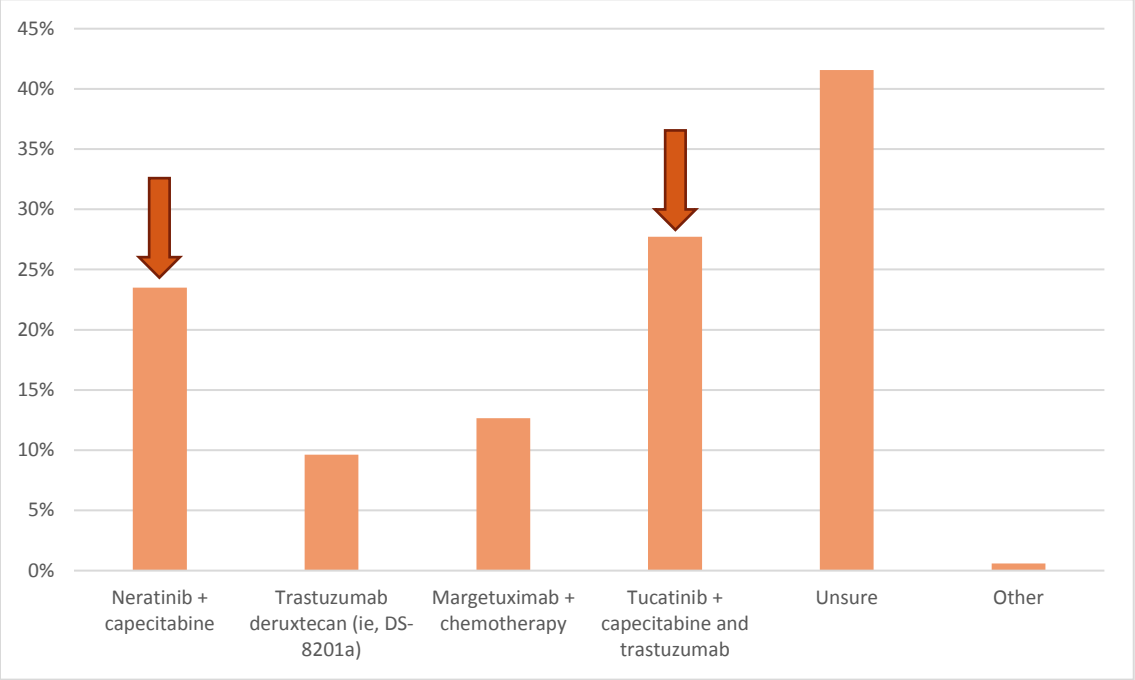
Experts indicated that enrolling this patient on a clinical trial evaluating 1 of 2 investigational HER2-targeted TKIs (neratinib or tucatinib) would be the optimal next step in the management of this patient with HER2-positive MBC and CNS metastases who received THCP and T-DM1 for early disease (**Figure 11, indicated by arrows**). A majority of survey respondents were unsure what treatment approach would be best for this patient or chose approaches that were not recommended by the experts.

Systemic Therapy in CNS Disease

To gain an understanding of the degree to which clinicians are aware of CNS-active agents under investigation for the treatment of pre-treated HER2-positive MBC, we asked survey respondents the following question.

Which of the following agents has/have shown preliminary antitumor activity in the CNS for patients with progressive HER2-positive MBC and mildly symptomatic brain metastases after previous treatment with trastuzumab, pertuzumab, and T-DM1 (select all that apply)?

Figure 12. Clinician awareness of regimens with activity in patients with progressive HER2-positive MBC and CNS disease (n = 166).



Consistent with survey responses to Case #4, only approximately 25% of respondents were aware that neratinib plus capecitabine and tucatinib plus capecitabine and trastuzumab have shown activity in patients with new CNS metastases after 2 previous lines of HER2-targeted therapy (**Figure 12, indicated by arrows**).

Breast cancer expert Sara A. Hurvitz, MD, FACP, was "*struck by the lack of consensus (and general confusion) about how to treat patients with CNS disease, [including] the lack of knowledge regarding new agents,*" a sentiment echoed by Sara Tolaney, MD, MPH.

Most Challenging Aspects of Managing Patients With CNS Disease

Survey respondents ranked the most to least challenging aspects in their care of patients with HER2-positive MBC and CNS metastases, with management of leptomeningeal disease followed by identifying radiation necrosis emerging as the most challenging (**Table 11**).

Table 11. Management Challenges in Patients With CNS Disease (n = 193)

Management Challenges, %	Most Difficult	⟷		Least Difficult
Managing patients with leptomeningeal disease	41.62	15.14	27.03	16.22
Identifying radiation necrosis following radiation therapy	13.90	34.76	31.55	19.79
Choosing between SRS vs WBRT	21.08	25.95	20.54	32.43
Choosing between surgical resection and SRS vs both for oligometastatic lesions	23.81	24.87	20.11	31.22

Interviewees expanded on this suite of challenges to include cognitive decline, steroid management, quality of life, trigger for discussing palliative care/life expectancy, speech and mobility impairment, symptoms (eg, headaches, dizziness, weakness, fatigue), behavioral changes (eg, depression), localized pain (eg, from gamma knife pain), lack of therapeutic efficacy, and social and functional issues (eg, loss of income, ability to work, insurance) (**Table 12**).

Table 12. Challenges Associated With CNS Disease

Clinical Challenges
Poor survival, worsening quality of life, quickly, short survival and so on. [provider 14, MD, hematology/oncology, community]
We have to put them on steroids so they're already in a weakened state from their systemic therapy. So the steroid, the addition of the steroid is a little bit challenging to manage, especially if they have side effects from their systemic therapy, which is usually diarrhea and fatigue. [provider 17, APN, radiation oncology, academic]
Controlling the disease is hard. I mean, we are talking now as like it is so easy, but many times this is a major problem and controlling the disease is a problem. You may give radiation, you may get control of a few months and then, 3 or 4 months later, it's progressing again. [provider 7, MD, hematology/oncology, private practice]
Functional Challenges
When brain mets are present, there's an overall level of progression that, you know, you start to see in the patient and they're not quite prepared for that, going from being completely mobile and independent, and some patients have a lot of weakness and dizziness and problems with vision. [provider 15, APN, hematology/oncology, community]

Most of them, it affects their ability to work. So they have a loss of income, sometimes a loss of insurance. It's really not so much symptom management; it's more functionality and being able to carry on regular activities with daily living. And being able to provide for themselves or their families. [provider 22, APN, radiation oncology, community]

Necrosis

Unfortunately, we don't have a very good way to tell whether it is necrosis or progression of disease. So there's some special MRI sequences we can do, but the results and now from even according to the literature, it's not really satisfying, a lot of time you still just don't know. So, in those situations, you either follow the patients and do another scan, because if it's necrosis eventually they become silent. If it's a tumor, it's going to continue to progress. [provider 18, MD, radiation oncology, community]

We see isolated brain mets more in HER2-positive patients who have received HER2-directed therapy as the first sign of relapse compared with HER2-negative patients…which is a shame because if you see an isolated relapse years after initial treatment, then it raises the issue of whether treatment directed towards the CNS with CNS-penetrating capabilities would be beneficial and, unfortunately, we don't have that yet. [provider 21, MD, radiation oncology, community]

Radiation Oncology Perspectives

The radiation oncologists (n = 2, both community) we interviewed viewed radiation as important palliative treatment in the metastatic setting, but also noted recent data suggesting a survival benefit of radiation in patients with oligometastases. Said one radiation oncologist: *I don't think that has been applied in routine daily practice, but I think that's something coming on the horizon*. [provider 18, MD, radiation oncology, community]

These clinicians held different perspectives on the role of and lesion cut-offs for stereotactic radiosurgery (SRS) vs whole-brain radiation. One noted that while whole-brain radiation has applicability in the context of very widespread metastases, the trend is to avoid whole-brain radiation therapy because of adverse events. She felt that SRS is becoming more routine for up to as many as 10 lesions on the basis of single institution studies. However, a radiation oncology APN pointed out that payer concerns pose barriers to SRS.

> *Insurance is a different issue and with a lot of them I'm very frustrated. You know, they have certain guidelines. Like, for example, some insurance companies say, "Okay, 3 brain metastases you can do radiosurgery, 4 you can't," and I can't and I hate to be forced into giving whole-brain to a patient when I know there are better options available.* [provider 17, APN, radiation oncology, academic]

Another radiation oncologist felt that the safety and efficacy of radiosurgery has only been proven in patients with up to 4 lesions.

> *We don't have randomized data that radiosurgery is as safe as whole brain. We've done patients with radiosurgery with more extensive disease, but usually, you know, we sort of cap it around 10 at the most. Anybody with less than 4, I strongly recommend radiosurgery to preserve their cognitive function, since there's no benefit to whole brain as far as survival, although there's benefit to whole brain in terms of control of their disease elsewhere in their brain, not in the radiosurgery-treated location.* [provider 21, MD, radiation oncology, community]

Both radiation oncologists typically recommended stopping chemotherapy during whole-brain radiation.

> *Normally, I don't have any restriction or I don't change their medication they are taking. Maybe sometimes I'll put them—I'll see if we're adding a medication, just to control the edema if they have symptoms of intracranial pressure, but otherwise I don't change their medication. I don't like to do whole-brain radiation concurrent with chemotherapy, so sometimes, if it's okay with the medical oncologist, they will stop the chemotherapy during the course of radiation therapy.* [provider 18, MD, radiation oncology, community]

> *I don't think that being on HER2-directed therapy is a contraindication to getting radiation, so I don't encourage stopping that treatment. However, if they're on Herceptin coupled with a systemic agent, then I usually would recommend withholding the systemic agent other than Herceptin or whatever the HER2-directed therapy may be. So most of the time they continue the HER2-directed therapy, but stop the chemotherapy.* [provider 21, MD, radiation oncology, community]

These community clinicians collaborated with their medical oncology colleagues via tumor boards and telephone. They were aware that their oncology colleagues were using T-DM1 through tumor board discussions and had a general perception that oncologists in their practice are early adopters ("they adapt very quickly").

> *Our medical oncologists have just started using it, so we've just started seeing that. I don't have a lot of experience, because those patients are new on that treatment…I'm kind of aware of the data because I went to a meeting and they presented data, it seems very promising.* [provider 18, MD, radiation oncology, community]

However, radiation oncology clinicians were unsure if their oncology colleagues were using novel investigational agents outside clinical trial participation (a typical response was "*My guess? I think they do*.")

Practice Gap #6: Challenges in Selecting Optimal Therapy for Patients With HER2-Positive MBC and Disease Progression Following Treatment With Current Standard of Care Therapies

Clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1 for HER2-positive MBC and are unfamiliar with investigational agents/regimens that have shown clinical activity in heavily pretreated patients.

Lack of a Standard of Care in the Third-line Setting for HER-2 Positive MBC

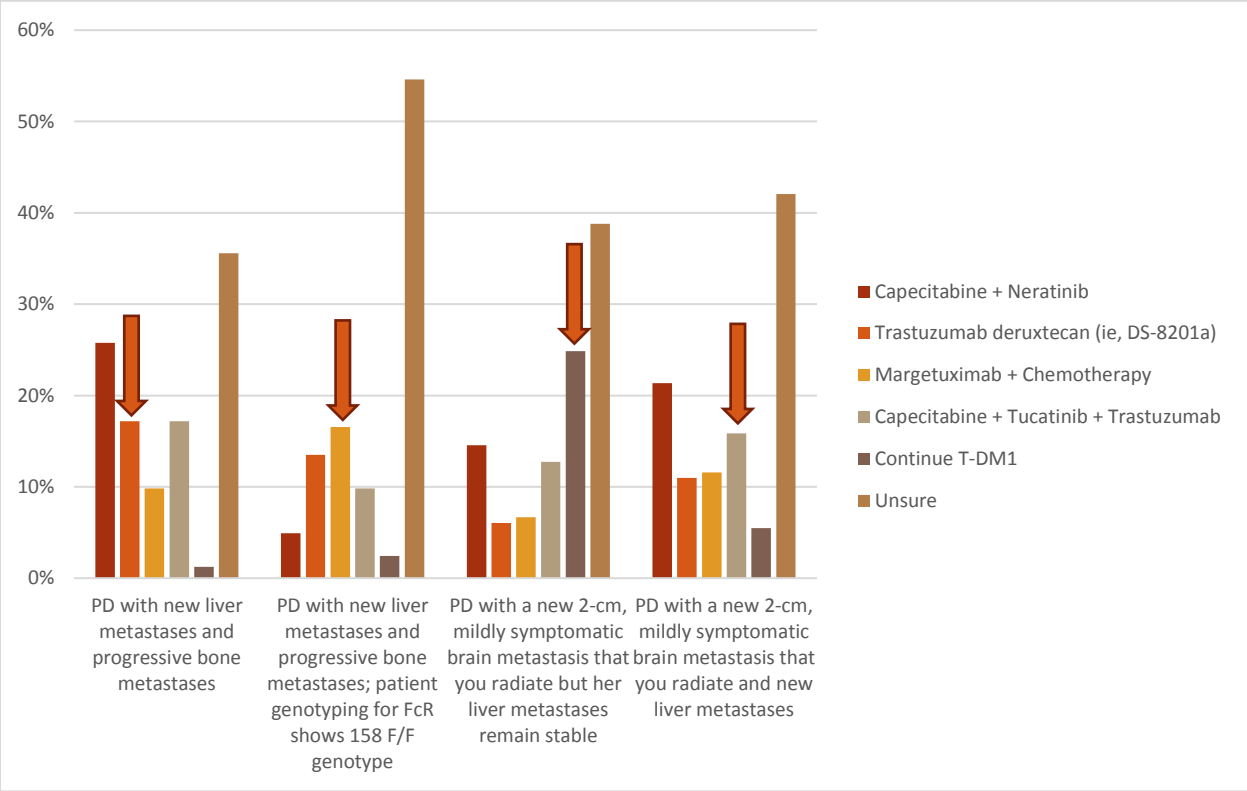
Despite strong standard-of-care options for the first- and second-line treatment of HER2-positive MBC, there is currently no standard-of-care therapy for the treatment of HER2-positive MBC after trastuzumab, pertuzumab, and T-DM1.[16] As introduced above, several novel HER2-targeted agents are under active investigation to fill this unmet need as well as to find better options for the prevention and treatment of CNS metastases. The HER2-targeted TKIs tucatinib and neratinib both have shown efficacy in patients who had received at least 2 regimens targeting HER2 and against CNS disease.[5,17,18] Furthermore, the HER2-targeted antibody margetuximab plus chemotherapy demonstrated a small but significant improvement vs trastuzumab plus chemotherapy in the phase III SOPHIA trial (5.8 vs 4.9 months; HR: 0.76; *P* = .033), with patients carrying a FCγRIII CD16A-F allele appearing to experience the greatest benefit.[24] There are also several improved HER2-targeted antibody–drug conjugates in clinical development. As mentioned above, trastuzumab deruxtecan (DS-8201), the closest new anti-HER2 antibody–drug conjugate to the clinic, showed an ORR of 54.5% in patients with HER2-positive MBC who were pretreated with T-DM1, as well as trastuzumab and pertuzumab in the majority of patients, with median duration of response and PFS not yet being reached.[6] Trastuzumab deruxtecan is being evaluated in phase III trials.[25.26]

Case #5: Choice of Therapy After 2 Previous Lines of HER2-Targeted Therapy

A 59-year-old woman with ER-negative, HER2-positive BC and metastases to her bones received first-line THP, and then developed progressive disease in her liver for which she received second-line T-DM1 for 8 months until again experiencing progressive disease.

Given the known limited activity of currently available regimens in the third-line setting, please indicate your top preferred choice of third-line therapy for each of the following clinical scenarios for this patient whose disease progressed while receiving T-DM1, assuming that all of the listed agents are available.

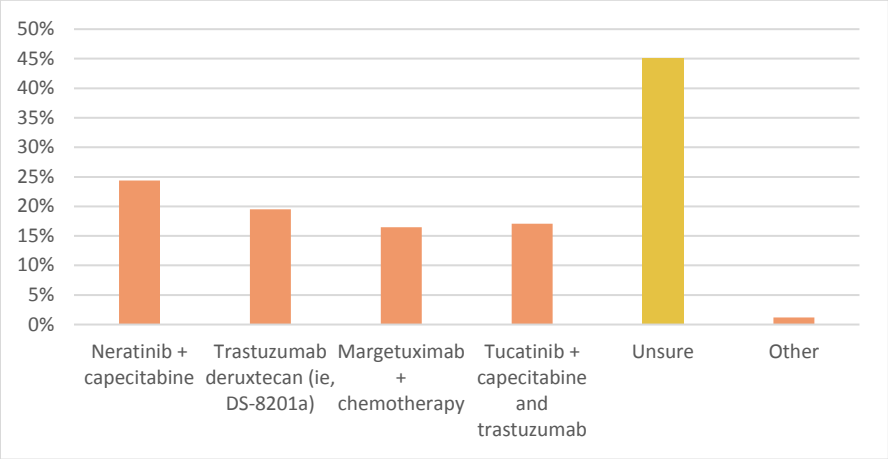
Figure 13. Preferred choice of third-line therapy in select patient scenarios of disease progression on T-DM1 (n = 165).



Arrows indicate reasonable options as defined by clinical experts (**Figure 13**). Surveyed clinicians are challenged to identify optimal third-line therapy following progression after THP and T-DM1.

Furthermore, surveyed clinicians were asked to select all of the investigational regimens that have demonstrated activity in the setting of progression after THP and T-DM1 (**Figure 14**).

Figure 14. Awareness of investigational agents in patients who received 2 or more previous lines of anti-HER2 therapy for MBC (n = 164).



Consistent with survey responses to Case #5, surveyed clinicians were unaware that there is evidence of clinical activity in heavily pretreated patients for ALL 4 of the investigational agents/regimens listed.

Contextualizing Therapy at Progression

Interviewed clinicians defined progression in the following ways:

- Unable to achieve median PFS
- Not responding to 2-3 cycles of treatment
- Symptomatic or radiographic progression as per RECIST criteria
- Changes in tumor markers.

Many of these clinicians were using T-DM1 as second-line therapy, but therapy beyond this setting was much more complex to ascertain. A small group said they were using novel or investigational agents at this point in therapy. **Table 13** illustrates the perspectives of clinicians concerning therapy at progression after multiple HER2-targeted therapies.

Table 13. Perspectives on Optimal Third-line Therapy

Chemotherapy and HER2 Blockade
In HER2-positive breast cancer, it's quite often that they can go for a third- and fourth-line treatment if they have a good performance status, or even if their performance status is not that good. I mean, apart from various comorbidities or age-related or factors that you cannot change with treatment, mostly all the patients go for a third-line treatment option, and particularly with an anti-HER2 therapy, either chemotherapy or an oral chemo-free option, just to ensure more quality of life. [provider 5, MD, oncology, academic]

If they have received hormonal therapy along with HER2-directed therapy, then they will switch to chemotherapy. If they already received one sort of chemo, I will switch to a different kind of chemotherapy. [provider 6, MD, hematology/oncology, private practice]
The best sequence. Let me think about that. So I think a lot of times that past chemo plus HER2-targeted agents in the first-line, past T-DM1. I think at that point a lot of it just becomes discussion of kind of toxicity and which chemo regimens they would or wouldn't want to have based on side effects plus Herceptin, really, essentially. [provider 13, MD, hematology/oncology, community]
If I have a sort of algorithm it's primarily going to be Perjeta-based treatment first, followed by T-DM1–type treatment second, followed by something like lapatinib third, and then probably a variety of Herceptin/chemo combos in fourth and fifth and so on afterwards. [provider 11, MD, oncology, private practice]
Novel/Investigational Agents
Targeted therapies, like Tykerb or—I don't know that there's a lot of targeted therapies approved for HER2, other than the Herceptin and Kadcyla. We've given pertuzumab to them in the adjuvant setting, so we're not reintroducing that. So, Kadcyla and then we do capecitabine, they're a load of Tykerb and look for trials. I mean we usually have trials available for those type of patients and that's why we have a fairly good number of ladies on trials. [provider 19, NP, oncology, private practice]
Depending on what they have been on, I usually try to use—yes, I still consider to use Perjeta and Herceptin in first line if I can, depending on what they've had before, if anything, and then follow up with Kadcyla as second line. And that's when I've tried to send patients for clinical trial for some of the other drugs that are being developed. [provider 23, MD, oncology, private practice]
If the patient progresses, then Kadcyla followed by either neratinib or lapatinib-containing therapy, so lapatinib plus capecitabine or neratinib plus capecitabine, depending on what we feel is the best tolerable regimen, as well as with metastasis neratinib may be favored in that situation. [provider 14, MD, hematology/oncology, community]
We still go with anti–T-DM1, we go to anti–T-DM1. If, again, if we don't see a quick response, we quickly go to the TKI therapy. And in this case we have now 2, actually. We have neratinib for adjuvant therapy, but actually, neratinib is a drug. I was a PI on first-line metastatic disease with neratinib over 10 years ago, but that study never showed life so the drug never got approved for the metastatic setting. And, finally, they found a way to approve it in the so-called "extended adjuvant" therapy, but now we start so see some more data in the metastatic setting, so there is no doubt it's a more potent drug than Tykerb, but it's also potentially more toxic to the GI tract. [provider 7, MD, hematology/oncology, private practice]
[We] go through the Herceptin, Perjeta, taxane, T-DM1…there certainly are third-line options. I mean, the most common third-line option is lapatinib/Xeloda. The NALA trial was just presented at ASCO 2019 and that compared neratinib/Xeloda with lapatinib/Xeloda. The results for neratinib/Xeloda were a little bit better, including a little bit better intracranial efficacy, so in terms of brain metastases, but neratinib/Xeloda is extremely hard to tolerate in terms of diarrhea. I have not had very much success with that regimen. [provider 26, MD, hematology/oncology, academic]

Practice Gap #7: Challenges in Treating Patients With Low HER2 Expression

There was broad consensus among interviewed clinicians that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies and low awareness that there are emerging therapeutic options for patients with low HER2 expression.

Treatment Selection in Patients with MBC and Low HER2 Expression

The results of the phase III NSABP B-47 trial demonstrated that patients with "HER2-low" early BC, defined as IHC1+/2+/ISH-, did not benefit from adjuvant trastuzumab and therefore should be treated as if they are HER2-negative.[20] Fortunately, new investigational HER2-targeted antibody–drug conjugates are showing promising efficacy in this patient population.[16] Trastuzumab deruxtecan (DS-8201) achieved an ORR of 50% (17/34) in patients with MBC and low HER2 expression in a phase I study.[6] Trastuzumab duocarmazine (SYD985) has also shown activity in this setting, achieving an ORR of 27% in hormone receptor–positive, HER2-low MBC and an ORR of 40% in hormone receptor–negative, HER2-low MBC.[21,22]

Clinician Rationale for Therapy Selection in Patients With MBC and Low HER2 Expression

Although many of the clinicians we interviewed noted that the best way to determine HER2 status remains an evolving question for research vs a practical concern in clinical settings, there was broad consensus that they would not treat patients with low or indeterminate HER2 expression with anti-HER2 therapies.

> *You hit the mark or you don't. If you don't hit the mark you're not HER2 positive.* [provider 24, MD, oncology, academic]

> *This was studied extensively in an NSABP trial and it was totally negative. There is no value of anti-HER2 in these patients.* [provider 7, MD, hematology/oncology, private practice]

Medical oncologists noted cytotoxic chemotherapy without HER2-directed therapy as the most common management approach and were aware of emerging therapies that might be appropriate for patients with low expression (only 1 clinician referred explicitly to trastuzumab deruxtecan). A few private practice and community-based oncologists reported that they would, in some equivocal cases, consider continuation of HER2-blockade in the metastatic setting.

> *We bring this up at tumor board all the time.* ***The guidelines would say don't treat. If you're asking me what I do, I sometimes will offer them just Herceptin****. I'll give them Herceptin and docetaxel, as an example. I have definitely seen some weak—some lower positive —I've seen responses subjectively, and I think there is some data. It's not huge data, but there are some data points to support some patients benefit. My rationale is Herceptin has very low toxicity, so I would offer it to the patient and watch their heart test every 3 months.* [provider 25, DO, oncology, community]

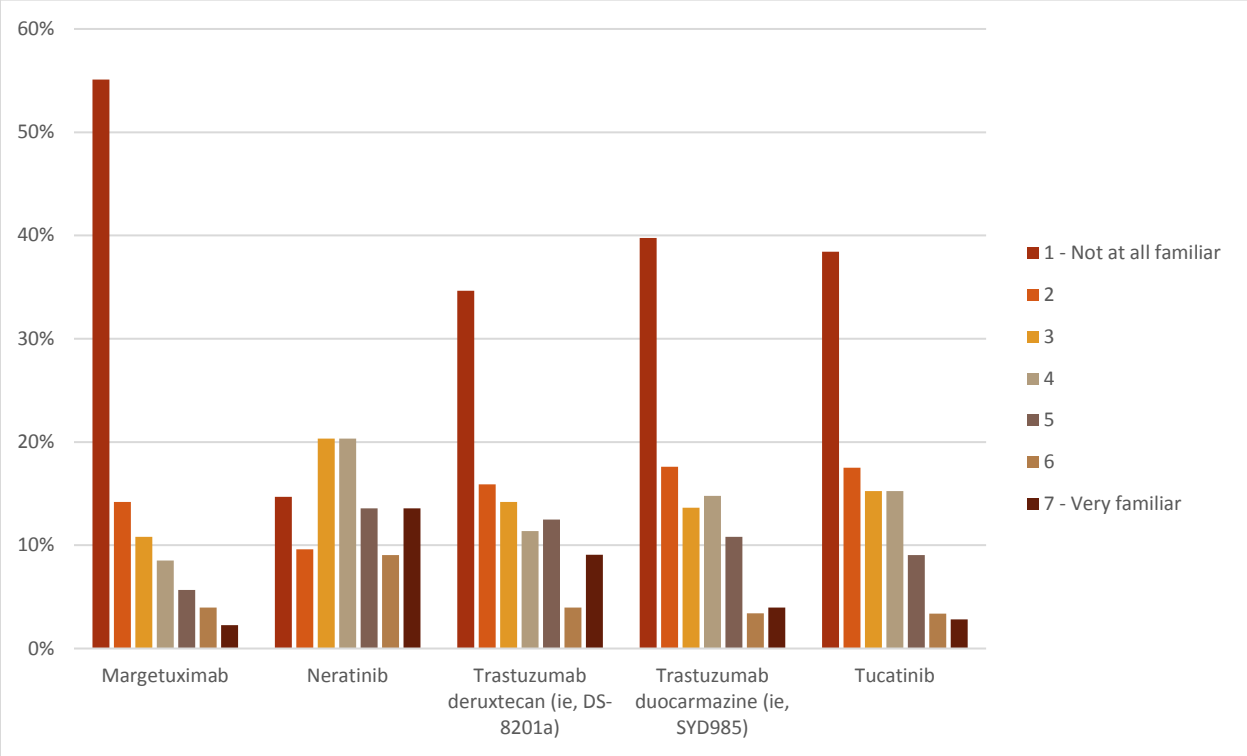
APNs were generally unaware of how low expression is treated in their practice setting.

Practice Gap #8: Deficits in Familiarity With Novel Agents

Clinicians are largely unfamiliar with novel agents being developed for the treatment of HER2-positive MBC or their associated toxicity profiles, and in interviews, their mechanisms of action. A majority consider only FDA approval based on phase III clinical data as sufficient evidence to incorporate a new agent or regimen into their practice for patients with HER2-positive MBC.

Survey data show that most clinicians are unfamiliar with several investigational agents currently being evaluated for HER2-positive MBC in ongoing randomized phase II and III trials (**Figure 15**). The highest level of familiarity among clinicians was with neratinib, which is currently approved by the FDA as extended adjuvant therapy for patients with HER2-positive early-stage BC.[27]

Figure 15. Awareness of investigational therapies in randomized phase II/III trials (n = 177).



Furthermore, only 30% of survey respondents (n = 156) were able to identify tucatinib as a more selective HER2 TKI compared with lapatinib and neratinib, both of which are currently approved for different indications in patients with HER2-positive BC.

This trend of unfamiliarity with investigational agents was mirrored among interviewed clinicians as illustrated by **Table 14**. Although approximately one third of interviewees mentioned being aware of either investigational HER2-targeted TKIs or antibody–drug conjugates, few were able to identify specific drugs in these classes or describe their mechanisms of action. Clinicians most frequently referred to neratinib. Notably, clinicians who referred to specific drugs by name were involved in clinical trials.

Both Sara Tolaney, MD, MPH, and Sara A. Hurvitz, MD, FACP, were surprised by how many clinicians were unfamiliar with the new drugs and their mechanisms of action, with Sara A. Hurvitz, MD, FACP, remarking, "*Being in the field, I thought that everyone had heard about these agents…but the general lack of knowledge…certainly supports the need for CME programs*" on this topic.

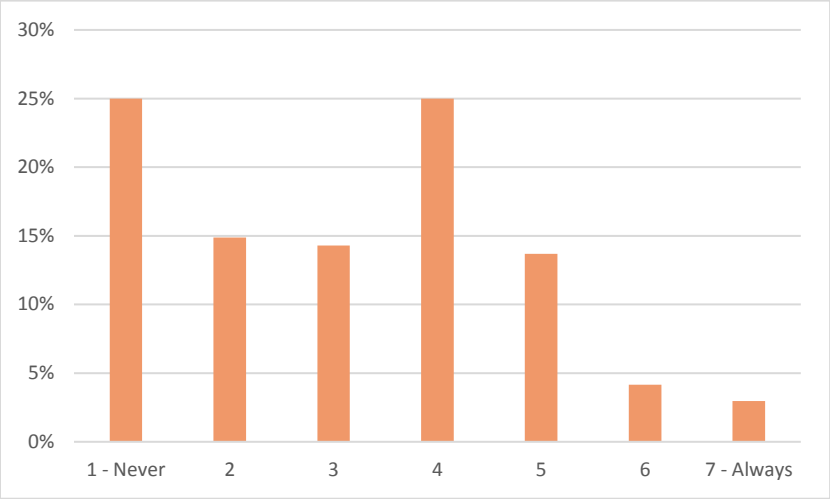
Table 14. Clinician Identification of Novel/Investigational Agents

Antibody–Drug Conjugates
There's another one that's coming down the pike, it's a Seattle Genetics product. I don't remember it right off the bat. [provider 14, MD, hematology/oncology, community]
Off the top of my head, I would just say the TULIP trial. [provider 2, MD, hematology/oncology, academic]
I mentioned trastuzumab diotoxin-something—I forgot its full name. Again, it looks very compelling data, the one I saw, and it's already moved to phase III trial. [provider 7, MD, hematology/oncology, private practice]
I'd say—somewhat. There's some exciting novel agents coming down the pipeline which I've sort of heard about with regards to specific antibodies targeting HER2. You know, the 8201 really is the one that I've heard the most about. What's stuck out in my mind is just the fact that they're targeting HER2-low disease as well. [provider 13, MD, hematology/oncology, community]
TKIs
I'm sure I've heard the spiel but…[provider 19, NP, oncology, private practice]
I think that there are TKIs, which are obviously affecting downstream signaling, but I wouldn't know much beyond that. [provider 11, MD, oncology, private practice]
The ones that target HER2. So, give me an example. Nothing immediately comes to mind. [provider 12, MD, hematology/oncology, private practice]

Scenarios Under Which Clinicians Will Use New Agents

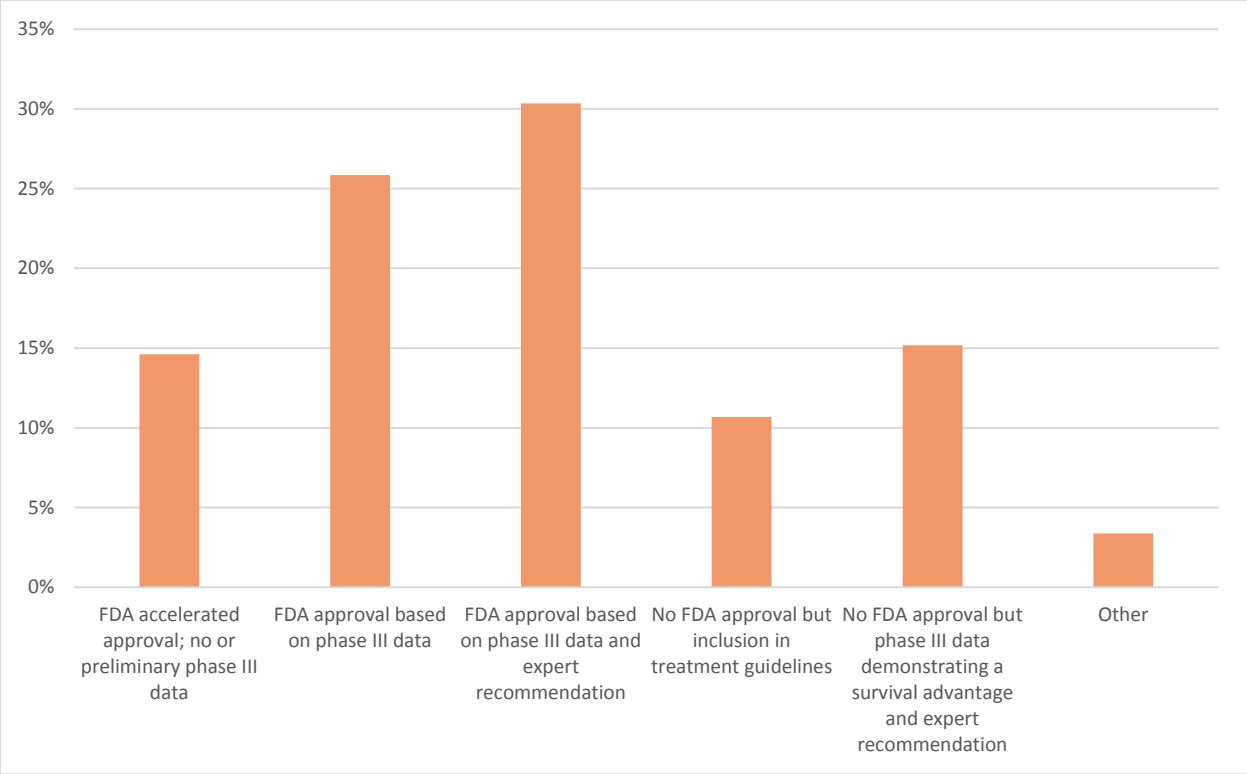
Over one half of surveyed clinicians are unlikely to use newly approved or investigational therapies if they are not familiar with how the agents work (**Figure 16**). Given the lack of familiarity of clinicians with the agents under development for HER2-positive MBC noted earlier (ie, neratinib, tucatinib, margetuximab, trastuzumab deruxtecan, and trastuzumab duocarmazine), it is unlikely that they would consider these agents as options for their patients on a trial or when they become available in the clinic.

Figure 16. Likelihood of using new agents if unfamiliar with drug class or mechanism of action (n = 168).



More than one half of survey respondents (55%; n = 130 respondents) indicated that they consider FDA approval based on phase III evidence sufficient evidence to incorporate a new agent or regimen into their practice for patients with HER2-positive MBC (**Figure 17**).

Figure 17. Preferred level of evidence for using new agents (n = 178).



The clinicians we interviewed provide additional context to the trends observed in the survey. A majority across setting and specialty noted they would use novel agents if accompanied by phase III clinical data, and the rest said they would when approved by the FDA and when other treatment options were exhausted (**Table 15**). One interviewed clinician, who described himself/herself as an "*early adopter,*" said that they would use investigational agents in practice following treatment with T-DM1, or following third-line treatment.

Table 15. Rationale for Using New Agents

FDA Approved
In terms of using new drugs that are approved, I feel very comfortable doing that based on both safety and efficacy data. [provider 26, MD, hematology/oncology, academic]
Once they're FDA approved, usually, that's when we integrate them into our treatment pathways. [provider 16, MD, oncology, community]
Phase III Clinical Data
Phase III trials are preferred where you are getting, you know, the investigational agent vs the standard of care. [provider 2, MD, hematology, academic]
I think the best is phase III clinical trials. But sometimes we can start looking at the phase II and the mature data again of phase III. [provider 6, MD, hematology/oncology, private practice]
They do if there is strong data over—let's say—Herceptin's been around for a while and if there's data suggesting that the treatment is superior or—either instead of or in combination, particularly when it comes to survival, OS, and then possibly as a second or third line of treatment if the first line fails. [provider 21, MD, radiation oncology, community]
Other Treatment Exhausted
At the tail end, either if they are just cycling too fast through their therapies or they are just not responding to therapy when biomarker wise and analyzing off-path, they really should be responding but they're not, then I feel like maybe they just need different drugs that we don't have as part of standard regimen. [provider 4, MD, hematology/oncology, community]
I would say any patient who has disease progression beyond the—I would say the top 3. So you always get concerned about the HER2-positive patient that should have had a durable response who's seen pertuzumab, who has seen T-DM1. Yeah, those are the patients that you kind of need to think a little bit out of the box. [provider 24, MD, oncology, academic]
Investigational
Very, very likely. I'm very excited about that. The question—so, I'm an early adopter, so if there's an opportunity, as I mentioned. So then the next question you might ask is: where if I might use and so on. And so then my answer would be post Kadcyla, before even neratinib or lapatinib, based on what I feel, what I perceive is the better efficacy and the better tolerability. So, basically, Herceptin, Perjeta chemotherapy, hormones, whatever the case may be, followed by Kadcyla, followed by novel agent. [provider 14, MD, hematology/oncology, community]

Identification of Adverse Events Associated With HER2-Targeted Agents

Many surveyed clinicians were not able to identify the most concerning adverse events associated with various agents used in the treatment of patients with HER2-positive MBC as well as agents under investigation in this setting (**Table 16, most concerning adverse events for each agent highlighted in gold**). This was particularly evident among agents that have no currently FDA-approved indications (ie, trastuzumab deruxtecan, margetuximab, and tucatinib). According to clinical experts, a lack of knowledge about an agent's toxicities and their management can be another barrier to uptake of new agents.

Table 16. Identification of Concerning Adverse Events Associated With Agents Used in HER2-Positive MBC (n = 154)

Adverse Events, %	Pertuzumab	T-DM1	Neratinib	Trastuzumab deruxtecan (DS-8201a)	Margetuximab	Tucatinib
Diarrhea	49.35	9.74	49.35	9.74	9.74	19.43
Infusion-related reaction	25.90 (rare)	15.83	6.47	22.30	33.09	4.32
Interstitial lung disease	11.11	14.81	14.81	16.30	11.11	6.67
Increased AST/ALT	10.22	35.04	18.25	10.95	8.76	12.41
Neuropathy	11.19	29.85	8.21	12.69	8.96	8.96
Thrombocytopenia	7.14	35.00	13.57	12.14	10.71	11.43
General myelosuppression	12.14	28.57	17.14	20.00	14.29	12.14

Practice Gap #9: Inconsistencies in Defining Quality of Life and Palliative Care

Although quality of life factors into discussions about goal and expectation setting, there is little consensus among clinicians about how best to define quality of life. Similarly, clinicians view palliative care as an important component of addressing quality of life but vary in how they define palliative care and when they initiate discussions about palliative care with their patients.

Quality of Life

Clinicians identified several factors as being linked to quality of life, including disease control, toxicities, and pain. Clinicians factored quality of life into discussions about goal and expectation setting but varied in how they defined quality of life (**Table 17**).

Table 17. Defining Quality of Life

Quality of life is something that is not obvious from the data*. Not all studies have looked at quality of life, so I would say we would kind of summarize that the most important quality-of-life determinant is (a) is the disease able to be controlled and (b) [what is] the type of toxicity one would expect from the treatment? So if we are diligent and appropriately following and managing the side effects then, hopefully, we can maintain quality of life and minimize the deterioration and if we control the disease, we will also maintain the quality of life. That is what is expected, but in terms of numerical and statistical results, we don't always have that.* [provider 14, MD, hematology/oncology, community]
It's whatever the patient defines it as and that changes along their disease trajectory*. We see it change. Something that's unacceptable in their mind at maybe the time of initial diagnosis becomes acceptable when they are faced with maybe stopping treatment and going on to kind of a hospice-type situation. So we have to constantly re-evaluate that.* [provider 17, APN, radiation oncology, academic]
A lot of docs get patients really fixated on bloodwork and markers and this and that and my approach is different from that. I'm very patient centered, so it's like, "How are you feeling?" and "How is this disease affecting your activities of daily living?" and that's what I measure. [provider 23, MD, oncology, private practice]

APNs and NPs were more likely to view quality of life as less of a fixed entity and more as a consideration that changes as patients move through treatment options. APNs and NPs also described quality of life as something they would be more likely to explicitly discuss with patients than would oncologists or other specialists.

Palliative Care

Clinicians viewed palliative care as an important component of addressing quality of life but varied in how they defined this concept. Clinicians seemed split on defining palliative care as equivalent to supportive care or defining it as end-of-life planning (**Table 18**). Others distinguished symptom management in early treatment from end-of-life planning, but referred to both as palliative care. As one PA put it:

> *It's really interesting you bring that up, because I was just at ASCO and they were talking about the difference between palliative and supportive care and that* ***they're using them interchangeably when they're really not****.* [provider 9, APN, oncology, academic]

Clinicians also differed in their timing of discussing palliative care with their patients. Broadly, discussions about palliative care occurred either at the initial treatment planning visit or later in the disease/treatment trajectory as therapy failed. The timing of palliative care discussion likely hinges on how clinicians define palliative care. Clinicians who viewed palliative care as symptom management and/or supportive care throughout the treatment trajectory were more likely to introduce palliative care into early discussions with patients and to view it as integral to oncology care. Clinicians who viewed palliative care as end-of-life planning were more likely to initiate a discussion about palliative care after multiple lines of treatment (**Table 18**).

Table 18. Definitions for Palliative Care
Palliative Care as Symptom Management
*What I usually do in patients regardless of the breast cancer or the type of cancer, when you are dealing with advanced cancer, whether the patient is symptomatic or asymptomatic**, I usually encourage and make sure that they are seen and been plugged in with a palliative care specialist**, not only about symptom management but also managing the expectation, managing anxiety, and all of the other things that come with the cancer diagnosis.* [provider 14, MD, hematology/oncology, community]
*We actually frame it from the standpoint of that **it's an extra layer of support**. That it does not mean hospice. We are pretty upfront with that, that it's another team member or members to manage their symptoms, to optimize their quality of life basically.* [provider 17, APN, radiation oncology, academic]
***We talk about palliative care at the very beginning of the stage IV disease discussion**. In fact, we refer newly diagnosed stage IV patients to our palliative care to fine-tune any of the kind of symptomatic treatments that they're already on. We've learned that early use of palliative care, both medicinal as well as psychosocial support, makes patients live longer and live better, so that's a standard of care in our cancer center.* [provider 12, MD, hematology/oncology, private practice]
Palliative Care as End-of-Life Planning
***End of life planning is during later end of cancer journey**, not from the beginning because a lot of patients, they don't want to hear from the start but they are willing to listen at the later point of their treatment journey.* [provider 6, MD, hematology/oncology, private practice]
***We talk about if they're getting towards the end of what we can offer them medically**—like, if they've had multiple lines of therapy and they continue to progress, then we typically say, "Well, this is like a third-line therapy and the results from this might not be so good, so it's also an option to not do the therapy, just do best supportive care, palliative care, where we're just trying to minimize symptoms related to cancer, but we're not actively treating it with anything." So we kind of usually introduce that when we think we're getting towards someone who has less than 6 months to a year to live, we start talking about those types of things*. [provider 16, MD, oncology, community]
*It depends on the situation. If I have an elderly patient coming in a wheelchair, of course we'll talk about end of life from day 1, but when I'm talking to a young patient—and we have a lot of people in their 40s and 50s—and here **we're telling them the survival median is 5 years, you can go 10 years, especially if they have limited metastatic disease, they are not going to be interested in hearing this at all.*** [provider 7, MD, hematology/oncology, private practice]

Main Clinical Challenges in the Optimal Treatment of HER2-Positive MBC

The top 3 clinical challenges that interview participants identified as barriers to optimal treatment and patient management were disease progression, symptom management, and CNS disease (Figure 18).

Figure 18. Frequency of reported clinical challenges in interviews (n = 26).

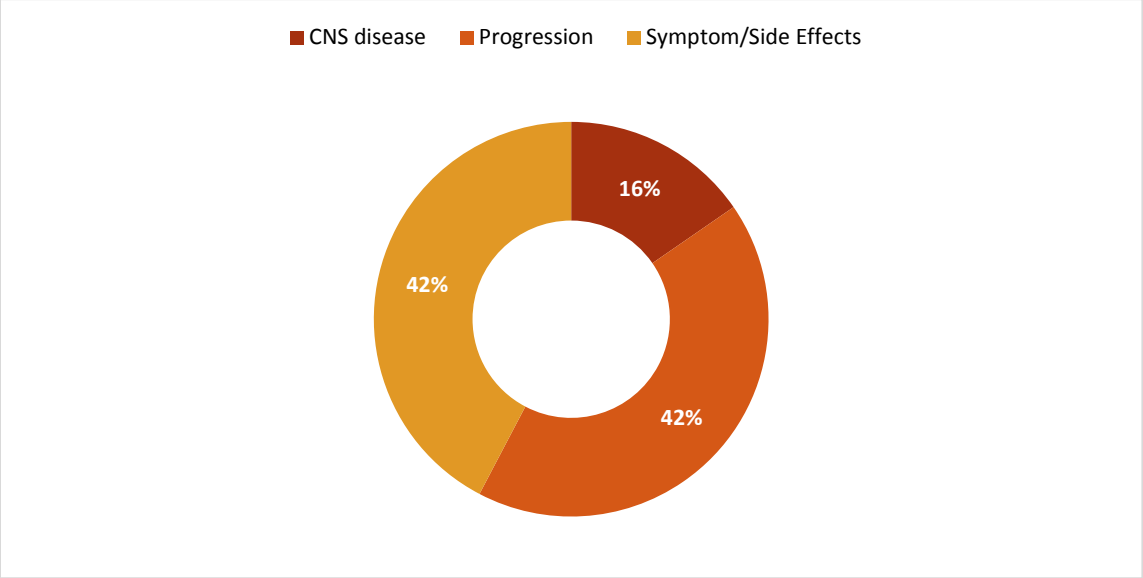


Table 19 summarizes how participants described these challenges.

Table 19. Clinician Descriptions of Barriers to Optimal Treatment

Symptom and Adverse Event Management
▪ *I guess I would say some of the symptoms. Symptoms management with those patients as far as, you know, some of the therapies can cause the diarrhea pretty bad. So that would be 1 of the main ones and just the fatigue, just the not feeling well. Less often any cardiac stuff.* [provider 17, APN, radiation oncology, academic]
▪ *Occasionally, we start to see a cardiac problem. I mean, when you start to see a drop in ejection fraction, etc, which may happen, sometimes you have to do what's best for the patient and sometimes we have changed therapy to the oral TKIs because of that.* [provider 7, MD, hematology/oncology, private practice]
▪ *Symptom management. You know, side effect management. Dealing with the fear of recurrence. Helping patients manage being able to still function while going through treatment. When someone's got to have chemotherapy and surgery, radiation, how am I going to help them to continue to function in the workplace, possibly, as we're talking mostly women here, if they have families, if they have children, you know. These are all the challenges. Helping them deal with all the emotional impacts of it. You know, self-image issues with losing hair, with losing breasts, all these body image changes. It's a lot.* [provider 10, APN, oncology, community]
▪ *A lot of my younger patients, they do tend to have more side effects, maybe because I'm using more chemotherapy or the fact that they just don't get breaks, like others can. They kind of move from one line to the next line in fairly rapid succession. So side effect management becomes pretty hard for a lot of people. There's a lot of back and forth to the clinic. Sometimes I have to admit*

them to the hospital. Management of diarrhea is pretty challenging and that tends to be a not uncommon side effect on anti-HER2 drugs. So that becomes difficult because it requires a lot of education, people are very hesitant taking Imodium or lomodal or whatever. So there's just a lot of back and forth. [provider 4, MD, hematology/oncology, community]

Progression

- *Number 2 is patients who become refractory or progress on Kadcyla. Although we have at least 1 other option or 2 other options, the duration of response is short, the toxicity is significant and that's not—there is room for improvement in those particular patients for outcome.* [provider 14, MD, hematology/oncology, community]
- *With HER2, we usually can kind of extend people's lives by years, but eventually they all can usually end up succumbing to the disease and so that's a challenge when you're dealing with younger patients and they have families and they're worried about passing and leaving—you know, who's going to take care of their kids or their parents or whoever else they're kind of taking care of. So it's challenging to deal with that.* [provider 16, MD, oncology, community]
- *The challenges are that the literature sometimes is more limited about the success rate of radiation in particular cases that may not be so common and the follow up for patients with HER2-positive cancer's not as long as the HER2 negative because even though it's been around for, now, nearly, maybe a decade and a half or so, we still don't have as much follow up as we do with other patients*. [provider 21, MD, radiation oncology, community]
- *A lot of the drugs that we use for metastatic disease only have been moved up earlier in treatment and so my concern has always been, when the patient progresses, when they have metastatic disease and they progress and we've used so many of this drug already upfront, how we're going to have to treat that. Also, patients may have a limit to their insurance allocation and drugs are so expensive and women are living so long with metastatic disease that they get to that limit, then how are they going to pay for treatment?* [provider 23, MD, oncology, private practice]

CNS Disease

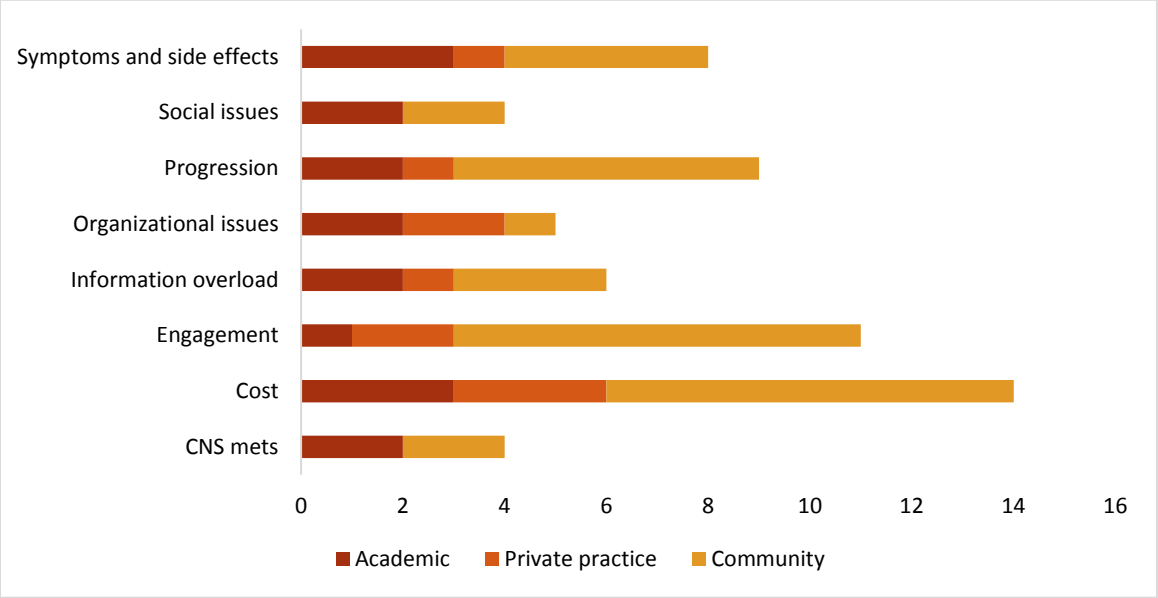
- *Number 1 on my list would be brain metastases. You know, depending on the study that you look at, 30% to 50% of women with metastatic HER2-positive breast cancer will have brain metastases and we have many, many drugs that treat HER2-positive breast cancer, but we do not have many drugs that cross the blood–brain barrier and are effective in the treatment of breast cancer once it's spread to the brain. So that's a huge clinical problem and even though we've made strides in the OS of HER2-positive breast cancer over time, we actually have not yet made strides in women who develop brain mets; their survival is still about 2 years after formation of a brain met. And we're getting there. There are some drugs coming down the pipeline. One of them is called tucatinib, neratinib has CNS penetrability, so does lapatinib. T-DM1, which is the second line, which is standard of care in the second line, has some CNS activity as well.* [provider 26, MD, hematology/oncology, academic]
- *Brain metastases is a big issue and the agents are not as effective in the brain. I think that's a big problem*. [provider 26, DO, oncology, community]
- *The biggest clinical challenge, in my mind, is occurrence of or progression of CNS disease, intracranial metastasis, CNS metastasis. Those patients have a poor prognosis. Currently, existing therapy, very few of them have good data and a few of them good activity, so there's a tremendous unmet need, which may be fulfilled in the near future or at least to some extent would be filled by some of the newer active agents that are coming down the pike.* [provider 14, MD, hematology/oncology, community]
- *HER2 positive, they tend to metastasize to the brain, so sometimes if they have brain mets, that becomes an issue*. [provider 2, MD, hematology/oncology, community]

Patient Engagement

- *The other challenge is to keep patients engaged. In my experience with these patients, the first 6 months to a year they are very engaged; beyond that, the enthusiasm sort of cools down and they are coming in all the time, getting treatment. You have to keep them energized. You have to remind them what we are doing here to keep them involved, because this is a long therapy and it gets boring and some patients lose interest. Like, "Okay, I feel fine, I don't know if I want to keep doing this." It's our job to keep them engaged.* [provider 7, MD, hematology/oncology, private practice]
- *I do think categorically when you're first meeting patients that are HER2 positive and telling them the duration of therapy, everybody's face sinks when you tell them it's going to be a year of therapy, but it doesn't carry over to noncompliance. Everybody's compliant, but there is this moment when they're like, "A whole year?," so you have to get people to buy in.* [provider 24, MD, oncology, academic]
- *The biggest challenge, I would say, in advanced cancer ends up being engagement with palliative care. You know, I think we try to encourage patients to see palliative care earlier. I think there's still a stigma around palliative care being mostly for hospice only. And so I think often times they end up getting seen by palliative care later than I would've liked despite kind of encouraging it early on. And I see that's quite the biggest barrier that I see that really impacts patient quality of life.* [provider 13, MD, hematology/oncology, community]

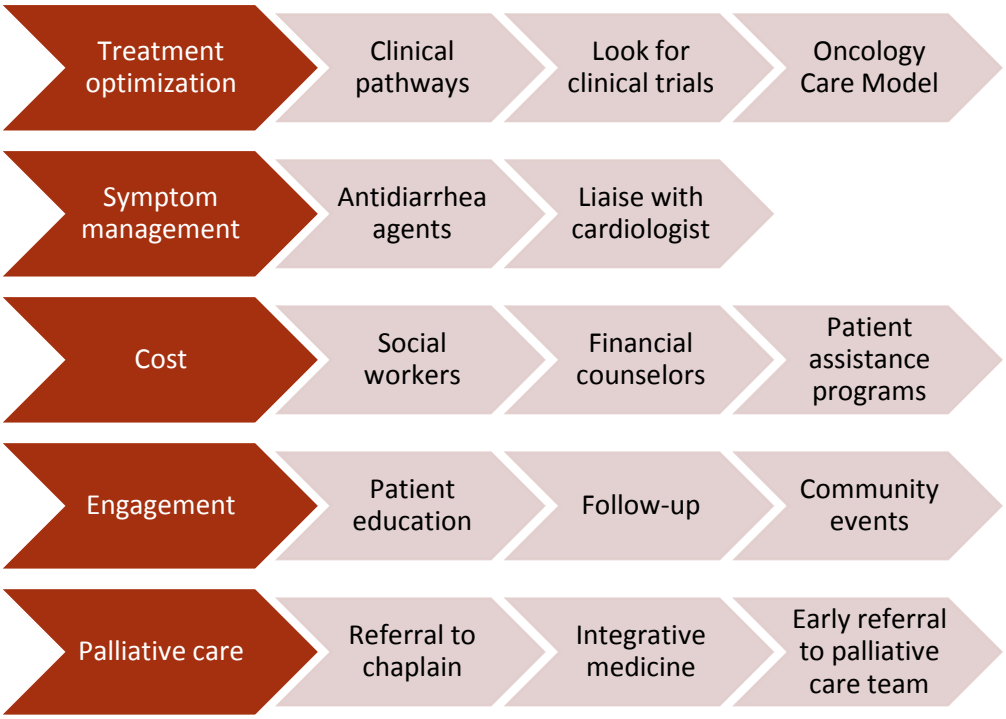
In addition to the cost of treatment, interviewed clinicians also pointed to a range of other social, organizational, and interpersonal challenges, such as how best to: 1) keep current with novel and investigational therapies; 2) sustain patient engagement across the treatment trajectory; and 3) address cost and access to treatment (**Figure 19**). The top priorities for radiation oncology clinicians were cost, patient engagement, and managing radiation adverse events.

Figure 19. Frequency of challenges mentioned by interviewed clinicians (n = 61).



Interviewed clinicians noted the following range of strategies that their practice settings are using to address the challenges they described (**Figure 20**).

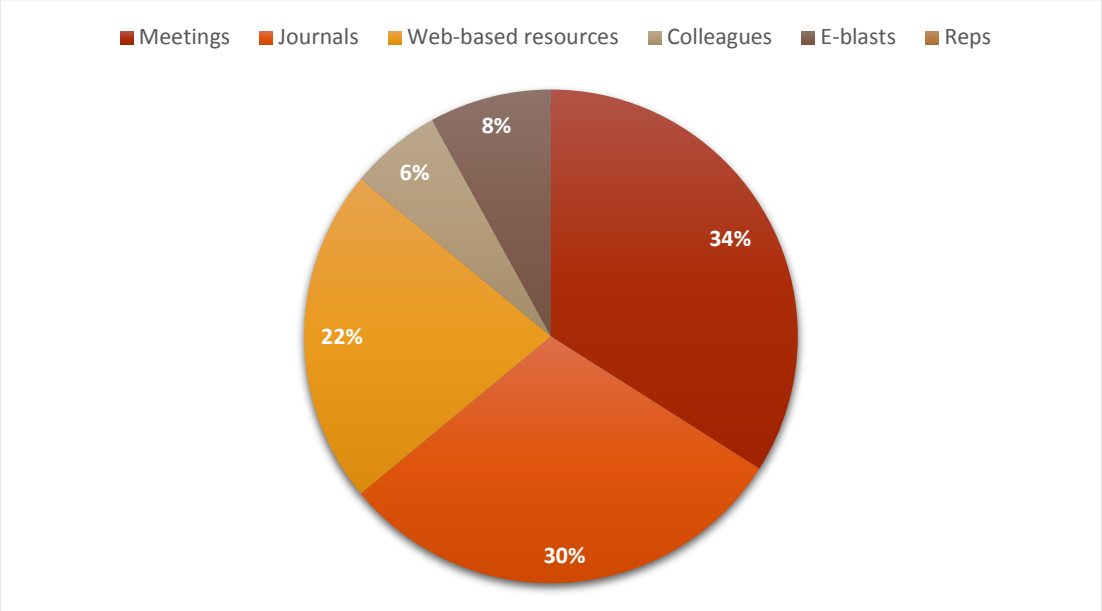
Figure 20. Stated strategies to address practice challenges.



Preferred Educational Sources and Formats

Figure 21 shows the range of information sources that interviewed clinicians rely on to stay current with treatment and management developments in HER2-positive MBC.

Figure 21. Preferred education sources reported in interviews (n = 50).



The *Journal of Clinical Oncology* and the *New England Journal of Medicine* were the most frequently cited journals; many also cited ASCO Post and Oncology Nurse Advisor as reliable sources of information. Oncologists cited ASCO, San Antonio Breast Cancer Conference, and the American Association for Cancer Research conference as frequently attended meetings. Radiation oncology clinicians cited the American Society of Radiation Oncologists annual meeting. Participants also emphasized the importance of conversations with peers in tumor boards and locally organized weekly or monthly meetings as important spaces for discussions about patient management as well as sources of information about new agents, clinical trial data, and other management issues. UpToDate, Clinical Care Options, Research to Practice, OncLive, and Medscape were cited as frequently accessed online resources.

Time was a major factor in participant selection of educational format. Participants valued the accessibility and immediacy of online tools, information, and resources, but they preferred being able to go to meetings, interact with colleagues, discuss cases, and learn from subject matter experts. Podcasts and webcasts were valued for their easily digestible formats "*with a human touch*."

Most participants identified in-person meetings as the pre-eminent learning scenario, followed by online resources such as webcasts and downloadable slide presentations.

> *I want to hear it first hand, so that's why I am at ASCO every year, but I also follow the latest and the greatest that is being presented and published and so on. But I also appreciate greatly the Clinical Care Options' review, the slide sets, the summary of the data, as well as the video from some of the symposia that are available along with slides and so on. So I appreciate all of that.* [provider 14, MD, hematology/oncology, community]

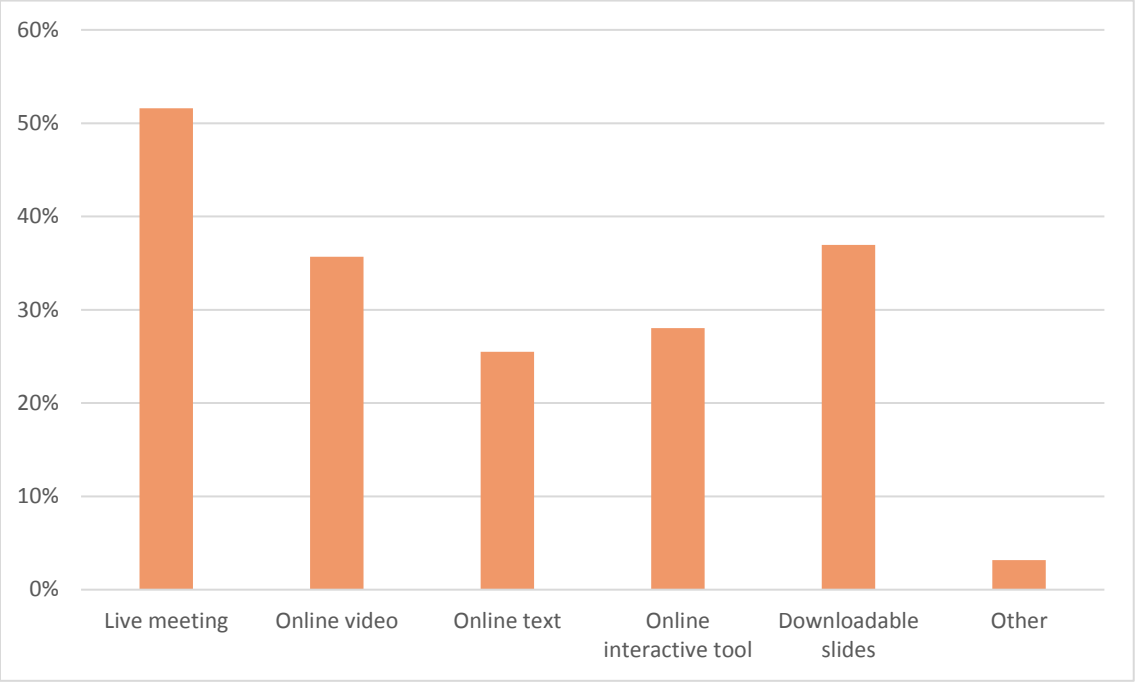
> *I love meetings, especially the breakout sessions. I like going to a lot of the pharma presentations; so I know they're biased, but still you get a lot of information and you can ask direct questions.* [provider 9, APN, oncology, academic]

> *Well, for convenience, preference is online, but if it's a new drug that I'm responsible for administering, I do like a site visit, especially for something that's new.* [provider 10, APN, oncology, community]

> *I learn more visually, so I like looking at when someone's talking and you have slides in front of you, so that helps.* [provider 2, MD, hematology/oncology, academic]

Survey results regarding preferred education sources echoed that of the interviews (**Figure 22**).

Figure 22. Preferred education sources reported in the survey (n = 157).



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Understanding the Educational Needs of Healthcare Providers on Novel Treatments in Urothelial Carcinoma

Table of Contents

EXECUTIVE SUMMARY

Background

Urothelial carcinoma (UC) is the second most common malignancy of the genitourinary system and is the sixth most common cancer in the United States. Novel treatment approaches for UC have had a significant impact on the management of patients, including the use of immune checkpoint inhibitors (ICIs) and the FGFR inhibitor erdafitinib. In addition, positive preclinical and early clinical results have been reported for many new targeted agents in UC, including antibody–drug conjugates like enfortumab vedotin.

Study Goal

The goal of this comprehensive needs assessment was to understand current clinical practice in managing patients with UC and identify the current educational needs of healthcare providers who are involved in the care of patients with UC. Clinical Care Options (CCO) and Thistle Editorial, LLC, strategically designed a multimethod assessment involving an in-depth qualitative exploration of current approaches to practice and a quantitative survey of current practice trends and specific challenges faced by healthcare providers responsible for treatment decisions for patients with UC.

Design and Methodology

This 2-phase, mixed-methods needs assessment study consisted of qualitative telephone interviews (Phase 1) and an online survey developed with input from 2 recognized experts in UC (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of medical oncologists, urologic oncologists, oncology nurses, and other healthcare providers responsible for the treatment decisions for patients with UC. Phase 1 continued to accrue participants until the target sample size was reached.

Phase 2 (quantitative) examined current practice trends and clinician knowledge of newly emerging and novel treatment options for patients with UC. In Phase 2, accrual of participants continued until a reliable representative sampling of the target population was obtained and the predetermined deadline for data analysis and report generation was reached.

Participants in this study were recruited using targeted emails offering a small amount of compensation from CCO to ensure a representative sample of healthcare providers. In Phase 2, emails were sent at regular intervals to recruit additional survey participants until the predetermined deadline for data analysis and reporting was reached. Survey results and overall response trends of the survey questions were monitored throughout this process to ensure that the responses obtained reflected a representative sampling of different healthcare provider specialties.

This report contextualizes the key qualitative findings by reference to overall practice trends from both US and ex-US surveys.

Key Clinical Practice Gaps

Managing patients with UC, especially with advanced disease, is emotionally exhausting and clinically challenging for clinicians. Although the interview participants in this study presented themselves as assiduous in their pursuit of the best possible treatment for their patients, our analysis points to the following clinical practice and performance gaps for oncologists, urologists, and other clinicians who are involved in the management of patients with UC in both academic and community settings:

Practice Gap 1: Approaches to Decision-Making, Communication, and Multidisciplinary Care in Early-Stage UC

While managing patients with early-stage disease, many clinicians are communicating with clinicians from other specialties, planning treatment strategies, and making decisions without the benefit of a multidisciplinary tumor board or other clinical decision support resources. There is a perception among some clinicians that patients, oncologists, and urologists are hesitant to use neoadjuvant therapy, and urologists feel somewhat unsupported in monitoring patients with low-grade disease for recurrence.

Practice Gap 2: Confusion Regarding Testing for PD-L1 Expression in Patients Ineligible for Cisplatin Chemotherapy

In August 2018, the FDA updated the label for first-line pembrolizumab and atezolizumab to require specific PD-L1 expression levels for patients with UC who are ineligible for cisplatin-based chemotherapy, but many clinicians are unsure of the best use of PD-L1 testing for their patients. Many clinicians are unsure of the correct PD-L1 expression cutoff level for initiating ICI therapy, some clinicians do not view PD-L1 testing as a clinical requirement for treatment initiation in this setting, and others may be testing for PD-L1 unnecessarily for some patients (eg, those who are ineligible for any platinum-based chemotherapy).

Practice Gap 3: Challenges in Selecting First-line Therapy

In contrast to experts who only consider ICIs as preferred options for patients who cannot tolerate cisplatin or carboplatin or for patients who may be able to tolerate carboplatin but reach the FDA-approved PD-L1 expression cutoff, many clinicians in this study view ICIs as preferred options for patients in the first-line setting. Clinicians are challenged to use these agents appropriately, with some attributing equivalence to these agents in the first-line setting based on second-line data. In addition, although clinicians use clinical criteria to select therapy, they struggle to differentiate who may be ineligible for treatment with cisplatin vs those who are ineligible for any platinum agent and have difficulty integrating these criteria in their decision-making alongside nonclinical criteria such as tolerability and patient preference. Few survey respondents were familiar with patient engagement as an intervention to integrate them as active participants in their own care, and clinicians likely need support to manage immune-related adverse events (irAEs) in ways that are consistent with current consensus-based recommendations.

Practice Gap 4: Challenges in Selecting Second-line Therapy and Beyond

Overall, clinicians seemed to feel that they at least had some options for patients treated with chemotherapy vs checkpoint inhibitors in the first-line setting; however, there remains considerable variation in second-line therapy selection.

Practice Gap 5: Deficits in Clinical Trial Referral
Although clinicians emphasize the value of clinical trials in the management of patients with UC, many work in practice settings that have limited access to clinical trials via tertiary centers or professional networks.

Practice Gap 6: Deficits in Familiarity With Novel Agents
Clinicians are largely unfamiliar with novel agents, and depth of awareness varies among those who say that they are aware of novel agents. Clinicians familiar with novel agents are more likely to be involved in or have access to clinical trials.

Key Recommendations

This study highlights a global need for education and resource exposure across professional roles, provider types, practice settings, years of experience, and patient volume in the following areas:

Recommendation 1: Decision-Making, Communication, and Multidisciplinary Care in Early-Stage UC
Clinicians need resources that support multidisciplinary pathways in UC and reinforce the importance of team-based approaches to care, the role of urologists in monitoring patients with low-grade disease, and the clinical benefits of neoadjuvant treatment.

Recommendation 2: Optimizing Molecular Testing
Clinicians require guidance on how to identify scenarios in which PD-L1 status testing is appropriate in the first-line setting and how to select and interpret the results of the appropriate PD-L1 assay. Clinicians need clarification on PD-L1 expression thresholds and their interpretation for clinical decision-making, as well as exposure to clinical decision resources (eg, multidisciplinary tumor boards and clinical pathways) that support clinical trial matching. Furthermore, as new targeted therapies requiring additional biomarker testing are approved, such as *FGFR* alterations for erdafitinib, clinicians will need ongoing education on this topic.

Recommendation 3: Optimizing First-line Therapy Selection
Clinicians need access to expert perspectives on the appropriate therapeutic strategy for patients in the first-line setting, including when to use chemotherapy vs immunotherapy and understanding the recent label updates on ICIs. Clinicians also need expert guidance on how to integrate clinical and nonclinical criteria into their decision-making and exposure to strategies that support patient engagement and enable patients to actively participate in their own care. Finally, clinicians need direction on strategies to manage irAEs in ways that are consistent with current recommendations and that involve multidisciplinary discussions with nononcology specialists with expertise in the unique characteristics and management of irAEs.

Recommendation 4: Optimizing Second-line Therapy Selection
Clinicians need access to expert perspectives on the appropriate selection of therapies for patients in the second-line setting and beyond, including guidance on optimal sequencing, how to rapidly integrate novel agents into clinical practice after regulatory approval, and how best to access ongoing clinical trials.

Recommendation 5: Optimizing Clinical Trial Referral
Clinicians need resources that increase their awareness of and ability to access available clinical trials as part of their routine approach to managing patients with UC and that they can provide to patients to help them navigate the challenges associated with participating on clinical trials.

Recommendation 6: Building Familiarity With Novel Agents
Clinicians need support to recognize the mechanisms of action of newly approved or investigational therapies used for patients with UC. Such recognition could help to build comfort and confidence in using agents sooner after regulatory approval.

Study Design and Methodology

Background

UC is the second most common malignancy of the genitourinary system and is the sixth most common cancer in the United States.[1] Novel treatment approaches for UC have had a significant impact on the management of patients. In particular, the approval of 5 ICIs marked a new paradigm in the treatment of UC for patients with advanced or metastatic disease. Currently, pembrolizumab and atezolizumab are approved as first-line therapy for patients with UC who are unable to tolerate any platinum-based chemotherapy or for those patients who are ineligible for cisplatin-based chemotherapy and whose tumors express PD-L1 (PD-L1 combined positive score [CPS] ≥ 10 using the Dako PD-L1 IHC 22C3 PharmDx Assay for pembrolizumab or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area using the Ventana PD-L1 [SP142] Assay for atezolizumab). ICI therapy may start to move into earlier lines of therapy on the basis of preliminary results for 2 phase II trials of atezolizumab (ABACUS) and pembrolizumab (PURE-01) in the neoadjuvant setting for muscle-invasive bladder cancer.[1,2] In addition, pembrolizumab, atezolizumb, nivolumab, durvalumb, and avelumab are approved as therapy for patients whose disease has progressed following platinum-based chemotherapy. Although ICI therapy has demonstrated durable efficacy in many patients with advanced UC, not all respond and nearly all patients eventually experience disease progression, creating a clinical challenge in an already difficult-to-treat disease.[3]

To meet this medical need, positive preclinical and early clinical results have been reported for many new targeted agents in UC, including the antibody–drug conjugate enfortumab vedotin and the FGFR inhibitor erdafitinib, which has demonstrated efficacy in heavily pretreated UC.[4,5] On April 12, 2019, the FDA granted accelerated approval to erdafitinib for patients with locally advanced or metastatic UC with susceptible *FGFR3* or *FGFR2* genetic alterations after progression during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, based on recent clinical trials. This regulatory approval was based on Study BLC2001 in patients who had progressed on or after at least 1 previous chemotherapy and included patients who had progressed after treatment with an ICI.[5,6] Phase III trials are ongoing, with the THOR trial investigating erdafitinib in the second-line setting (NCT03390504).

A phase II trial investigating enfortumab vedotin in patients (n = 125) who had been previously treated with ICIs and chemotherapy recently reported an ORR of 44% and a CR of 12%.[7] The median PFS and OS with enfortumab vedotin was 5.8 months and 11.7 months, respectively.[7] Based on these data, the FDA granted Breakthrough Therapy designation for enfortumab vedotin, and the phase III EV-301 trial is exploring the efficacy of enfortumab vedotin vs chemotherapy for patients who progress after ICI therapy and have also received platinum-based chemotherapy (NCT03474107).[8]

In addition to enfortumab vedotin, several other antibody–drug conjugates are in clinical development, including sacituzumab govitecan and ASG-15ME for advanced UC and oportuzumab monatox for early-stage UC.[9,10] CCO's data suggest that unless clinicians fully understand the mechanisms of action and safety and efficacy data of new agents, they are substantially less likely to integrate them into practice.[11-13] Therefore, it is critical to understand the current educational needs of healthcare providers on novel agents being investigated in UC to ensure that they are enrolling the proper patients onto clinical trials and are adequately prepared to confidently and safely use these new agents when they are clinically available.

Study Design

Following a review of the literature and CCO internal data, this 2-phase, mixed-methods needs assessment study was designed to include qualitative telephone interviews (Phase 1) and a quantitative online survey (Phase 2). Phase 1 of the study explored gaps in the knowledge, skills, and clinical confidence of US medical oncologists, urologic oncologists, oncology nurses, and other healthcare providers responsible for the treatment decisions for patients with UC. Phase 2 examined practice trends and knowledge of current and future treatment options for patients with UC.

The study design included informed consent and measures to ensure protection and confidentiality of participants. Participants were offered an ethically acceptable level of compensation (ie, fair market value, but not enough to create coercion) to increase the number of participants and improve the statistical power as well as the likelihood that our study cohort is representative of the general US oncology specialist healthcare provider population.

Qualitative Phase

Semistructured interviews were designed to explore intuitive decision-making factors influencing clinical reasoning.[14,15] We conducted a series of confidential, 30- to 45-minute telephone interviews, directed by an interview topic guide based on literature review, faculty input, and synthesis. Qualitative interviews were conducted between March 25, 2019, and April 5, 2019.

Interviews were transcribed verbatim and imported into NVivo 12 for Mac (*QSR International*), a software package designed to support systematic analysis of unstructured textual data. Analysis was based on grounded theory and an open-ended process of constant comparison that generates themes, descriptive patterns, and hypotheses as an ongoing, iterative process.[16] This approach included 4 components:

1. Data immersion and familiarization
2. Descriptive coding and node generation
3. Thematic coding and analysis
4. Subgroup analysis by demographic and other relevant attributes

Transcript content was coded into descriptive categories, or "nodes" that were tagged to sections of text. Following descriptive node generation, a second round of coding identified potential themes of relevance until we achieved thematic saturation. Indicators of themes included words, phrases, or segments of text that were used in a similar fashion by respondents across or within interviews and that pointed to an emerging idea or concept. Qualitative findings were also examined for educationally

significant differences among subgroups (ie, practice setting, specialty, designation) and reported where relevant. The conclusions for the overall group are, for the most part, relevant across all subgroups.

Quantitative Phase

We fielded an in-depth quantitative survey to identify practice trends concerning integrating new agents and therapeutic advances in the care of patients with UC, sources of information consulted for best practices and/or education, gaps in knowledge, competence, and performance, and barriers to adoption of new treatment options.

Oncology clinicians treating patients with UC were recruited to complete a 10- to 15-minute online survey. Matthew I. Milowsky, MD, Professor of Medicine at the Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill in Chapel Hill, North Carolina, and Matthew Galsky, MD, Professor of Medicine and Director of Genitourinary Medical Oncology at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai in New York, New York—both nationally recognized experts in UC—worked with educational and survey design/assessment experts to develop case scenarios and clinical questions to assess gaps in optimal patient management, trends in care, knowledge of clinical trials and investigational agents, and self-identified barriers to optimal care.

The quantitative online survey was conducted March 19, 2019, to May 21, 2019. The online survey questions and answer options were updated to reflect the new FDA indications for erdafitinib that occurred during the open polling period for this study.

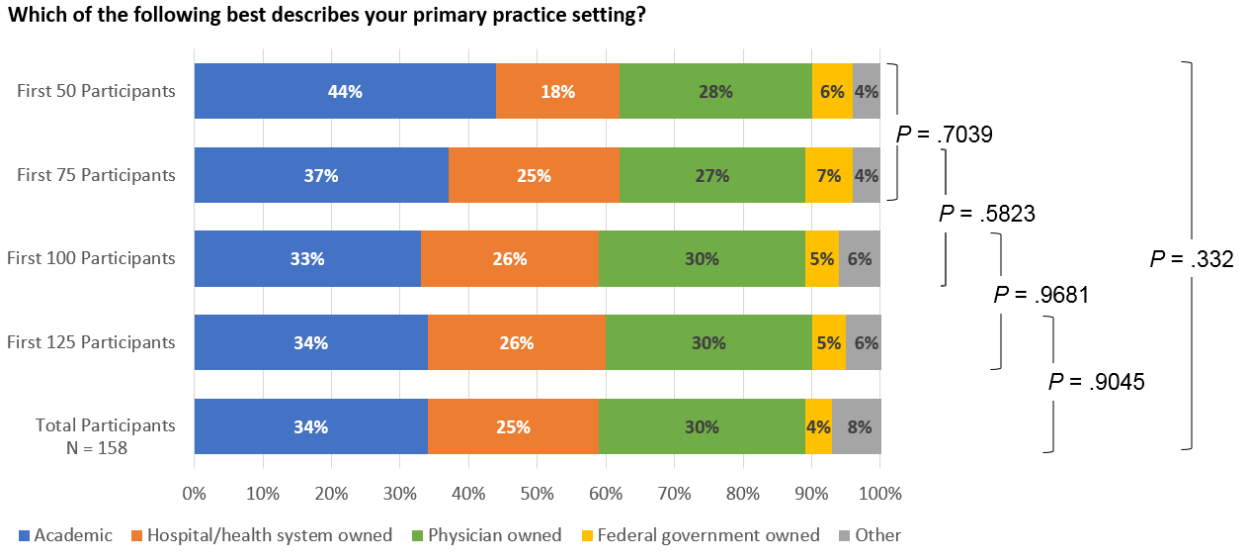
Recruitment

Invitations to participate in both phases of the study were sent through email to a list of CCO members and US clinic contacts. CCO Oncology membership includes more than 163,000 clinicians worldwide, including more than 26,000 physicians in the United States, of whom more than 16,000 define themselves as having a specialized interest in medical oncology or hematology/oncology. In Phase 2, we extended the survey to clinicians outside the US to expand survey yield.

In Phase 1, US participants were accrued until the target sample size was reached. In Phase 2, accrual of participants continued until a reliable representative sampling of the target population was obtained. Periodic emails were sent to recruit additional survey participants until the predetermined deadline for data analysis and reporting was reached. Survey results and overall response trends of the survey questions were monitored throughout this process to ensure that the responses obtained reflected a representative sampling of different healthcare provider specialties. Initial recruitment emails were sent to the US CCO Oncology membership, and once a representative and sufficient sampling of US-based healthcare providers was achieved, emails were sent to CCO Oncology membership outside of the US (ex-US) to increase the overall number of participants in the Phase 2 study.

Both US and ex-US surveys were sufficient samples to represent their respective larger populations (Figure 1). Statistical analysis of survey results and response trends showed no statistically significant difference in responses to any survey question as participants continued to accrue.

Figure 1. Example of Statistical Analysis to Confirm Representative Sampling of Online Recruitment



Participant Characteristics

We conducted qualitative interviews between March 25, 2019, and April 5, 2019. For the qualitative phase, we recruited 30 clinicians who described themselves as practicing in US academic centers, community cancer centers, private practice, or community-based settings (Table 1). All interviews were completed prior to approval of erdafitinib. A majority of interview participants were physicians (MDs, 23; MBBS, 2; DO, 1) with a decision-making role regarding treatment; 4 participants were nurse practitioners (NPs). Of the recruited physicians, 5 were practicing urologists, and 4 of the 5 urologists worked in academic settings. Six of the 9 private practice participants also noted they were affiliated with a community hospital.

The quantitative survey was conducted March to May 2019. Erdafitinib was approved during data collection for the online survey, and survey questions and answer options were updated to reflect this approval. The survey yielded 156 US-based participants; therefore, we extended the survey to clinicians outside the US and accrued 335 additional participants (Table 1). A comparison of survey responses from US-based clinicians vs ex-US clinicians showed similar practice trends.

Table 1. Demographic Characteristics of Participants				
Specialty	**Qualitative, n (n = 30)**	**Quantitative US, n (%) (n = 156)**	**Quantitative ex-US, n (%) (n = 335)**	**Quantitative Total, n (%) (N = 491)**
Oncology	8	62 (39.70)	250 (74.63)	321 (63.54)
Urology	5	18 (11.50)	32 (9.55)	50 (10.18)
Hematology/oncology	17	68 (43.60)	32 (9.55)	100 (20.37)
Radiation oncology	NA	1 (0.64)	16 (4.78)	17 (3.46)
Surgical oncology	NA	3 (1.92)	2 (0.60)	5 (1.02)
Primary care	NA	4 (2.56)	2 (0.60)	6 (1.22)
Pharmacy	NA	0	1 (0.30)	1 (0.20)
Years of Practice				
< 5	NA	19 (12.18)	21 (6.33)	40 (8.15)
5-10		46 (29.49)	77 (23.19)	123 (25.05)
11-15		19 (12.18)	88 (26.51)	107 (21.79)
16-20		24 (15.38)	52 (15.66)	76 (15.48)
> **20**		48 (30.77)	49 (28.31)	97 (19.76)
Practice Setting				
Academic	11	51 (32.69)	86 (25.60)	137 (27.90)
Community cancer center	3	NA	NA	NA
Hospital/health system owned	NA	39 (25.00)	104 (30.95)	143 (29.12)
Private practice/physician owned	7	48 (30.77)	26 (7.74)	74 (15.07)
Federal government owned	NA	6 (3.85)	NA	6 (1.22)
Community-based practice/other	9	12 (7.69)	7 (2.08)	19 (3.87)
Cancer center	NA	NA	109 (32.44)	109 (22.20)
UC Patients/Month				
< 5	NA	43 (27.92)	128 (38.21)	171 (34.83)
5-10		51 (33.12)	117 (34.93)	168 (34.22)
11-15		25 (16.23)	50 (14.93)	75 (15.27)
16-20		16 (10.39)	19 (5.67)	35 (7.13)
> 20		19 (12.34)	21 (6.27)	40 (8.15)

NA, not applicable.

The urologists reported that they see patients across all stages of UC, and each described themselves as the clinician who typically makes the UC diagnosis. Oncology clinicians stated that they treated patients across "a wide spectrum" including neoadjuvant, adjuvant, and metastatic stages of treatment but estimated that most of the patients they see have recurrent metastatic disease (60% to 70%).

Practice Gap 1: Approaches to Decision-Making, Communication, and Multidisciplinary Care in Early-Stage UC

While managing patients with early-stage disease, many clinicians are communicating with clinicians from other specialties, planning treatment strategies, and making decisions without the benefit of a consensus-oriented multidisciplinary tumor board or other clinical decision support resources. There is a perception among some clinicians that patients, oncologists, and urologists are hesitant to use neoadjuvant therapy, and urologists feel somewhat unsupported in monitoring patients with low-grade disease for recurrence.

Tumor Boards

Most interview participants across all practice settings participated in tumor boards to review and discuss treatment planning for patients with UC. Participants identified urologists, medical oncologists, radiation oncologists, pathologists, and radiologists as tumor board members. A few participants also mentioned an extended range of members including nurse practitioners, social workers, and nutritionists, and almost one third of participants described having or were about to hire nurse navigators to help coordinate and guide patients through the treatment journey.

However, tumor board format and the multidisciplinary tenor of discussion varied. Less than one half of participants viewed themselves as members of a multidisciplinary team (n = 12), but these clinicians tended to describe a more formal, **consensus-based** approach in which patient cases were reviewed and treatment planned with input across multidisciplinary team members.

> *I work in a comprehensive cancer center affiliated with an academic teaching hospital. It's a multispecialty practice and we are 8 of us and, essentially, my role is, as a medical oncologist, is to—**we work, first of all, closely** with our surgical oncology colleagues, interventional radiologists, the radiation oncologist, the pathologist—is to come up with a treatment plan and then try to as much stick with that treatment plan **so that you're communicating and giving the same sort of information to the patients who are navigating through this journey**, seeing multiple specialties and things and all.* [MD, hematology/oncology, community cancer center, provider 26]

> *That's **really the partnership of these 5 folks**, you know, sitting together in a multidisciplinary tumor board **looking at decision-making**. Or, if it isn't in a tumor board, it's in a phone call or electronic medical record detailing our discussions. There are times when, you know, the surgeon decides that it's up to the rest of us, you know, for whatever reason, you know, then, you know, we deal with that end of it after that. By and large, we talk to each other . . . **we do this in a very prospective, calculated manner**.* [MD, hematology/oncology, academic setting, provider 15]

Participants who viewed themselves as **primary decision-makers** described the tumor board as an approach in which consensus was less of a goal and in which the medical oncologist made the primary decision.

> *I would say 90% of patients are presented prospectively at a weekly tumor board and the decision is made at that level. **The decision is not binding.** In other words, basically, by that time **someone like me is in charge** because, you know, with the types of patients we're talking about, it's really a medical oncology issue. And **if I disagree, I don't have to take the tumor board's recommendation**, but generally, we hash it out at tumor board and that's where a recommendation is generated.* [MD, oncology, academic setting, provider 7]

Three of the 12 participants based in an academic setting did not participate in tumor boards. One of these participants was an NP who worked in an outpatient setting where treatment planning and decisions were made at the point of care by the treating oncologists, and 2 participants were urologists who said they coordinated with oncologists by "phone, emails, sharing medical records." Other participants who did not have access to or participate in tumor boards described a process of direct communication with the relevant clinicians vs discussion in a multidisciplinary group.

> *I'm in a group practice. We don't have a formal tumor board with other specialties. We basically* ***base our communications individually****; otherwise, by phone and email is the most common way. For example, if urology picks up a patient, they want to do surgery. But it turns out muscle-invasive disease, so they want to refer for neoadjuvant before surgery, so they will either, depending on the practice, somebody will either text me or email me, "Patient come to you, please see." It can be very short, like 2 sentences: "He's neoadjuvant. I'll send the records through." So that's how the patients get to me for neoadjuvant setting.* [MD, hematology/oncology, private practice, provider 21]

Multidisciplinary Care and Communication Pathways

Some oncologists drew attention to the lack of one care standard or coordination process in UC and, in particular, noted the absence of multidisciplinary care pathways in which urologists could work closely with them and were "*able to see the whole disease picture*." These participants see patients who present late in the disease trajectory with high-volume disease and they would love to see patients referred earlier for systemic therapy.

> *The multidisciplinary care is still hit or miss; again I think it's still concentrated enough, you—big institutions, so a lot of smaller places, you know,* ***they still do kind of piecemeal approach in treatment****.* [MBBS, hematology/oncology, academic setting, provider 5]

> ***If we could do to bladder cancer what has been done for breast cancer, right?*** *So, women have really made breast cancer such a critical topic and look at the amount of effort and attention that is done for that, you know, and if we could do something along those lines for patients with bladder cancer that would really make a big difference*. [MD, urology, academic setting, provider 5]

Urologists also expressed some dissatisfaction about current multidisciplinary pathways and, in particular, follow-up. They felt the keen challenge of *getting the patients to follow up when they have a low-grade disease and keep them coming back so you can see if their disease is recurring.* [DO, urology, academic setting, provider 12]

Neoadjuvant Therapy

Although not all interview participants were able to quantify the volume of patients that they treat at different stages of disease, most estimated that they treat approximately 20% to 25% of their patients with UC with neoadjuvant therapy prior to surgery and a smaller percentage (10% to 20%) in the adjuvant setting. Neoadjuvant platinum-based chemotherapy has been shown to confer survival advantage on patients with muscle-invasive UC prior to surgery, and most participants cited this survival advantage as the rationale for its use prior to surgery. Participants who described their approach in the neoadjuvant setting identified cisplatin/gemcitabine as their preferred neoadjuvant approach in cisplatin-eligible patients; 2 participants noted that MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) was still commonly used; 3 identified carboplatin-based treatment for cisplatin-ineligible patients; and 2 participants, who also said they routinely use PD-1/PD-L1 testing at diagnosis of locally advanced or metastatic disease, commented that immunotherapies were increasingly being used for cisplatin-ineligible patients in the neoadjuvant setting. Rationales for these choices were based on the view that they reflected "standard practice," the availability of more data for one approach vs another, or the emergence of more robust data (Table 2).

Table 2. Examples of Rationales for Neoadjuvant Treatment
Rationale for Carboplatin-Based Approach
The neoadjuvant chemo, you know, mostly I use cisplatin/gemcitabine, but some patients may not be a cisplatin candidate, so this is debatable, but I'm still using it, so you can use carboplatin/gemcitabine. **[MD, private practice, hematology/oncology, provider 21]**
Rationale for Cisplatin-Based/MVAC Approach
For neoadjuvant setting, the doctor usually decides between dose-dense MVAC or cisplatin/gemcitabine, but most of the time, we choose cisplatin/gemcitabine because the oncologist said that it hasn't been proven that, you know, one is better than the other or maybe not inferior to the other, but either way it's more side effects with dose-dense MVAC than cisplatin/gemcitabine, so we usually use the cis/gem regimen. **[NP, hematology/oncology, community cancer center, provider 20]**
Rationale for PD-L1 Inhibitors
If a patient is cisplatin-ineligible, then we go for PD-1/PD-L1 inhibitors. That is the standard practice. **[MD, urology, academic setting, provider 23]**
If they're not chemo eligible, then we usually talk about immunotherapies. **[MD, hematology/oncology, community-based, provider 13]**

Three community/private practice participants noted that they provided very little neoadjuvant therapy and, as illustrated in the following quote, attributed low rates to urologist or patient hesitancy:

> *However, the problem [is] because . . . sometimes the patient doesn't want to do it, or the surgeon doesn't want to do it. Even though the data—this is one of the few cancers where there's been long-standing good data for neoadjuvant treatment, the urologists are hesitant to do it for one of several reasons. First of all, they're* ***afraid*** *the patient is going to be too beaten up by the chemotherapy and they won't be fit for surgery. Number two, they* ***just want to get the surgery done****. They don't understand the value of the literature. And especially in the community and private practice setting, that's much more prevalent because quite honestly, they're economically incentivized to do otherwise. And then thirdly, I think it's sometimes the* ***patient preference****. I mean, the survival advantage is not great, so we need better data. There are better treatments, but they haven't been studied as well in the neoadjuvant setting as they have in the metastatic setting.* [MD, oncology, private practice, provider 11]

Recommendation 1

Develop resources to support multidisciplinary pathways in UC that reinforce the importance of team-based approaches to care, the role of urologists in monitoring patients with low-grade disease, and the benefits of neoadjuvant treatment. Although we did not collect data on participant age, it may be that consensus-based participants are younger clinicians who value multidisciplinary approaches and are **accustomed to working in teams**, whereas those who view themselves as decision-makers are redolent of an older, **self-reliant** category of clinician. These categorizations have potential implications for education content, format, and target audience.

Practice Gap 2: Confusion Regarding Testing for PD-L1 Expression in Patients Ineligible for Cisplatin Chemotherapy

In August 2018, the FDA updated the label for first-line pembrolizumab and atezolizumab to require specific PD-L1 expression levels for patients with UC who are ineligible for cisplatin-based chemotherapy, but many clinicians are unsure of the best use of PD-L1 testing for their patients. Many clinicians are unsure of the correct PD-L1 expression cutoff level for initiating ICI therapy, some clinicians do not view PD-L1 testing as a clinical requirement for treatment initiation in this setting, and others may be testing for PD-L1 unnecessarily for some patients (eg, those who are ineligible for any platinum-based chemotherapy).

FDA Labeling for PD-L1 Status Testing

In June 2018, the FDA updated the labels for pembrolizumab and atezolizumab to include specific requirements for PD-L1 status for cisplatin-ineligible patients with UC. Recent unpublished data cited by the FDA showed that low PD-L1 expression resulted in lower OS with single-agent pembrolizumab or atezolizumab vs chemotherapy. Therefore, frontline use of pembrolizumab is restricted by a CPS ≥ 10% for cisplatin-ineligible patients and atezolizumab is restricted by PD-L1 expression on immune cells of ≥ 5% in this patient population. Patients ineligible for any platinum-based chemotherapy may still receive pembrolizumab or atezolizumab without the need for PD-L1 expression testing, whereas those eligible for cisplatin should still receive cisplatin-based chemotherapy prior to immune checkpoint inhibition. Based on data from the quantitative survey, only 30% to 40% of clinicians are testing appropriately, and others may be testing unnecessarily. Many are using the test results as a rationale for initiating immunotherapy regardless of expression threshold.

Patterns of PD-L1 Testing in Clinical Practice

Survey data indicate the range of scenarios in which clinicians report they are testing for PD-L1 expression (Figure 2a, Figure 2b).

Figure 2a. US scenarios of PD-L1 biomarker testing (n = 121).

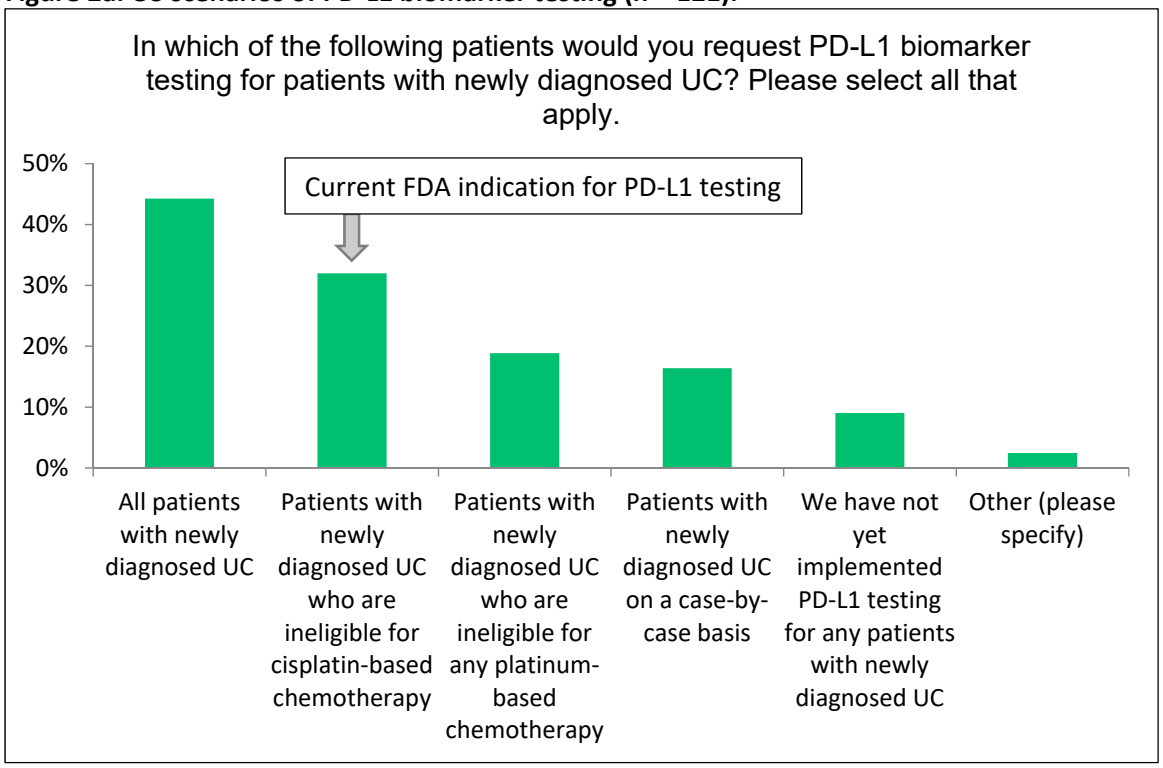
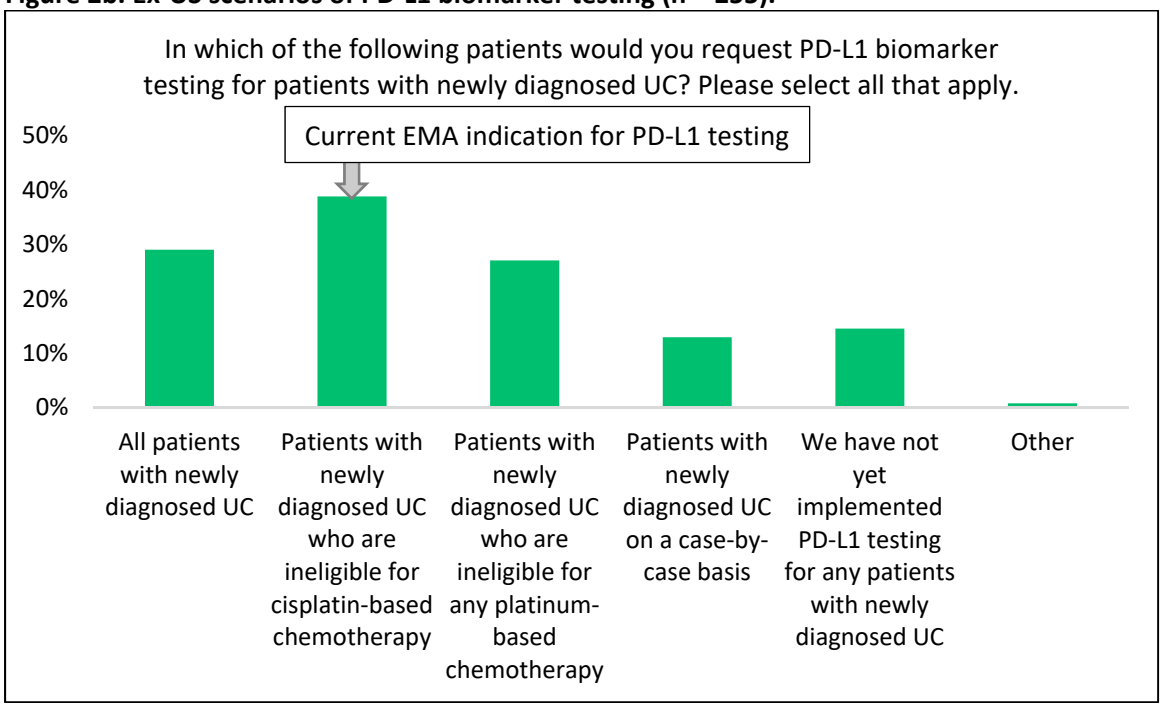


Figure 2b. Ex-US scenarios of PD-L1 biomarker testing (n = 255).



Similarly, most interview participants (n = 22) reported testing for PD-L1 expression in any patients diagnosed with locally advanced or metastatic disease or in patients who are ineligible for treatment with cisplatin.

*We have made a **standard of care** that everybody, when pathologists see a bladder cancer, they must do the PD-L1 testing.* [MBBS, hematology/oncology, community based, provider 2]

*For those who are cisplatin eligible, I'm not routinely doing any particular molecular testing. For those who are **cisplatin ineligible,** I am doing PD-L1 testing, usually with the 22C3 antibody.* [MD, oncology, academic setting, provider 25]

Three of the urologists and a community cancer center NP were unaware if molecular testing was being used in their institution.

Rationale for PD-L1 Testing

Interview participants differed in how they viewed and used the results from PD-L1 testing in their clinical practice. A majority (n = 17) used **any** PD-L1 positivity as a data point to support the rationale for immunotherapy as a treatment option for cisplatin-ineligible patients (Table 3). This group did not appear to focus on specific thresholds for PD-L1 expression; they did not state that a particular threshold would steer them toward one therapy or another; and they did not differentiate between CPS and PD-L1 expression.

Table 3. Examples of Statements Concerning How any PD-L1 Positivity Supports Immunotherapy
*We use PD-L1 and PD-1 immunostaining, you know, for decision on immunotherapy. I am perfectly fine with pembrolizumab, durvalumab, atezolizumab, nivolumab. When you look at all the study results, practically it's the same success. **If you respond to one, you'll probably respond to all of them**.* [MD, urology, academic, provider 15]
*We use what do you call it, stroma marker, PD-1, PD-L1 expression from the tumor tissue. So, if a patient is cisplatin ineligible, then we go for PD-1, PD-L1 inhibitors. That is the standard practice. One is PD-1 inhibitor; the other one is PD-L1 inhibitors. **They did not find any major difference** between these 2 groups of agents.* [MD, urology, academic setting, provider 23]
*At this moment, usually it's PD-L1 testing. It's fairly, I guess, recent where **we have the tests for PD-L1 to understand the patient's eligibility for immunotherapy** but that's really the only thing I test for routinely now. PD-L1 expression; that needs to be expressed in order to support using immunotherapy there. So if that were to happen, you can use immunotherapy.* [MD, oncology, private practice, provider 27]
*The PD-L1 is helpful, but not necessarily a—let me put it this way. **Even patients who may not express PD-L1 on the tumor sample may still be eligible to be treated**.* [MD, oncology, community based, provider 24]
*We obviously do PD-L1, but it's not**—treatment is not yet necessarily driven by PD-L1 expression**. We do biomarkers on everybody. Not that we rely on them to be actionable . . .* [MD, hematology/oncology, academic setting, provider 14]
***And it would be helpful to see if they're a PD-L1 expresser or not. But even regardless of that marker, if I don't think that they can handle the chemo, then I'll just go straight to immunotherapy.* [MD, hematology/oncology, academic setting, provider 18]**

A smaller group (n = 6) was more specific in describing the thresholds of PD-L1 expression that they use as a guide to checkpoint inhibitor selection and also differentiated between the threshold via CPS scores vs PD-L1 expression on immune cells (Table 4).

Table 4. Examples of Statements on How Specific Thresholds Support a Particular Checkpoint Inhibitor
There's the CPS score, like a cumulative score of risk PS score and that's ***for every different immunotherapy medication, there's a different scoring****, I guess. If somebody is cisplatin ineligible, I can use the PD-L1; CPS score has to be over 10% for the pembro and I think CPS has to be over 5% for the Tecentriq.* [MD, hematology/oncology, community based, provider 13]
If you want to use Keytruda, either you—because what happens is in the prior authorization from the insurance company they're asking you – some insurance companies just ask you if it's PD-L1 negative or positive and that's easy, I just check positive, right? Some of them actually ask me, "Is the CPS greater than 10%?" ***I don't have the data and that can be posing a problem, so I may have to use Tecentriq****, even though I favor Keytruda more because the data, I think, is a bit better.* [MD, hematology/oncology, private practice, provider 21]
If a patient is not eligible for a platinum-based chemotherapy, definitely we send for PD-L1 and the combined positive proportion score or CPS on the specimen. ***I think the preferred agent is Keytruda; the reason is that it is based on the PD-L1 expression for pembrolizumab****. I guess you need to get the CPS score*. [MBBS, hematology/oncology, academic setting, provider 5]
Now with metastatic UC, ***with the approval of Keytruda, we're kind of forced to do CPS testing early on****. If the CPS expresses, we could potentially use PD-1 blockade early and that's why it's kind of imperative that we get CPS scores on patients with metastatic disease. I tend to use Keytruda more than any other agent such as, you know, the PD-L1 blocker.* [MD, hematology/oncology, community cancer center, provider 29]
We usually define PD-L1 high greater than 5%, *and these patients will receive pembrolizumab or nivolumab upfront.* [MD, hematology/oncology, community based, provider 16]
We ***routinely do, you know, at least PD-L1*** *on these patients. Within our practice, our go-to is definitely nivolumab. We have had a lot of success with the drug manufacturer, with financial assistance.* [NP, hematology/oncology, private practice, provider 22]

The focus on specific expression thresholds may reflect the fact that many payers require considerable precision in the documentation submitted as part of the prior authorization process. For instance, a private practice oncologist commented that even though she considers the OS data for pembrolizumab more favorable compared with atezolizumab (albeit in the second-line setting), she uses atezolizumab first line because there are logistical barriers that prevent her from using pembrolizumab. This participant is using Foundation One panel testing, which provides a PD-L1 expression percentage for pembrolizumab vs the CPS required by payers for authorization, and she finds that many payers will not accept a percentage in lieu of the CPS.

Participants may also be testing because they hear demand from patients for treatment with checkpoint inhibitors. For instance, two oncologists commented:

> *But the patient sometimes for the borderline, you know, could be carboplatin, could be immunotherapy, a taxane, not a cisplatin candidate.* ***The patient can now [be] causing a problem for us to make decisions*** *because if you ask the patient, the patient says, "I don't want a chemotherapy; just give some immunotherapy.* ***I heard a lot about it already on the Internet****—no chemotherapy."* [MD, hematology/oncology, private practice, provider 21]

> *If they're not eligible then, honestly we are rooting for either Keytruda or atezo, as immunotherapy is pretty well tolerated, to the most degree, as long as side effects are very much reviewed and detailed and monitored.* ***And the patients actually want to get immunotherapy.*** *The advertisements alone on TV has pushed the bar to the other end of patients being aggressive to ask for that therapy early on vs wanting the chemo side effects that potentially they could go through and they don't want to.* [NP, hematology/oncology, community based, provider 28]

However, not all participants view testing as a clinical requirement for immunotherapy initiation. For instance, some participants (n = 8) reported that they were not using PD-L1 testing on the grounds that they feel such testing has no validity in UC.

> *We don't do the PD-L1 because **it doesn't do good**.* [MD, hematology/oncology, community based, provider 4]

> *The fact of the matter is that **PD-1 levels, or PD-L1 levels, have no relevance right now** in dealing with [UC].* [MD, oncology, community based, provider 17]

Panel Testing

Almost one half (n = 12) of participants were using next-generation sequencing comprehensive genomic panel testing in addition to PD-1/PD-L1 expression, although this approach was not necessarily routine. Most state that they are using the FDA-approved Foundation One panel (*Foundation Medicine*, Cambridge, MA) to identify potential actionable mutations in patients with metastatic disease who are progressing on first-line therapy. One participant is also using liquid biopsy (Guardant 360) to look for rare mutations in patients who present with late metastases. The markers or mutations that this group identified as significant in UC, and that might be identified as part of a comprehensive genomic panel, include HER2-neu expression (n = 4), FGFR (n = 1), MSI (n = 2), TMB (n = 2), PI3 kinase/various RAS and RAF mutations (n = 1), mTOR (n = 1), and NTRK (n = 1).

Participants varied in how they appeared to use next-generation sequencing testing. Some reviewed genomic test results in the context of a multidisciplinary tumor board, as illustrated in the following quote:

> *For metastatic beyond first line, I usually send for genomic analysis on them, and **we have a genomic tumor board that we run in collaboration** with our neighboring academic cancer center and we discuss the results with them.* [MBBS, hematology/oncology, community based, provider 2]

Other participants were more equivocal about the role and utility of genomic testing. Although they were using genomic sequencing, as one participant noted, this "*gives us some information, but **that's usually not used to necessarily guide** sort of initial—or even I would say a second-line—treatment at this point*." [MD, hematology/oncology, private practice, provider 30]

These different perspectives on how panel testing is being used raise questions about how participants are interpreting and using the results of panel testing for clinical decision-making. Although it appears as though some participants are using the results of panel testing for clinical decision-making, they are also relying on the information contained in the genomic report. As new targeted therapies requiring additional biomarker testing are approved, such as *FGFR* alterations for erdafitinib, the importance of biomarker testing will increase.

Next-generation sequencing reports often contain volumes of unfamiliar information that clinicians are seldom skilled in interpreting and that require considerable and often dedicated effort to identify phase I or phase II trials that might match their patients' needs. Whereas other studies such as the ASCO Workforce Study show that younger clinicians are typically more abreast with molecular testing such as

next-generation sequencing than their older colleagues,[17] challenges undoubtedly remain in interpreting the results of panel sequencing for clinical decision-making and in matching patients to treatment options, including clinical trials (as also suggested in data from our study).[18] Our data underscore the importance of education to address these interpretative challenges.

Recommendation 2
Clinicians require guidance on how to identify scenarios in which PD-L1 status testing is appropriate in the first-line setting and how to select the appropriate PD-L1 test. Clinicians also need clarification on expression thresholds and their interpretation for clinical decision-making, as well as exposure to clinical decision resources (eg, multidisciplinary tumor boards and clinical pathways) that support clinical trial matching.

Practice Gap 3: Challenges in Selecting First-line Therapy

In contrast to experts who only consider ICIs as preferred options for patients who cannot tolerate cisplatin or carboplatin or for patients who may be able to tolerate carboplatin but reach the FDA-approved PD-L1 expression cutoff, many clinicians in this study view ICIs as preferred options for patients in the first-line setting. Clinicians are challenged to use these agents appropriately, with some attributing equivalence to these agents in the first-line setting based on second-line data. In addition, although clinicians use clinical criteria to select therapy, they struggle to differentiate who may be ineligible for treatment with cisplatin vs those who are ineligible for any platinum agent and have difficulty integrating these criteria in their decision-making alongside nonclinical criteria such as tolerability and patient preference. Few survey respondents were familiar with patient engagement as an intervention to integrate them as active participants in their own care, and clinicians likely need support to manage irAEs in ways that are consistent with current consensus-based recommendations.

Current First-line Therapy Recommendations
The recommended initial therapy for patients with metastatic UC is cisplatin-based chemotherapy. Current regimen options include DD-MVAC, gemcitabine plus cisplatin, and paclitaxel plus gemcitabine and cisplatin. Gemcitabine plus carboplatin provides an option for patients who are candidates for chemotherapy but are unable to receive cisplatin due to specific comorbidities. As mentioned previously, pembrolizumab and atezolizumab are options for patients who are ineligible for any platinum-based chemotherapy (cisplatin or carboplatin) or for those who are ineligible for treatment with cisplatin with PD-L1 expression reaching the FDA-approved PD-L1 expression cutoff.[19,20] Additional nonplatinum regimens include gemcitabine plus a taxane (paclitaxel or docetaxel) or single-agent taxanes, but experts generally reserve these additional chemotherapy regimens as salvage therapy for patients who progress on ICI therapy.

Clinical Criteria for Cisplatin-Based Chemotherapy

Current recommendations for determining ineligibility for cisplatin-based chemotherapy include impaired renal function, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, creatinine clearance < 60 mL/min, hearing loss 25 dB at 2 contiguous frequencies, grade ≥ 2 peripheral neuropathy, and New York Heart Association ≥ class III heart failure.[21] However, determining eligibility for carboplatin-based chemotherapy or other chemotherapy is still somewhat undefined.

Survey data suggest that a range of criteria are used by clinicians for distinguishing a patient who is chemotherapy ineligible vs a patient who is cisplatin ineligible, including ECOG PS, renal function, hearing loss, peripheral neuropathy, and heart failure. Survey data show the range of criteria that both US-based and ex-US–based clinicians are using to determine chemotherapy eligibility for their patients (Figure 3a, Figure 3b).

Figure 3a. Criteria for determining chemotherapy eligibility reported by US clinicians (n = 125).

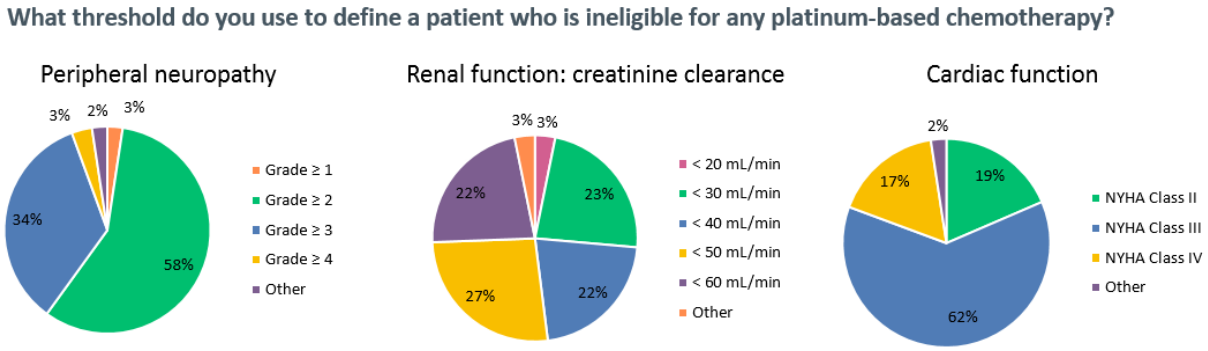
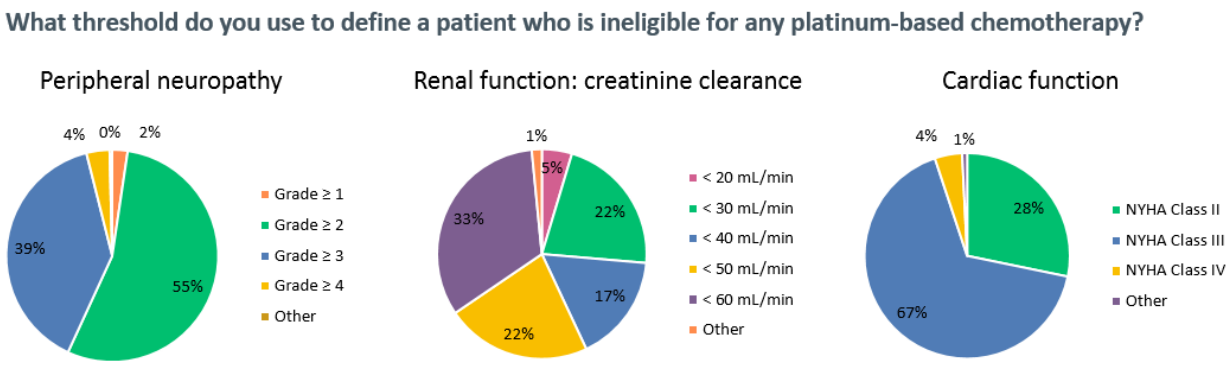


Figure 3b. Criteria for determining chemotherapy eligibility reported by ex-US clinicians (n = 255).



All but one participant (a urologist) identified most of these recommended clinical criteria as their primary considerations in determining patient eligibility for cisplatin-based chemotherapy. Performance status was mentioned most frequently as the key criterion.

> *It's renal function, hearing loss, peripheral neuropathy, prior treatment with cisplatin. Those are the big criteria.* [MD, hematology/oncology, academic setting, provider 7]

> *We definitely take into account performance status, support at home, renal function, comorbidities.* [NP, hematology/oncology, private practice, provider 22]

> *Usually, it's the performance status that makes me decide on the choice of treatment. Performance status and other comorbidities is a big deciding factor . . . kidney function, if they have hearing loss, if they have neuropathy.* [MBBS, hematology/oncology, community based, provider 2]

It's a host of factors, but their overall performance status, if they have a PS of 0 or 1, no severe hearing loss, no preexisting greater than grade 2 neuropathy, no decompensated heart failure, and their GFR is greater than 50 is my cutoff for cisplatin, based on either serum or 24-hour urine creatinine. [MD, oncology, academic setting, provider 25]

Other criteria mentioned by interview participants included tolerability, previous therapy in the neoadjuvant setting, reimbursement, compliance, and patient preference.

Tolerability

Participants identified tolerability as a particular challenge in determining patient eligibility for chemotherapy and in therapy selection. Although some participants (n = 6) commented that many patients tolerate cisplatin well, most participants described cisplatin as "harsh," "not an easy treatment to get," "not an easy regimen," and "very challenging." Therapy selection (between cisplatin and carboplatin) was described as a process of identifying "which toxicity can you live with" in which clinicians had to "kind of pick your poison." Participants described using a range of strategies to mitigate adverse events, including follow-up laboratory monitoring, prophylactic hydration, managing gastrointestinal adverse events, and antiemetic protocols. Physician participants noted the importance of the nursing team, and NP participants emphasized their role in adverse event management.

We have developed a social worker, nurse, front desk communication systems from the personal chart that patients have electronically for themselves, ways of communicating through that, to telephone, to text, to email, a variety of different ways of doing that. Lots of information. They all sign consents. They all get informed about their therapies and—but yeah, it requires close supervision. [MD, hematology/oncology, academic setting, provider 14]

Patient Preference

Few participants explicitly mentioned the importance of involving patients in discussions about treatment or of taking patient preference into consideration. For a small group of nonacademic clinicians (n = 5), patient preference was important to support shared decision-making.

*The expectation the patients are—what sort of things they are expecting from the treatment, the side effects and all, are kind of discussed and then a decision is—**a consensus decision is made**.* [MD, hematology/oncology, community cancer center, provider 26]

*It's just **based upon your agreement with the patient and yourself**. It's not a single factor; it's a combination of different things [that] come together in front of you. And also, I tell you the patient's perspective will play a big decision—make an impact on decision because they can tell you . . . they might be very young; they can tell you, "No chemo." You know, "If you give chemo, I will just go to another practice." So, that's something that happens all the time.* [MD, hematology/oncology, private practice, provider 21]

***What does the patient want?** That's probably the biggest thing that we often forget is, what do you want? So if an individual is 82 years old with bladder cancer and they have a grandson who is going to get bar mitzvahed in October or a niece that's going to get married in November, that's a different way than saying, "I just want to make it to . . ." or, "I just want to get through*

Passover or Easter," or, "I've got a graduation coming up." It's what they want. And I relate to this. I have learned in these 10 years that it takes a lot of time to talk to people and say, "What is it that you want, not what I want? I'm here to make your life, as long as you have it, better." [MD, oncology, community based, provider 17]

Indeed, few participants were familiar with patient engagement as an intervention to integrate patients as active participants in their own care. When we asked participants how they engaged patients in their care or if they had participated in any patient engagement training, typical responses included, "*I'm not entirely familiar with what patient engagement practices are*" or "*I don't know what that means*."

Preferred Chemotherapy Regimen

Survey data show that clinicians commonly consider cisplatin/gemcitabine an option for younger patients with locally advanced/metastatic UC and consider immunotherapy an option for patients with better performance status and PD-L1 positivity (Figure 4a, Figure 4b).

Figure 4a. US clinicians preferred options for newly diagnosed locally advanced/metastatic UC (n = 123).

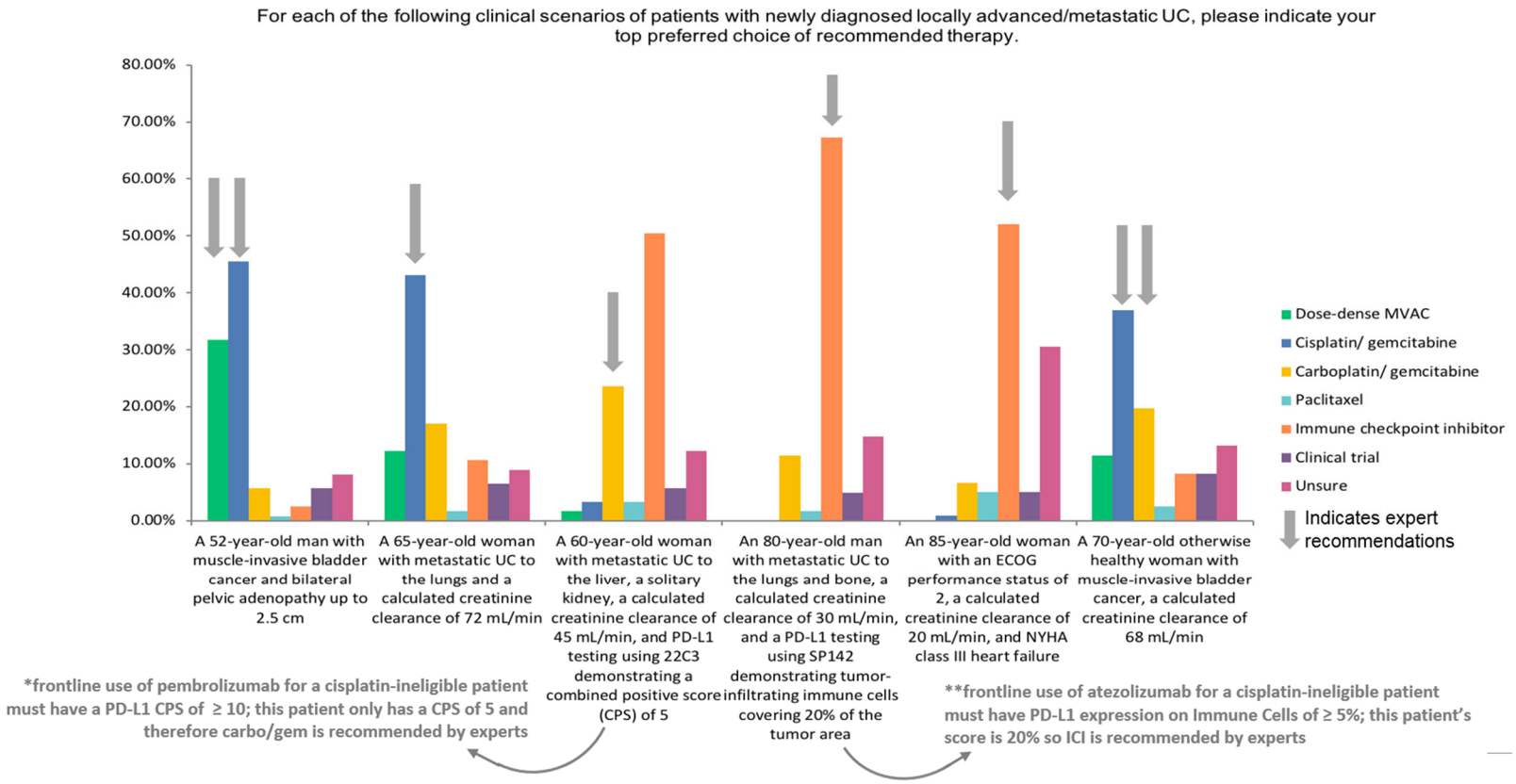
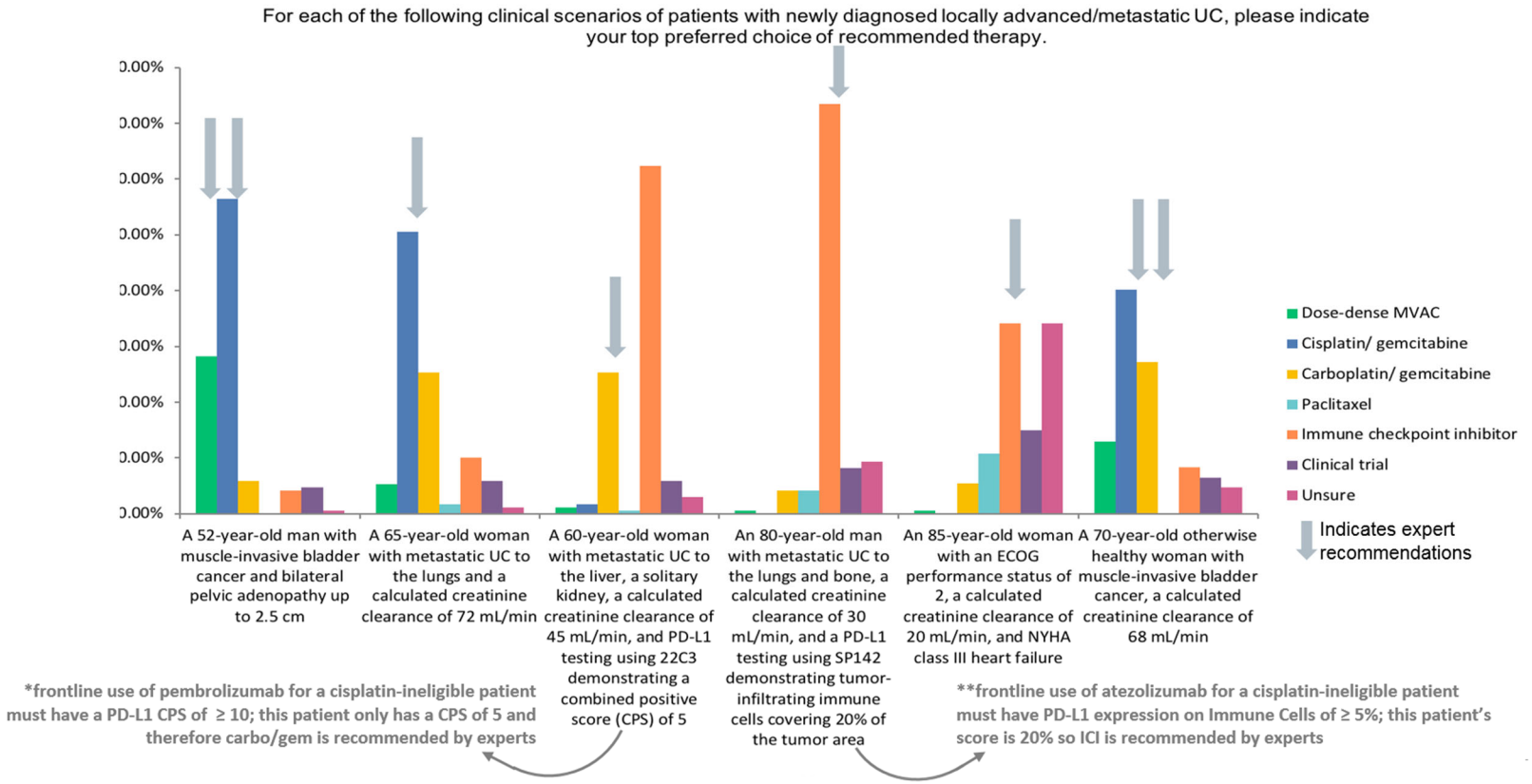


Figure 4b. Ex-US clinicians preferred options for newly diagnosed locally advanced/metastatic UC (n = 257).



The data presented in Figures 4a and 4b suggest that although clinicians generally select cisplatin-based treatment for eligible patients, there is confusion on optimal use of ICI for the third and fourth cases. In case 3, a cisplatin-ineligible patient with a CPS of 5 does not meet the FDA-approved cutoff for PD-L1 expression and, therefore, should receive carboplatin-based chemotherapy. In case 4, an older, cisplatin-ineligible patient with immune cells of 20% meets the FDA-approved cutoff for PD-L1 expression of ≥ 5% and should receive an ICI. Interview findings largely paralleled survey data concerning initial therapy and provide insight into how clinicians are thinking about the options available to the available to them.

Cisplatin-Eligible Patients: Standard of Care

Most interview participants described initiating therapy "immediately" after diagnosis of metastatic disease following imaging and laboratory studies, assessment of eligibility for cisplatin-chemotherapy, and molecular analysis (if being used). "Immediate" for this sample means 2-3 days or 2-3 weeks depending on the studies required, insurance preauthorization, and how involved patients are in discussions about treatment planning.

Most interview participants said they typically try to offer cisplatin-based chemotherapy to medically fit patients (as outlined above) and view cisplatin-gemcitabine as the standard of care. MVAC was also noted as a standard (if more toxic) first-line option as illustrated by the following quotes:

> *For platinum-eligible patients,* ***it's usually for somebody who's young and with good kidney function*** *and no neuropathy, I would probably go with a cisplatin-based regimen, maybe cis-gem.* [MD, hematology/oncology, community based, provider 13]

> *If you have* ***somebody who is very young who doesn't have any other risk factors****, ie, for some reason he's got bladder cancer—because it's a male-dominant disease, it's not a woman-dominant disease and he has no environmental exposures or mutational abnormalities, was not a smoker, then that person would probably get cisplatin but probably would be getting it under the care of somebody who is going to be doing some experimental therapy later down the line because he will be strong enough to get it.* [MD, oncology, community based, provider 17]

> *The first-line treatment,* ***as everybody does still****, is gemcitabine/cisplatin or MVAC.* [MD, urology, academic setting, provider 23]

One urologist was unfamiliar with any of the chemotherapy regimens in the first-line setting and viewed systemic treatment as the purview of oncologists.

Cisplatin-Ineligible Patients: Immunotherapy as Preferred Option

One third of interview participants identified carboplatin combined with gemcitabine as the main alternative for patients who are eligible for platinum-based chemotherapy but for whom cisplatin is not an option. Taxanes including paclitaxel and docetaxel were also mentioned as options.

Two thirds of the interview participants across specialties and practice settings view immunotherapy as a **game changer** for patients whom they consider ineligible for cisplatin-based chemotherapy (and in some cases for patients with locally advanced disease and locoregional positive nodes) and see

immunotherapy as a **preferred option** (Table 5). Many of these clinicians say they prefer to use an ICI rather than the cisplatin alternatives described above; most in this group are routinely testing for PD-L1 expression at diagnosis of metastatic disease, and as described above, most are using **any** positive PD-L1 expression as a rationale for using immunotherapy in the first-line setting.

Table 5. Examples of Statements Supporting Immunotherapy as a First-line Option
Patients who have other comorbidities, for example, kidney dysfunction that makes platinum difficult to use or they have baseline neuropathy and baseline, you know, performance status less than 1-2. So the ***immunotherapy agent that I would choose for these patients usually is pembrolizumab.*** [MBBS, hematology/oncology, community based, provider 2]
If their GFR is lower than 60, we cannot give cisplatin, even though carboplatin can be given, but that's not our advice. So, ***if a patient is cisplatin ineligible, then we go for PD-1, PD-L1 inhibitors.*** *That is the standard practice.* [MD, urology, academic setting, provider 23]
If they are not cisplatin eligible, I try to assess PD-L1 status and if they are PD-L1 positive, then I consider first-line anti–PD-1 therapy, and if they are cisplatin—and ***if they are PD-L1 negative, then I usually will do a chemotherapy doublet of carboplatin and gemcitabine****.* [MD, oncology, academic setting, provider 25]
Definitely patients who have significantly compromised renal function, for sure. I mean, absolutely. So . . . I mean, and ***those patients are going to go right to a checkpoint inhibitor.*** [MD, hematology/oncology, academic setting, provider 8]
You know, we're really not huge fans here of giving patients carboplatin vs platin ineligible. ***You know, so in those patients, we generally will do frontline immunotherapy*** *if they're cisplatin ineligible.* [NP, oncology, academic setting, provider 10]
If somebody is not chemo eligible, then ***I go to immunotherapy first line****.* [MD, hematology/oncology, community based, provider 13]
If they're PD-L1 high, then we need a checkpoint there. Patients who are ineligible and PD-L1 high—we usually define PD-L1 high greater than 5%, and ***these patients will receive pembrolizumab or nivolumab upfront.*** [MD, hematology/oncology, community based, provider 16]
When I see a patient with metastatic bladder and I feel like they cannot tolerate gem-cis, then by all means, I would do immunotherapy. And it would be helpful to have—to see if they're a PD-L1 expresser or not. But even ***regardless of that marker, if I don't think that they can handle the chemo, then I'll just go straight to immunotherapy****.* [MD, hematology/oncology, academic setting, provider 18]
Before approval of the checkpoint inhibitors, yes, we did used to prescribe gemcitabine, paclitaxel, or docetaxel as a choice. But now that we have the option of checkpoint inhibitors, ***we're definitely favoring that ahead of any other form of treatment.*** [MD, oncology, community based, provider 24]
Lately there's been a big shift—lately, meaning in the last, probably, year's time—a big shift towards primarily everybody choosing, give or take, with immunotherapy. [NP, hematology/oncology, community based, provider 28]

Some participants in private practice commented that although reimbursement barriers pose a disincentive to selecting immunotherapy in the frontline setting, they recognize its potential benefit for some cisplatin-ineligible patients and, on occasion, explore this option for patients for whom other options have failed.

> *I think* ***the real thing is to think about giving immunotherapy upfront,*** *and I know there are trials in progress because immune checkpoint inhibitors are now being studied and being moved up to first line. The problem in the community setting in doing that on a study is you're going to run into massive headaches with denials of reimbursement. These drugs are fantastically expensive, so* ***for a small practice like us, that's just a nightmare*** *. . . [but] you can make an argument in a patient who wasn't a candidate for first-line platinum-based therapy who had—you had tried to palliate with other measures—that you could give checkpoint inhibitor therapy.* [MD, oncology, private practice, provider 11]

Preferred Checkpoint Inhibitors in the First-line Setting

Pembrolizumab

One half of the interview participants across all practice settings cited pembrolizumab as the checkpoint inhibitor that they preferred in the first-line setting for patients who are ineligible for treatment with cisplatin. As noted above, most in this group are routinely testing for PD-L1 expression at diagnosis of metastatic disease and most are using **any** PD-L1 expression as a rationale for using immunotherapy in the first-line setting. The reasons that participants offered for using this agent include familiarity using it in other tumor types and the strength of clinical data compared with other agents, especially atezolizumab (Table 6).

Table 6. Stated Rationales for Pembrolizumab

Familiarity	Strength of Clinical Data
*I'm **already using Keytruda in different malignancies**. I'm more aware of it; it has more approvals. So it's easier for me, for my staff, to get that schedule. We know the supply, we know the cost of it, so we have more patients on Keytruda, so that's why I just continue in different type of cancers the same type of treatment*. [MD, hematology/oncology, private practice, provider 1]	*It has phase III survival data in the second-line setting and so based on that is why it has sort of been my preferred agent for use with—but in the first-line cis-ineligible, you know, we don't have survival data yet and so I think pembro or atezo are both, you know, potential options, but **because of the pembro second-line data, I use pembro more frequently.*** [MD, oncology, academic setting, provider 25]
*I like the pembro, the Keytruda, because **we have so much experience with that**. Atezo was the first drug approved for bladder, for UC. However, it's sort of gone behind now, so I rarely ever use atezo, to be honest with you. I prefer Keytruda, or pembrolizumab because I'm used to it. I use it in other therapies, like lung cancer first line and beyond, in MSI-high tumors and lymphoma, Hodgkin's, head and neck cancer. There's a lot of approvals for this drug and a lot of familiarity with the drug, basically*. [MD, hematology/oncology, community based, provider 9]	*I don't use Tecentriq so much; I think I prefer Keytruda. I like the data more so compared to the data for Tecentriq in first line. Maybe I heard some announcement that in first line maybe it didn't meet its marker, Tecentriq. Keytruda did. **I just heard about it; I don't know the complete data.** I read a headline that it missed its mark in the first line for Tecentriq. So **that sort of made me a little bit more ready for using Keytruda**.* [MD, hematology/oncology, private practice, provider 1]
	*Because of the survival data for pembrolizumab in the second line and the **lack of survival data for atezolizumab in the second line**, I've tended to mostly use pembrolizumab now in all lines of treatments if I'm using a checkpoint inhibitor because of that sort of failed data for atezolizumab in the second-line setting.* [MD, oncology, private practice, provider 27]

Atezolizumab

Almost one third (n = 9) of participants favored atezolizumab over other checkpoint inhibitors for patients who are ineligible for treatment with cisplatin in the first-line setting (Table 7). Although participants cited deeper experience with using this drug because it was first to come to market in UC, this view was often accompanied by a general sense that there was little difference between atezolizumab and pembrolizumab, or even though there was an OS difference between these agents, familiarity made atezolizumab easier to use.

Table 7. Familiarity as Rationale for Atezolizumab
I tend to use mostly Tecentriq. It was second to the market, ***so it was there pretty early****; it's been around for a while. Since then, Keytruda has come to the market with a very similar label, but I don't see any reason to deviate. It doesn't look any better; it certainly doesn't look any worse*. [MD, oncology, academic setting, provider 7]
I kind of like Tecentriq. I think that that was ***one of the first ones that came through the pipeline*** *and I kind of bow to the frontline agent, although we have plenty. Keytruda, you know, is all over the place with every kind of disease state known to man. So, yeah, I think they're all good, but I kind of fall a little bit on the Tecentriq side*. [MD, hematology/oncology, academic setting, provider 14]
In our practice, we have been kind of keeping it uniform, in the sense that we are using both of those agents and then—it's more of kind of like a comfort level and a comfort zone and like what's your gut feeling, okay, this will be better for—Keytruda vs Tecentriq. So, Tecentriq has more . . . ***we have more experience using that in the urothelial world, but of course more recent studies have shown about the no improvement in the OS with the Tecentriq*** *and all, but that was the first stage and really it was approved and all in the urothelial land, so we are using that*. [MD, hematology/oncology, community cancer center, provider 26]
I have, in urothelial cancer, been using Tecentriq, first choice, mostly ***because it was the first agent approved for urothelial cancer and I'm fairly familiar with it.*** *We are now beginning to use more also pembrolizumab. But my first choice is usually Tecentriq. First approved, good results, good clinical data, and familiarity with this agent*. [MD, oncology, community based, provider 24]
I think because ***for urothelial cancer, Tecentriq had an earlier indication*** *and is one of the few that has the frontline indication for those that are platinum intolerant or cannot—yeah, then I kind of go to that agent*. [MD, hematology/oncology, academic setting, provider 18]

Nivolumab

Four participants identified nivolumab as the checkpoint inhibitor that they would likely select for patients who are ineligible for platinum/cisplatin therapy in the first-line setting. Although nivolumab only has approval in second-line metastatic UC that has progressed during or after previous platinum-based chemotherapy, these clinicians are using nivolumab heavily in other tumor types and reported being able to access the drug through patient assistance programs. As a private practice NP explained:

> ***Within our practice, our go-to is definitely nivolumab.*** *We have had a lot of success with the drug manufacturer, with financial assistance. They have provided the drug for, oh my gosh, so many patients that either don't have insurance coverage or—they're really good at giving free drug to the patients. Yeah, it's not even necessarily financial. If a patient's off-label or doesn't meet the qualifications, you know, if we fill out certain paperwork requesting drug, they've actually given us some stuff off-label, which the physician I work with thinks that's really giving it for patients. So, therefore,* ***we've gotten so familiar with nivolumab [that] it's just kind of our go-to.*** [NP, hematology/oncology, private practice, provider 22]

Checkpoint Inhibitor Equivalence

Some participants (n = 5) expressed no preference for a particular checkpoint inhibitor or viewed them as largely interchangeable or equivalent; they routinely referenced clinical data that show similar response rates regardless of PD-L1 expression in the second-line setting (Table 8). These comments likely refer to the IMvigor211 trial in which 931 patients with metastatic UC and prior platinum-based chemotherapy treatment were randomly assigned to atezolizumab or chemotherapy; no significant improvement in OS was seen in the intervention arm among patients with ≥ 5% PD-L1 expression. The response rate was higher for patients with increased PD-L1 expression vs patients with < 5%, although this patient group also had a higher response to chemotherapy.

Table 8. Statements Suggesting Checkpoint Inhibitor Equivalence

Looking at the data of atezolizumab study, phase II and phase III, ***practically there was not any difference in between PD-L1 positive or PD-L1 negatives.*** *So I really think that, especially with the new trials now that are ongoing with chemotherapy together with PD-L1 or PD-1 inhibitors, actually* ***PD or PD-L1 positivity is not the main driver for us because in these patients, you practically don't have anything else.*** *You can't give them—according to less than, you know, 1% positivity, you can't give them anything. And the atezolizumab study, especially phase II, clearly showed that there was no difference in between PD-L1 positive and negative; they had a similar response rate.* [MD, urology, academic setting, provider 15]
We are now in a situation where we have 5 or 6 immune checkpoint inhibitors, all of them fit, and except for very isolated situations ***there's really not a lot of evidence that one is better than the other.*** *And so we're into "me too" land and I don't deviate because, you know, a drug rep tells me it's really cool to use their medication, you know.* [MD, oncology, academic setting, provider 7]
I am perfectly fine with pembrolizumab, durvalumab, atezolizumab, nivolumab. When you look at all the study results, ***practically it's the same success.*** [MD, urology, academic setting, provider 15]
I have no preferred agent. *I tend to use more pembrolizumab than nivo just because we tend to use in our office—pembro in the office for other indications like lung cancer with a lot of patients. So—but I don't have any strong feelings either way. They're—it's like, do you like Pepsi or do you like Coke. I mean, there's really no difference between them.* [MD, hematology/oncology, academic setting, provider 8]
I don't think there's any data that really says one is necessarily better than the other—there are lots of drugs out there. They're probably for the most part fairly similar. We tend to do probably a little bit more Tecentriq, I would say. That's because that was probably the first one approved. But, you know, I think we use a lot of Opdivo and other agents as well. Most of these have been tested mostly in patients who have progressed on platinum-based chemotherapy, but I think we sort of just extrapolate if they're not eligible for platinum, then they're going to get either PD-1 or PD-L1. And—and ***I don't think I can honestly tell you that one is better than the other.*** [MD, hematology/oncology, private practice, provider 30]

Managing Immune-Related Adverse Events

Interview participants viewed irAEs as challenging but mostly manageable. A majority described monitoring and management strategies that are consistent with recently published consensus-based recommendations including steroid therapy and patient education, although none of the interview participants mentioned collaboration with nononcology specialists, such as rheumatologists, endocrinologists, and dermatologists.[22,23]

> *Sometimes it is challenging to manage some of the side effects from treatment, but* ***it is a small percentage of people who have a very severe immune-related adverse event*** *to anti–PD-1 monotherapy, so there are a lot of patients who, thankfully, don't have to struggle*. [MD, oncology, academic setting, provider 25]

Unfortunately, ***the checkpoint inhibitors are not benign.*** *I mean, they do have their own problems . . .* ***we are getting a better handle on what to expect*** *and then when to expect—when do these things happen and all. Most of them are grade 1 and 2, which usually responds with steroids and all. I've hardly had any with a grade 4, though it's well described in the literature, but we don't have—I don't have any personal experience.* [MD, hematology/oncology, community cancer center, provider 26]

You've got to keep on top of them. The best prevention against side effects is foreknowledge and vigilance. ***Once you've committed to immunotherapy, you've got to monitor*** *for liver function grade and heart derangements, arthritis, skin, neurologic stuff, just good vigilance.* [MD, oncology, private practice, provider 10]

The side effects are different and that's what made it a little bit of a challenge *in the beginning, because you weren't dealing with the usual nausea, vomiting and, you know, some of the treatments that we would use to treat side effects actually turned off the effects of the immune checkpoint inhibitors. There's a million causes for the toxicities, like, you know, when they get colitis, lots of people get diarrhea. You don't want to turn off the immune checkpoint inhibitor if every patient has diarrhea because many of them, it's not the immune checkpoint inhibitor. So,* ***it took a little while getting used to, but it's not a big deal at this point.*** [MD, oncology, academic setting, provider 7]

We talk about immune-related side effects with the patient*, so colitis, skin rash are common side effects. Luckily, for my bladder cancer patients, I haven't encountered a lot of, you know, more than grade 1-2 toxicities and most of the time it is colitis or skin rash, but we do look for thyroiditis and hepatitis, nephritis. So we check all those periodically.* [MBBS, hematology/oncology, community based, provider 2]

Short-term steroids are the mainstay for managing grade 1/2 irAEs with, for most patients, continuation of checkpoint inhibitors. For grade 2-4 irAEs, therapy may be withheld and reinitiated once events have resolved. Some participants noted that at times, they did hold and restart treatment, although they did not specify the grade of irAE.

We definitely—we hold the therapy. ***That's probably our first thing is hold the therapy****, treat the issue that's going on, whether it's, you know, endocrinology or whatever needs to be attended to.* [NP, hematology/oncology, private practice, provider 22]

Most of the time, steroids are sufficient. Most of the time. So, I just start them on a high dose of steroids and then do a prolonged taper and ***then I do hold the drug till they're completely recovered*** *and then based on how much the side effect they had, the severity, might increase started later on.* [MD, hematology/oncology, private practice, provider 1]

It's a problem that you will have this, you know, side effects. From the other side, we will be able, 95% of this, very nicely to treat and ***we'll stop the therapy for a period of time*** *and then we'll see later on.* [MD, urology, academic setting, provider 15]

Provider 22 (first quote) said she and her colleagues initially hold therapy for any irAE. Provider 2 (second quote) appears to initiate steroids and simultaneously hold therapy without specifying irAE

grade. Provider 15 (third quote) did not mention steroids at all. These statements suggest that some clinicians might be managing irAEs by inappropriately holding therapy.

Recommendation 3
Clinicians need access to expert perspectives on the appropriate therapeutic strategy for patients in the first-line setting, including updates on ICI clinical data and the relevance of second-line data for first-line decision-making. Clinicians also need expert guidance on how to integrate clinical and nonclinical criteria into their decision-making, and exposure to strategies that support patient engagement and enable patients to actively participate in their own care. Finally, clinicians need direction on strategies to manage irAEs in ways that are consistent with current recommendations and that involve multidisciplinary discussions with nononcology specialists with expertise in the unique characteristics and management of irAEs.

Practice Gap 4: Challenges in Selecting Second-line Therapy

Overall, clinicians seemed to feel that they at least had some options for patients treated with chemotherapy vs checkpoint inhibitors in the first-line setting. However, there remains considerable variation in second-line therapy selection.

Current Treatment Recommendations
Five checkpoint inhibitors are approved for second-line therapy in UC (pembrolizumab and atezolizumab based on phase III data; nivolumab, avelumab, and durvalumab based on phase I and phase II data, phase I expansion cohort data, and phase I/II data, respectively). Second-line chemotherapy is considered an option for patients who are not candidates for immunotherapy and for those who progress during or after immunotherapy. In addition, on April 12, 2019, the FDA granted accelerated approval to erdafitinib for patients with locally advanced or metastatic UC with susceptible *FGFR3* or *FGFR2* genetic alterations after progression during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. This regulatory approval was based on Study BLC2001 in patients who had progressed on or after at least 1 previous chemotherapy and included patients who had progressed after treatment with an ICI.[6] Phase III trials are ongoing for each with the THOR trial investigating erdafitinib in the second-line setting (NCT03390504).

Interviews were completed prior to this approval.

Previously Treated With Chemotherapy

Current guidelines and many experts recommend ICI therapy as second-line postplatinum therapy. Similarly, survey data show that clinicians are most likely to opt for immunotherapy for patients previously treated with platinum-based chemotherapy, with pembrolizumab (45% of both US-based and ex-US–based clinicians) and atezolizumab being selected most often (22% and 20% of US-based and ex-US–based clinicians, respectively).

Interview data mirror this trend and provide insights into why clinicians may be choosing these options. Overall, clinicians seemed to feel that they at least had some options for patients who are progressing after first-line treatment with chemotherapy, vs patients who received ICIs in the first-line setting.

Straight to Immunotherapy

One half of the interview participants said that they would move straight to immunotherapy for patients previously treated with platinum-based chemotherapy as a matter of course ("several checkpoint inhibitors are approved for second-line therapy"; "it's a clear thing"). Table 9 summarizes participant rationales.

Table 9. Stated Rationales for Immunotherapy
I don't have to check PD-L1 status; ***I'm going to treat them automatically with Keytruda****.*
*All the drugs—atezo, nivo, pembro, durvalumab and avelumab—have all been approved for second line****. Pembro is a category one, as per NCCN****, so . . .* [MD, hematology/oncology, community based, provider 9]
If someone has truly become refractory or progressed through first line with platinum-based therapy and you've got to be careful about that because did they progress because they had a whole lot of side effects but they were sensitive or they were not treated because you couldn't treat intensively enough because of side effects, then ***I would go ahead and start treating them with one of the 5 checkpoint inhibitors*** *that are FDA-approved single agents and see how they do.* [MD, oncology, private practice, provider 11]
I'll go with the easier thing. If they've had frontline gem-cis and they did fairly well but then after a certain amount of treatment, we stopped it and then now they have progression and now we're on second line, then ***I probably would go straight to immunotherapy****. So that would be kind of the pathway*. [MD, hematology/oncology, academic setting, provider 18]

Rechallenge With Chemotherapy Followed by Immunotherapy

One third of participants said they would likely rechallenge a patient who progressed on chemotherapy with another chemotherapy agent (ie, from platinum to gemcitabine or vice versa) if their performance status was good or the progression-free interval was of sufficiently long duration before switching to ICIs (Table 10). This approach was described as a "general" or "standard" way of using chemotherapy across many tumor types but also reflected what participants viewed as the limited options available in the second-line setting.

Table 10. Stated Rationales for Rechallenging With Chemotherapy
*That depends what they got in first line and how they did. If, first line, they got a platinum-based regimen and they did exceedingly well, and by that I mean they had a prolonged progression-free interval where they didn't need any treatment****, I'm probably going to go right back there again****.* [MD, oncology, academic setting, provider 7]
*When you fail those [platinum, gemcitabine], in the metastatic setting there is taxanes and outside of that we really have very limited cytotoxic drugs. There is MVAC but not a huge number of patients can tolerate MVAC very well and probably—****I prefer using platinum and gemcitabine-based regimens****.* [MD, hematology/oncology, community cancer center, provider 29]
It's pretty standard. If a patient can tolerate traditional chemotherapy, cis/gem would be our first, but there are some patients who really don't want chemotherapy. You know, if that's the case, we would go to an immunotherapy. If those patients progressed, you know, ***we usually reapproach them about some type of low-dose chemotherapy that they can tolerate****. There are certain patients that can't have the immunotherapy, whether it be an advanced multiple sclerosis or something like that. So, it really depends on the patient, but basically it comes down to traditional chemo followed by immunotherapy. If we can't do that, it's the other way around, immunotherapy then and, hopefully, followed by some type of chemotherapy*. [NP, hematology/oncology, private practice, provider 22]

*If they were in shape to get chemo but it wasn't cisplatin then if I—**even if they expressed the appropriate level of PD-L1, I may still use—you would still use carboplatin and gemcitabine first** and then proceed to pembrolizumab*. [MD, oncology, private practice, provider 27]

*If a patient is very healthy, my second-line therapy will be MVAC (methotrexate, vinblastine, Adriamycin and cisplatin or carboplatin) and if I can't use the A, I'll use mitoxantrone. So it's an MVAC or an MVAC equivalent because it does have efficacy, it is a last stop, last chance, can I get him in remission or get him in a partial remission where I can do something else, like consolidating radiation therapy, or something of that nature. **Until the IOs show that they are equivalent or better than what we've got now and they haven't, we only have chemotherapy right now.** There is no evidence in giving immuno-oncologic agents in the second line has any difference—has any effectiveness.* [MD, oncology, community based, provider 17]

Previously Treated With Immunotherapy

Similar to expert recommendations at the time of the survey development, the survey data show that most clinicians in this study would opt for platinum-based chemotherapy (for eligible patients) or clinical trial for patients previously treated with immunotherapy (Figure 5a, Figure 5b). However, experts would now also consider erdafitinib for patients with susceptible *FGFR3* or *FGFR2* alterations after treatment with immunotherapy.

Figure 5a. US-based preferences for patients previously treated with immunotherapy (n = 121).

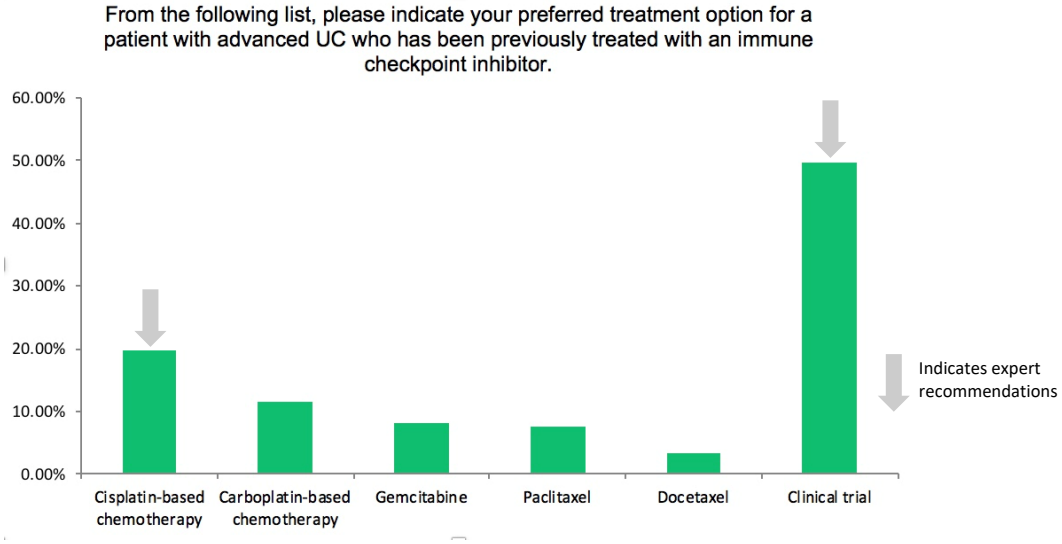
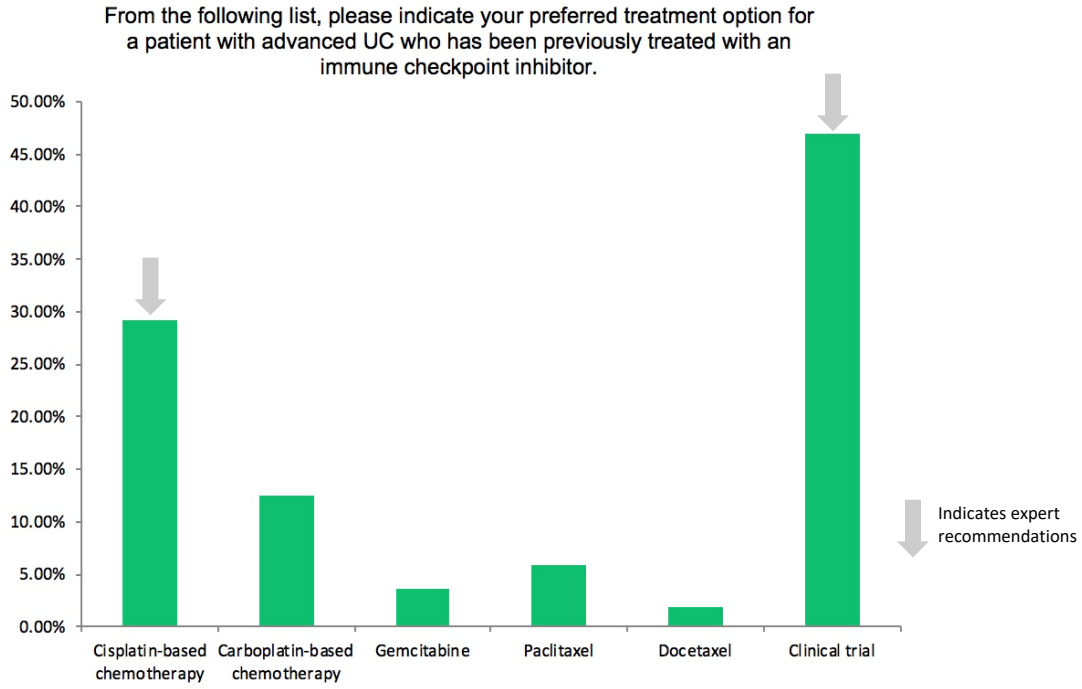


Figure 5b. Ex-US–based preferences for patients previously treated with immunotherapy (n = 254).



Interview findings were more varied than survey results. Participants acknowledged that treating patients after progression on immunotherapy was especially challenging.

Single-Agent Chemotherapy

Almost two thirds (60%) of interview participants said that they would use single-agent chemotherapy in the event of progression on immunotherapy. For some participants, the absence of an available clinical trial is a deciding factor in offering single-agent chemotherapy (typically gemcitabine if not previously offered) and leads to a feeling of "*being stuck with monotherapy*." In addition to gemcitabine, paclitaxel, docetaxel, nab-paclitaxel, and pemetrexed were all mentioned as potential options. Selection of the agent is, for the most part, based on performance status, previous therapy in the neoadjuvant setting, and—to some extent—hope (Table 11).

Table 11. Stated Rationales for Chemotherapy Agents in Second-line Setting
It is more challenging if the patient starts off at the checkpoint inhibitor because—and then progresses, because then if the rationale is to—if initially was not to have a platinum-based therapy because the patient was not eligible, ***it becomes more challenging in the second-line setting.*** [MBBS, hematology/oncology, academic setting, provider 5]
If they have already received a checkpoint inhibitor in the frontline and then they have progressed, then again, ***in some cases, I have used chemotherapy again; that's usually what I go.*** *And usually I go with agents like Paxil and gemcitabine, if they can handle that, or agents like single-agent gemcitabine, or Abraxane.* [MD, community cancer center, hematology/oncology, provider 26]
If the patient had immunotherapy first, they come to second line, depending on the patient, if the patient's clearly not a chemo candidate or combination chemo, first example, the patient might have a poor performance status, ***you either use chemo, like single agent such as gemcitabine as monotherapy or use Alimta even.*** *And if*

your patient's in good shape, you can use the combination carboplatin/gemcitabine. Or if your patient is really, really bad, you can send them to hospice. [MD, hematology/oncology, private practice, provider 21]
If they have received immune therapy in first line, then ***my subsequent line of treatment is possibly like single-agent gemcitabine****. Hardly I use a double-agent carbo. So mostly I fall back on gemcitabine. Now if they had already seen gemcitabine maybe in the neoadjuvant setting, then I might do any other type—either paclitaxel or docetaxel, even Abraxane.* [MD, hematology/oncology, private practice, provider 1]
Not much options left because chemo is not going to work in the second line; you already used the better option of immunotherapy. So—and there is no data to use sequential immunotherapy, so ***maybe we sometimes use single-agent Gemzar, which is like not that effective****, so really you don't have many options*. [MD, hematology/oncology, community based, provider 4]
If they got checkpoint inhibitor first line, then they're probably going to get chemo and if they're still up for chemo, then they may—they may not be a candidate for chemo; they may be more of a candidate for hospice. ***But if they're going to get chemo, the likelihood is they once again probably cannot tolerate platinum and they may get single-agent therapy****. So that's the approach. I mean, the second-line therapy is basically determined by what they got in first line.* ***B****ut they're probably not going to get a platinum. Unless they're candidates for platinum and if they have improved performance status or they're better off, they may get carbo/gemcitabine*. [MD, hematology/oncology, academic setting, provider 8]
If you've used immunotherapy first line then basically—and you're cisplatin ineligible, then ***there are single-agent therapies, like Abraxane, Taxol or docetaxel, gemcitabine, or trimetrexate that can be used.*** *I like the gem by itself.* [MD, hematology/oncology, community based, provider 9]
At that point, honestly, more the patient's range of side effects and trying to choose a chemotherapy that's less likely to exacerbate those comorbid symptoms and something that's not going to make the patient feel worse at that point, ***with the hope that there might be some benefit.*** [MD, oncology, community based, provider 19]

Other Options

The remaining one third of interview participants described 3 additional options they would consider for patients who progressed on immunotherapy:

1. Use an alternative agent off-label based on results from genomic-based testing.
2. Use doublet vs single-agent chemotherapy (eg, carboplatin or gemcitabine and paclitaxel).
3. Switch checkpoint inhibitor. Although there is no evidence to support this strategy, 3 participants said they would switch from a PD-1 to a PD-L1 or vice versa, as illustrated in the following quote:

> *We have a PD-1 and we have a PD-L1. Tecentriq is a PD-L1 and Opdivo and Keytruda are PD-1s, so if you had a PD-L1 and they progressed and it was well tolerated, I would try a PD-1 . . . If their TMB is high and had no toxicities or manageable toxicities with the prior therapy, that would be a very reasonable way to go.* ***You might try another PD-L1 after Tecentriq and it's progressed, to see if maybe that PD-L1 is a little different.*** [MD, hematology/oncology, academic setting, provider 14]

Previously Treated With Both Chemotherapy and Immunotherapy: Dealer's Choice

Survey results showed that a majority of clinicians (55.62%) prefer a clinical trial for patients who have progressed on both previous chemotherapy and immunotherapy. Interview data affirmed the importance of clinical trials and/or novel agents as a potential option for approximately one third of participants in the third-line setting, but the reality of practice for most clinicians was that such trials were not readily available. Most clinicians engaged in thought experiments as they described the various

modalities they might consider for patients whose disease progressed after both chemotherapy and immunotherapy, which included reverting to single-agent chemotherapy, trying combination approaches (eg, radiation and chemotherapy; chemotherapy and immunotherapy), or basing treatment on findings from genomic analysis. Several interview participants referred to this scenario as a "dealer's choice."

> ***You could anecdotally say, "Okay, well this, they progressed on pembrolizumab; let's try ipilimumab or durvalumab****, maybe there's a little bit of a better response rate. I mean* ***you could tweak it that way but there's not a lot of data to go on*** *but people do that in the community. And if that's failed, certainly there'd be molecular profiling, like we talked about, where you felt like unlikely they're going to respond to any other second-line agent.* ***You could go to third-line agent, you could try a taxane*** *but at that point I'd be thinking about molecular profiling or* ***referring to a clinical trial.*** [MD, oncology, private practice, provider 11]

> *Well,* ***the question is whether there's a clinical trial that they may be able to access****. The other possibility is that, hopefully, immunotherapy and chemotherapy together may work.* ***You go back to chemotherapy, possibly****, or we talked about the scenarios with checkpoint inhibitors and PD-L1. Then the other question is, what other novel therapies are out there? So, either those novel therapies are approved, like, let's say, venetoclax (BCL2 inhibitor) or some other drug that's approved for another indication.* [MD, hematology/oncology, academic setting, provider 14]

> *Yeah,* ***it just depends on what we find [on genomic analysis].*** *It could be an off-label use of an already approved drug in a different cancer or it could be a clinical trial. It just depends on what are the genomic findings.* [MBBS, hematology/oncology, community based, provider 2]

> *The third line, which is pretty much* ***you're okay to pick whatever these patients have not been exposed to; mostly commonly it would be Alimta (pemetrexed) or a taxane.*** *So, coming to fourth line, especially in fourth line, I do molecular sequencing; sometimes I find a different target. For example, I told you about HER2, which is supported by the literature; it's not something I come up with. After that, it's a clinical trial—just* ***you are not ready to give up****. So, of course, we talk about FGFR, you can send to clinical trial for FGFR inhibitors.* [MD, hematology/oncology, private practice, provider 21]

Overall, these participants gave the impression of being assiduous in their pursuit of additional treatment for patients who progressed after first-line and second-line systemic therapy, looking for and testing out potential options, and not being ready to abandon the potential for treatment. Yet the provisional nature of the therapeutic options available to them was evident as they used words such as "might," "possibly," "could," and "hope" to describe their potential options.

> *You've got somebody now with advanced metastatic disease. The question is,* ***how are you going to control that disease because they're incurable****? And you know, depending on the burden of disease they have, the number of sites involved of their disease, they're symptomatic and so the question is, what do I do now? And then these patients, you know,* ***you've got to try to control their disease and they're sick; their performance status is really deteriorating*** *with each passing cycle of therapy or course of therapy. So, the bottom line is you do the chemotherapy, then they progress, then* ***you hope that the immunotherapy will work and you kind of try to be upbeat and optimistic about that.*** *And then, after that, you know the chances*

of something working are very low. You're re-going to an immunotherapy or re-going to an alternate chemotherapy, and you look into hospice. At that point in time, really the next juncture point is to hospice unless you, you know, ***float out something from next-generation sequencing that might be a possible biomarker-driven actionable therapy****. But other than that, you're really—these patients are sick. These are some of the most sick patients that we have.* [MD, hematology/oncology, academic setting, provider 14]

Clinicians also emphasized the challenges of communicating with patients about their options, who might not be aware of how sick they are.

And we basically are kind of doing the palliative care talk, hospice talk, or quality of life talk inclusive of all of that. And I laugh because ***it's very hard because there's so many patients that they're just like, "Why didn't it work on me?"*** *And the role for surgery, they're always asking, "Why can't I get surgery? Why can't they just take it out?" And we're like, "It's spread to other areas, so we can't take out all those parts. You need all those parts, even though they're affected*." [NP, hematology/oncology, community based, provider 28]

I don't think that we really know what to do with those patients. *I mean, they're just—A, they're small number of patients overall in this disease site, and then when they've progressed after 2 therapies,* ***it becomes dealer's choice****. There's no standard of care here*. [MD, hematology/oncology, private practice, provider 30]

Recommendation 4
Clinicians need access to expert perspectives on the appropriate selection of therapies for patients in the second-line setting and beyond, including guidance on optimal sequencing, and how best to access ongoing clinical trials.

Practice Gap 5: Deficits in Clinical Trial Referral

Although clinicians emphasize the value of clinical trials in the management of patients with UC, many work in practice settings that have limited access to clinical trials via tertiary centers or professional networks.

Although almost 50% of participants from the online survey indicated that clinical trial would be the preference for patients who have progressed on ICI therapy, responses from both surveys showed that **only 20% of clinicians always talk with patients about clinical trials.** A majority discuss clinical trials much less frequently. Only 16% (n = 5) of interview participants, who all worked in settings that either ran or had access to clinical trials, said that they will evaluate patients at every line of treatment for clinical trial eligibility.

I will almost at every line of treatment be searching for a clinical trial option at one of the tertiary centers in our area. Currently, we're not running any ourselves. [MD, oncology, private practice, provider 27]

Survey data show that following progression after treatment with immunotherapy or after treatment with both chemotherapy and immunotherapy, approximately one half of clinicians prefer to refer patients for clinical trials (50% US and 55% ex-US). Consistent with these results, many interview participants also reported that they would prefer to refer eligible patients for clinical trial consideration following progression after treatment with immunotherapy or after treatment with both chemotherapy and immunotherapy. Many participants worked in settings that had access to clinical trials via tertiary centers or professional networks.

> *I usually just look for a clinical trial and I—we have a lady who is the coordinator and I will see if there's a clinical trial. We also have [a trial coordinator] in uro-oncology at the bigger hospital and I refer to him and see if he has anything that the patient can use. So he will try and get us, you know . . .* [MD, hematology/oncology, community based, provider 9]

> *Tertiary care centers that are close to us, within an hour drive, still have some trials and sometimes we refer patients down there to get on trials.* [MD, hematology/oncology, community based, provider 13]

> *We have access to some trials at my institution. I'm not a bladder cancer expert, so my first steps when I hear about patients or when I see patients for relapse disease is to see what trial they are eligible for.* [MD, hematology/oncology, community cancer center, provider 29]

> *[After relapse], if I felt like there was like a clinical trial and the patient was a candidate, that would be really actually my number 1 preference because other than that, you're just kind of stuck with single-agent chemotherapy, which is not a homerun by any means.* [MD, hematology/oncology, academic setting, provider 18]

However, the potential for referral was tempered for some participants, regardless of practice setting, by a perception that the availability of clinical trials was skewed toward metropolitan centers that are hard for many patients to access. Patient willingness to be considered for trial and easy-to-access information were also considered barriers to clinical trial referral.

> ***At this age of the patient, there are many of them, they would say, "Come on, you want me now to start some trial, be part of something?*** *I don't know what the arm I will be. I don't know, if it doesn't respond," but most of these trials, you know, they can do the crossover, so that's not a problem. But, old people, it's very difficult to tell them, "Let's go try something."* [MD, urology, academic setting, provider 15]

> *I'm familiar with the trials that are ongoing in my neighboring academic center, but* ***most of my patients do not want to travel beyond their state*** *to participate in a clinical trial and that's why enrollment is low.* [MBBS, hematology/oncology, community based, provider 2]

> *I tend to work with a lot of patients who are really more of a lower socio-economic status and so* ***it's hard for patients to cart back and forth to a larger center*** *and that takes time and some money to get back and forth and stuff like that but—and a lot of coordination and help and assistance from other people but yeah, I would absolutely consider a good performance status patient for a trial.* [MD, oncology, community based, provider 19]

*There's so much information out there because there's so many clinical trials out there—and look, ClinicalTrials.gov, actually, I think is the best sources because there's, I think, like a regulatory obligation for companies to post all their trials, so it's complete, which is important. But **not always the easiest thing to navigate**.* [MD, hematology/oncology, academic setting, provider 8]

Recommendation 5
Clinicians need resources that increase their awareness of and ability to access available clinical trials as part of their routine approach to managing patients with UC and that they can provide to patients to help them navigate the challenges associated with participating on clinical trials.

Practice Gap 6: Low Familiarity With and Limited Access to Novel Agents

Clinicians are largely unfamiliar with recently approved and emerging novel agents and depth of awareness varies among those who say they are aware of novel agents. Clinicians familiar with novel agents are more likely to be involved in or have access to clinical trials.

Survey respondents were somewhat able to match novel agents to their targets (Figure 6a, Figure 6b). Although clinicians are largely familiar with the mechanisms of action for agents approved for use in UC (atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab) or in other tumor types (lapatinib, ramucirumab), they are unfamiliar with the mechanisms of action for the recently approved (erdafitinib) and other investigational agents, including 2 that are in advanced stages of testing for UC (enfortumab vedotin and sacituzumab govitecan).

Figure 6a. US clinicians' ability to match agents to targets (n = 132).

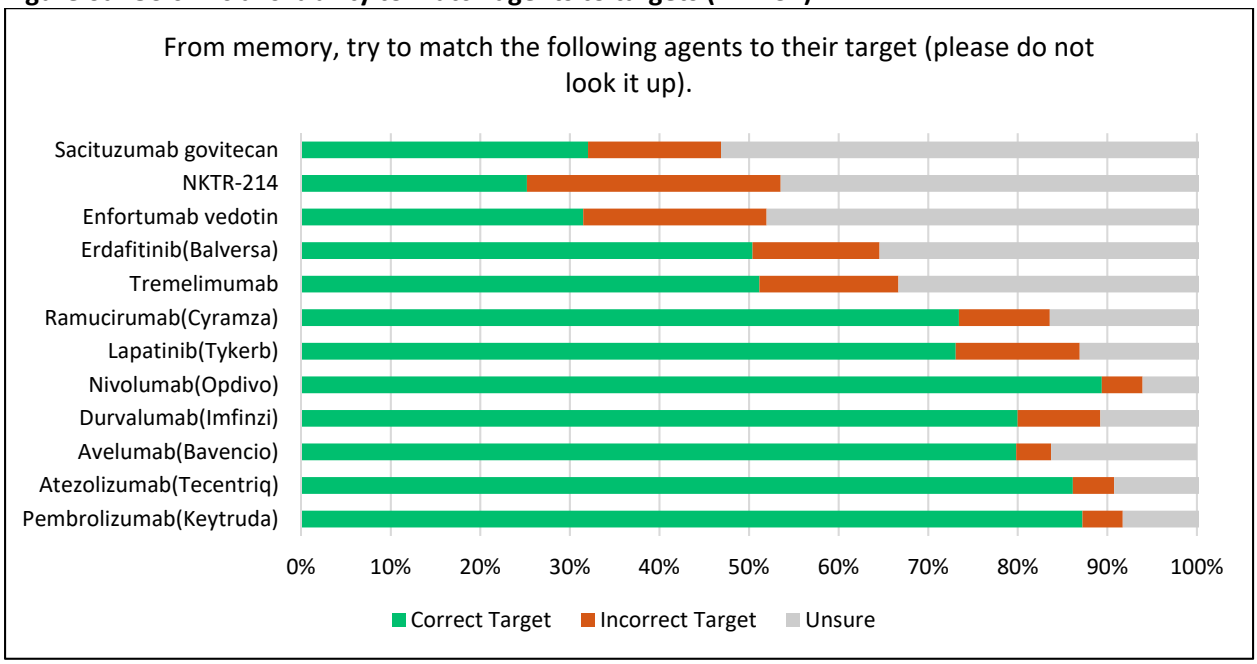
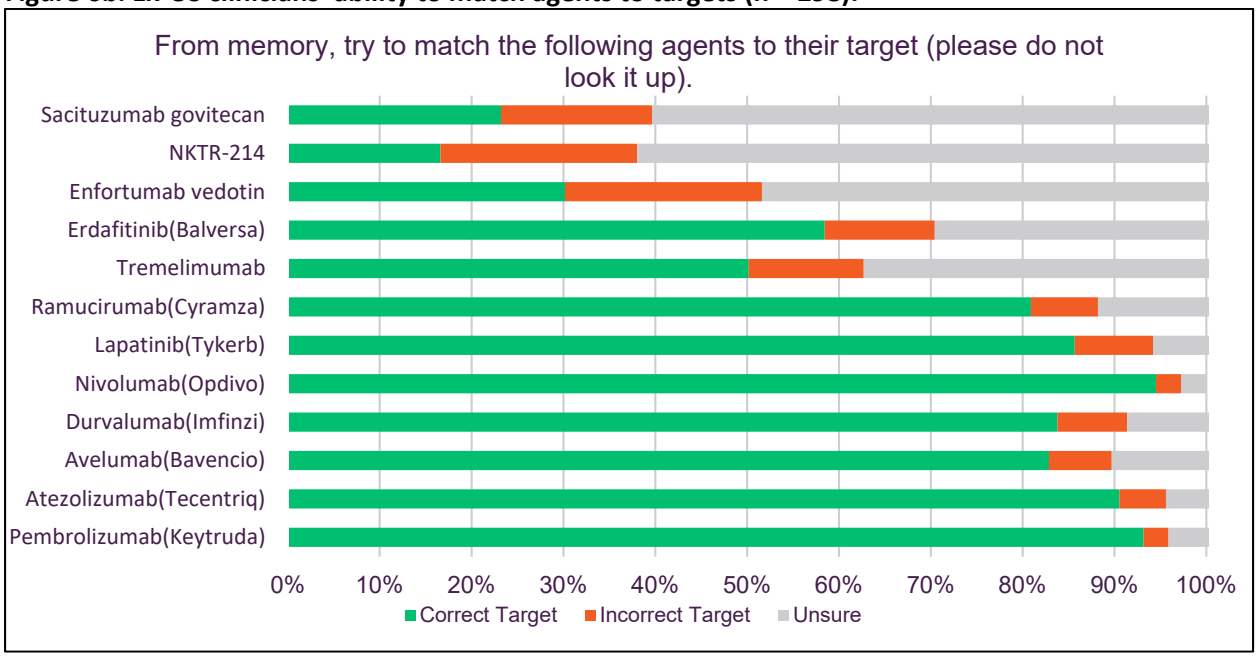


Figure 6b. Ex-US clinicians' ability to match agents to targets (n = 298).



Regardless of being able to identify mechanisms of action, approximately 20% of survey respondents (27% of US respondents and 16% of ex-US respondents) were able to identify enfortumab vedotin and approximately 50% of survey respondents (51% of US respondents and 45% of ex-US respondents) were able to identify the FGFR inhibitor erdafitinib as a therapies with either a Breakthrough Therapy designation or a recent FDA accelerated approval in UC (Figure 7a, Figure 7b).

Figure 7a. US clinicians' ability to identify therapies with either Breakthrough Therapy designation or recent FDA approval in UC (n = 136).

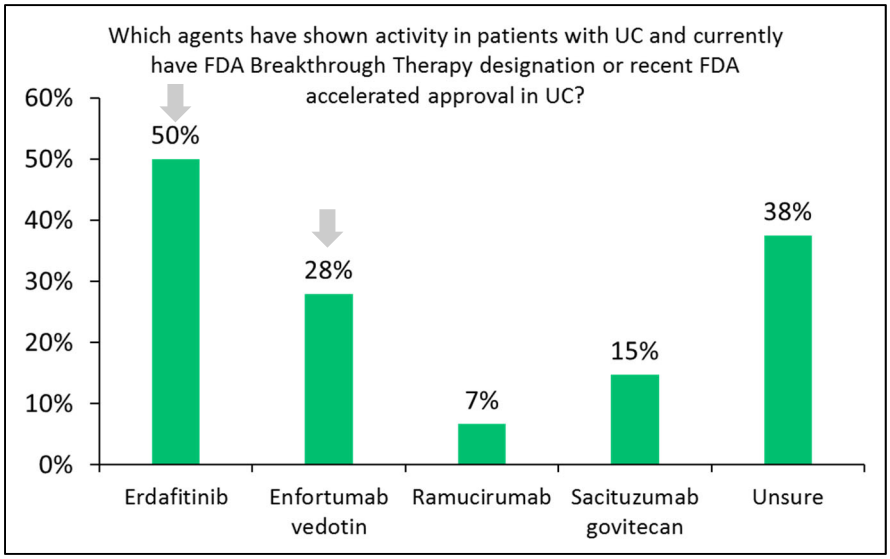
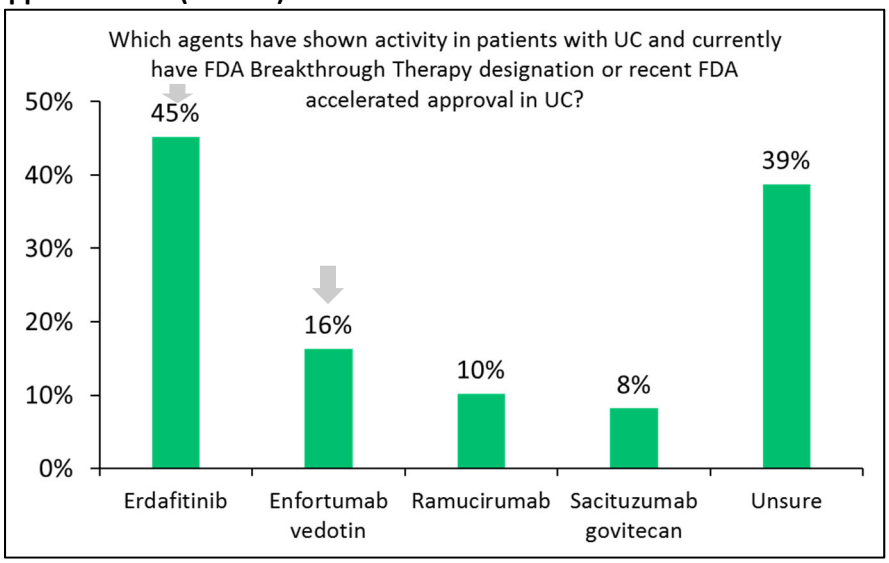


Figure 7b. Ex-US clinicians' ability to identify therapies with either Breakthrough Therapy designation or recent FDA approval in UC (n = 294).



When asked if they felt sufficiently familiar with the agent erdafitinib to use it in their clinical practice, approxiamtely 40% of US clinicians said that they were whereas only 20% of ex-US clincians agreed. Similarly, when asked if they felt sufficiently familiar with the agent enfortumab vedotin to use it in their clinical practice if approved, approximately 40% of US clinicians said that they were whereas only 10% of ex-US clincians agreed. Of interest, few clinicians view inclusion in guidelines without regulatory approval as a sufficient justification to incorporate a new agent into their practice, particularly for clinicians practicing outside the United States (Figure 8a, Figure 8b).

Figure 8a. US clinicians' comfort in using new/novel agents (n = 131).

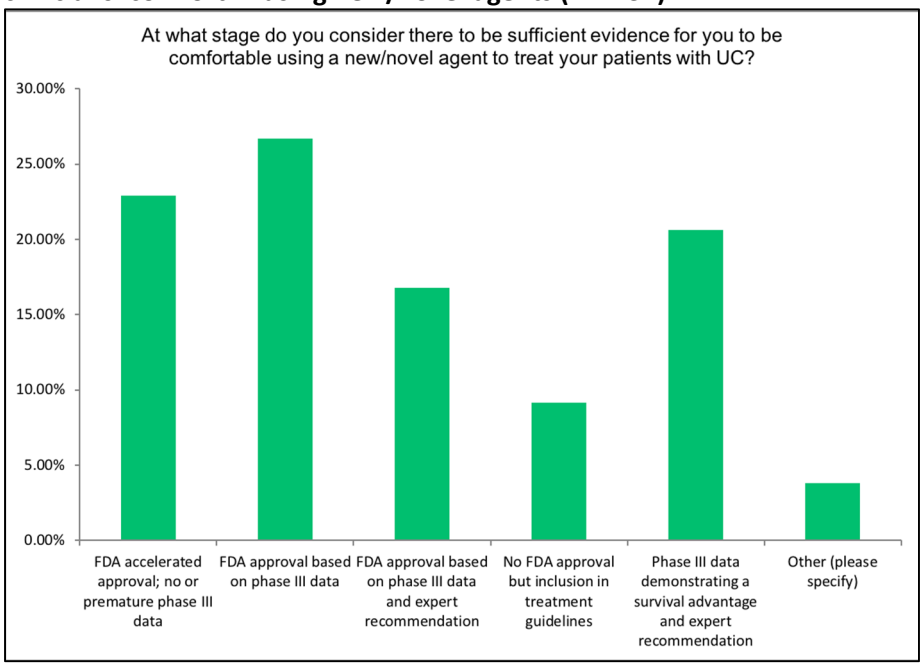
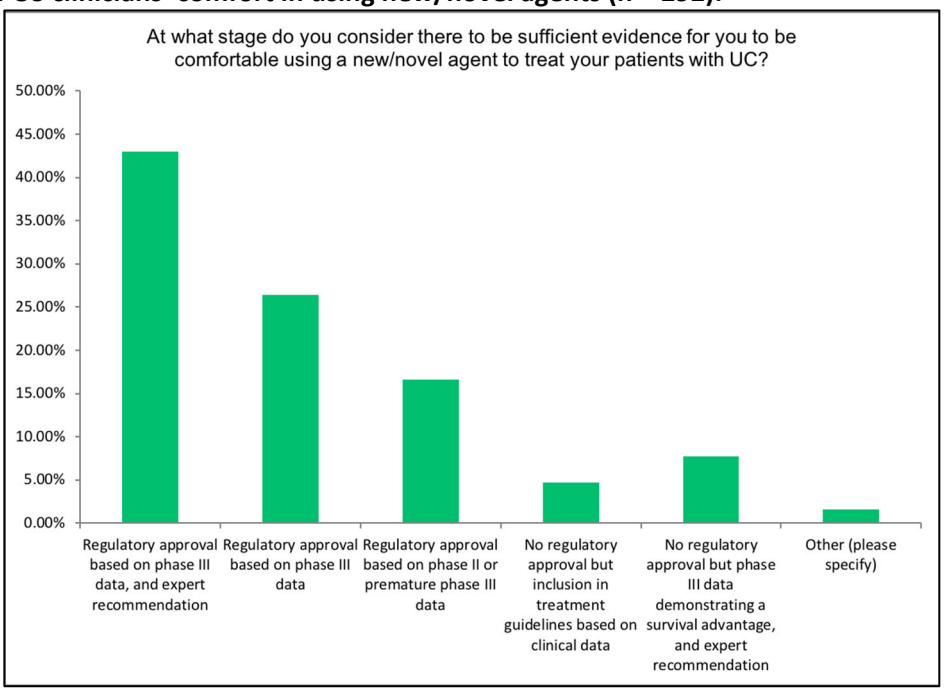


Figure 8b. Ex-US clinicians' comfort in using new/novel agents (n = 292).



A similar pattern of low familiarity with novel agents emerged in interviews.

Some Familiarity With Investigational/Novel Agents

Less than one half of interview participants (n = 14) said that they were familiar with novel agents, but depth of awareness varied. The participants (n = 7) who were able to discuss novel agents with some agility, including mechanisms of action, were involved in or had access to clinical trials.

> *I'm certainly familiar. So, enfortumab vedotin, sacituzumab govitecan,* ***we have that phase II clinical trial open here,*** *and we also have a study of rucaparib, which is a PARP inhibitor in metastatic use.* [MD, oncology, academic setting, provider 25]

> *The FGFR is the most prominent one, again, because of course there is about 20% to 30% of the urothelial cancers [that] may have the FGFR gene and so that is the most popular one. And* ***there are agents like erdafitinib and, again, which has been in clinical trials, and an oral agent, which has shown quite some activity for patients who have already received chemotherapy and checkpoint inhibitors and all****, so I think that is one novel agent which , I think, may have some future going forward.* [MD, hematology/oncology, community cancer center, provider 26]

> *The most—so* ***the most one I'm familiar with is—I think—I believe it's called erdafitinib, FGFR receptor inhibitor and 50% or urothelial cancers could express this FGFR*** *and if they do have it, they have a 40% to 60% response rate with this medication. I know it's going through the FDA for approval; I know it's not approved yet and I've emailed my pathologist 3 or 4 times in the past 6 months to ask them if this testing is commercially available so I can test some of my patients for it, but so far the answer has been no, it's not available yet, so . . .* [MD, hematology/oncology, community based, provider 13]

Low Familiarity With Investigational/Novel Agents

However, the remaining participants who said that they were familiar with investigational agents were seldom able to name any specific agents or identify their mechanisms of action.

> *I'm fairly familiar. I haven't seen anything that's a game-changer yet. I wouldn't be able to use them in the clinic. I'd have to refer. There is a company, they—I don't know where they are with this, a company called Agenus and* ***it was just a number, it was like C6110 autologous tumor vaccine,*** *and they had a number of checkpoint inhibitors and I forget the numbers*. [MD, oncology, private practice, provider 11]

> *I mean, targeted therapy is the new way to go if the patient actually has some targets available to reach out to.* ***I think there have been some studies FGFR mutations****. There's also the mTOR pathway, PI3K, but I don't know the drugs associated with that but I know that there are some studies that are in the works or they are doing.* [NP, hematology/oncology, community based, provider 28]

> *I think there are some trials with the HER2 inhibitors, lapatinib, I think is being explored with other checkpoint inhibitors, and* ***again there's this other antibody–drug conjugate;*** *I think there are different targets with the antibody–drug conjugates that are, I think, being explored and in various phases of trials, so that's fine.* [MBBS, hematology/oncology, academic setting, provider 5]

The remaining participants were unfamiliar with novel agents and many were quite candid about their lack of knowledge in this area.

> *A little bit familiar, so* ***not that aware of what exactly is in the pipeline at this point****, so—I mean I think there's some data looking into fibroblast growth factor receptor, things of that nature.* ***I don't know the exact agents that are kind of being designed to target those*** *and I think they're pretty far away from market at this point but yeah . . . I know that [FGFR is] a significant pathway in a number of urothelial carcinomas but beyond that****, I don't know the exact pathway****, no.* [MD, oncology, community based, provider 19]

> ***I think the "something vedotin"*** *sounds slightly familiar.* [NP, hematology/oncology, community cancer center, provider 20]

> *No,* ***I do not have any information.*** *[about investigational or novel agents].* [MD, hematology/oncology, private practice, provider 1]

> ***I'm not aware*** *of any new novel agents.* [MD, hematology/oncology, community based, provider 4]

> ***I don't pay any attention to phase I and phase II trials****. You can give me a name, maybe I've heard of it, but for the most part, I don't pay any attention to it. When I'm looking at early-phase data, because I'm older, I'll read the article because I know the guy. But if I don't know the guy, I don't read about it . . . and the mode of action? I don't know how my car works; do you think I know how these molecular things work? I don't know how they work.* [MD, oncology, community based, provider 17]

Overall, these clinicians are preoccupied with managing patients across tumor types and unable to keep up to date with agents specifically targeting UC.

Scenarios for Using New Agents

Only participants with some familiarity of investigational agents were able to describe scenarios in which they would consider using them. These were typically clinicians working in academic settings or in community settings with hospital affiliation. For the most part, clinical trials were the main setting in which they had acquired familiarity with novel agents and in which they felt it would appropriate to use novel agents.

> ***We are either part of the trial or we were part of the trial at some point****, so I think we had an open trial for the FG inhibitor trial, so we had some patients who did go on the trial and I think we had patients who of course were outside for, I think, some of the antibody–drug conjugate trial—we did not have that open—so I think there are some patients in the clinic who receive that or are receiving that in an outside facility also.* [MBBS, hematology/oncology, academic setting, provider 5]

> *It* ***depends on the phase of the trial****. In some of our phase I trials, no, we're not comfortable but, you know, you're giving patients , you know, an option of something that may help them****. In our phase II and our phase III trials, we've already seen the drugs, you know, work in other patients so we're more comfortable in that setting.*** *We rely a lot on our research team and also of the PI, having weekly phone calls with the actual sponsor of kind of knowing what side effects that's happened at other institutions with patients.* [NP, oncology, academic setting, provider 10]

> *I'm in the community situation so* ***I'd have to refer them to a clinical trials center*** *that is doing clinical trials. I keep abreast of the trials and say, "Look, I've got a guy who's not responding to second-line therapy. I hear you're opening this trial; I think he'd be a good candidate. Can you see him, get him in the clinic?"* [MD, oncology, private practice, provider 11]

> ***If we have a clinical trial.*** *I mean, we are a small practice so our clinical trial is not robust, so we do have a few trials but usually in the more common cancers, the breasts, the colons, the lungs. We have a few of those but we don't have any UC trials going on here. But, as I said, tertiary care centers that are close to us, within an hour drive, still have some trials and sometimes we refer patients down there to get on trials.* [MD, hematology/oncology, community based, provider 13]

Some participants said they would consider using investigational agents with "robust" or "solid" phase II data if they could acquire access to the drug with manufacturer support.

> ***I wouldn't do it earlier [than failure of both chemotherapy and immunotherapy] until there was data supporting that it was better than immunotherapy alone****. It would have to—and it would have to show the rigors of being better than single-agent alone. If it was a drug that has never been approved and is awaiting FDA approval for another indication,* ***I can't use it unless there's a clinical trial or expanded access to use it in these patients****, so the patient has to register in the trial. Would I use it? Absolutely, because the second-line therapy and third-line*

therapy after failure of chemotherapy and immunotherapy is dismal. [MD, hematology/oncology, academic setting, provider 14]

Usually in the context of a clinical trial, so whatever the trial sort of specifies. ***I haven't been doing any off-label therapy for any of these medications****, so that's the major barrier.* [MD, oncology, academic setting, provider 25]

As with survey results, most participants do not consider newer agents until they receive FDA approval.

Usually, in my practice, ***I will not use drugs which are being testing for at least 3 months after they are used in a clinical trial by somebody else.*** *I won't rush and use it myself immediately after the drug is advertised or approved by the FDA.* [MD, urology, academic setting, provider 23]

I do not have the time to follow phase I and phase II data. I kind of plug in when the registration trial, whether it's a phase II or phase III trial, is in progress. In other words, ***when this is going to become some sort of on-label therapy****, it's going to become commercially available and I'm going to need to know about it to make the right decisions,* ***that's when I—for this particular set of tumors—that's when I plug in.*** [MD, oncology, academic setting, provider 7]

Recommendation 6
Enable clinicians to recognize the mechanisms of action of approved or investigational therapies used for patients with UC. Such recognition could help to build comfort and confidence in using agents earlier in the approval trajectory.

Barriers to Optimizing Treatment in Metastatic UC

The top 3 challenges that interview participants identified as barriers to optimal treatment and patient management were the lack of effective and durable treatment options, the overall poor performance status of patients with UC, and low treatment tolerability (Figure 9).

Figure 9. Frequency of reported challenges in interviews.

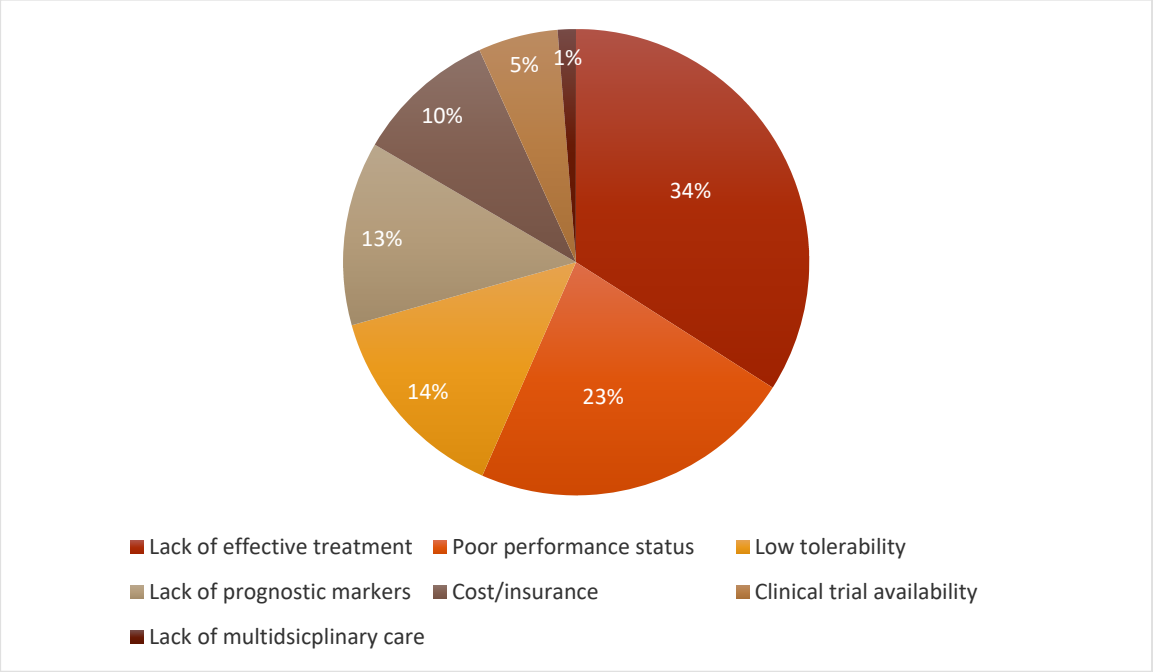


Table 12 summarizes how participants described these challenges.

Table 12. Descriptions of Barriers to Optimal Treatment

Lack of Effective Therapies
Participants consistently commented that they are doing the best they can to manage patients with metastatic UC with agents that are not especially active in this disease. ▪ *It's not like there's a great approach and a bad approach; there's a bunch of slightly differing, mediocre treatments.* [MD, oncology, academic setting, provider 7] ▪ *It's a tough disease to treat and you don't have many options except for the chemo cisplatin based or immunotherapy for cisplatin ineligible*. [MD, hematology/oncology, community based, provider 4] ▪ *We need improvement in a chemotherapy regimen that is really going to be of significant meaning.* [MD, urology, academic setting, provider 6] ▪ *There's no good agents . . . once you're beyond immunotherapy, not much options if patient doesn't have a good performance status and enrollment into a clinical trial is a problem due to difficulty with access.* [MBBS, hematology/oncology, community based, provider 2] ▪ *The challenge is to develop more tolerable treatment and more effective treatment, I think, more beneficial treatment that which can cause or can have a good response rate in overall survival. What we have so far is a sort of intervention.* [MD, hematology/oncology, private practice, provider 1]
Prognostic Markers and Patient Response to Therapy
Participants identified the absence of prognostic markers in general a key challenge. ▪ *We don't know if they're going to respond and each patient responds differently to different situations, so that's a challenge.* [MD, urology, academic setting, provider 23]

- *I think we need to be careful about how we choose our patients for treatment and we have to be careful working with the disease where patients are not expected to do very well long term.* [MD, hematology/oncology, community cancer center, provider 29]

Although participants welcomed the addition of checkpoint inhibitors to the treatment armamentarium and viewed checkpoint inhibitors as easier to manage than chemotherapy with the potential for durable responses, only a small proportion of patients respond to immunotherapy. Yet patients rarely understand this. Participants commented that patients are influenced by direct-to-consumer advertising on checkpoint inhibitors in lung cancer and assume "these drugs are curing everybody." This dynamic makes it challenging to set realistic expectations for patients.

- *The challenge is trying to tell them not every patient will have a positive effect from immunotherapy.* [NP, hematology/oncology, community based, provider 28]

Tolerability

Participants (especially NPs) commented on the toxicities associated with chemotherapy and the challenges associated of finding a therapy that patients will be able to tolerate.

- *Patients need more education on side effects or possible side effects with immunotherapy.* [NP, hematology/oncology, community cancer center, provider 20]
- *It's hard to manage side effects . . . certain patients may have a degree of nausea that's—you know, certain patients are tougher than others*. [NP, hematology/oncology, private practice, provider 22]
- *One of the big challenges, I would say, are getting patients to go through frontline chemotherapy or to go through chemotherapy because the cisplatin is not easy for people who are elderly to tolerate.* [MD, hematology/oncology, academic setting, provider 18]
- *The challenges are avoiding depression, fatigue, and nutrition.* [NP, hematology/oncology, community based, provider 28]

Performance Status

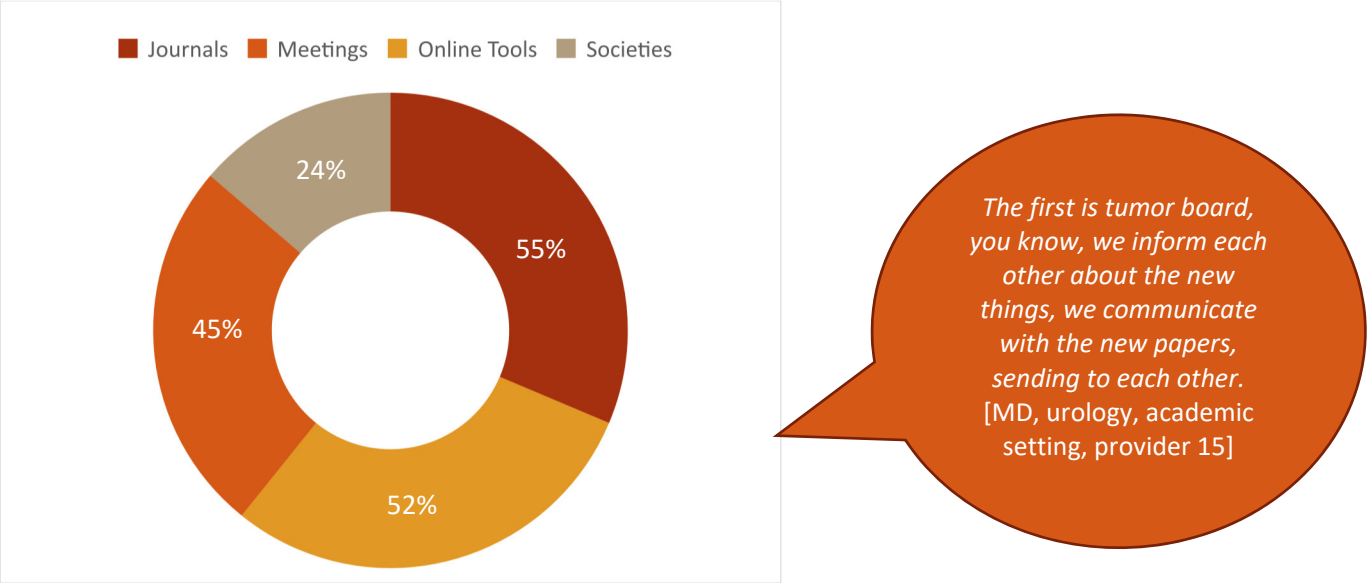
Participants consistently commented that patient age, performance status, smoking, obesity, and other comorbidities limit the efficacy of any treatment in the first-line setting. Time and again participants emphasized that patients with UC are "older" and "very sick" patients for whom it was challenging to select appropriate therapy. At second line, especially, there was a feeling among participants that patients lose the confidence and strength necessary to submit to further treatment.

- *Mentally, they're not very strong; they even, you know, give up. They don't have sort of the expectation or issues they had with you anymore because it's the same thing; they did everything you told them and they still progress, but that's sort of the natural course of disease, but they lose confidence in you, you can tell.* [MD, hematology/oncology, private practice, provider 21]
- *It's a, you know, older population with a lot of comorbidities is the first. The second is that, as a consequence of their disease, a lot of them have a lot of urologic complications with percutaneous nephrectomy tubes and recurrent infections or have had a cystectomy previously and so there are certain sort of postsurgical complications that they may have that makes treatment challenging. And then third, just the disease itself and a lot of them, because they're not cisplatin eligible, there aren't many lines of therapy for us to really try before you've sort of exhausted your options.* [MD, oncology, academic setting, provider 25]

Preferred Educational Sources and Formats

Interview participants did not feel that their practice settings were taking organizational steps to address any of the challenges they identified. Rather, they felt compelled to stay as up to date as possible with new data and clinical trial opportunities via a range of sources (Figure 10).

Figure 10. Preferred education sources reported in interviews.



Participants also noted email pulses concerning new agents and clinical trial data and pharmaceutical representatives as sources of information. The *Journal of Clinical Oncology* and *The New England Journal of Medicine* were the most frequently cited journals (although very few participants described particular journals); many also cited ASCO Post and Oncology Nurse Advisor as reliable sources of information. ASCO and ASH were cited as the most frequently attended meetings; ASCO Urology, ASCO GU, and AUA were also cited. Participants also emphasized the importance of tumor boards and conversations with peers as important spaces for discussions about patient management as well as sources of information about new agents and clinical trial data. UpToDate, Clinical Care Options, Research to Practice, OncLive, and Medscape were cited as frequently accessed online resources. Alarmingly, Google was also cited as a "first stop" by a couple of participants.

Time was a major factor in participant selection of educational format. Participants valued the accessibility and immediacy of online tools, information, and resources, but they preferred being able to go to meetings, interact with colleagues, discuss cases, and learn from subject matter experts. Podcasts and Webcasts were valued for their easily digestible formats "with a human touch."

> *I really like podcasts, so I think they're a great way to get access to super experts in the field. I'm a generalist so I see a lot of other stuff, other than just urothelial carcinoma and each subfield of oncology is so complex. I think those are a tremendous way to get kind of good, solid access to super experts, basically, in an educational kind of way.* [MD, oncology, community based, provider 19]

Most participants identified case-based, expert-led discussions as the pre-eminent learning scenario.

Recommendation 7
Interview participants identified the following resources that would support their efforts to address their paramount challenges:

- Dedicated UC patient education materials
- Easier access to molecular testing
- Guidance on how to integrate molecular profiling to identify patients for targeted therapies
- Patient assistance/access to foundation monies
- Communication tools to help with risk discussions in the context of treatment planning
- Curated clinical trial information resources
- Guidelines on sequencing
- Multidisciplinary conferences and CME

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Treatment Patterns for Metastatic HR-Positive Breast Cancer: Comparing Expert and Community Practice

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San Antonio Breast Cancer Symposium
December 10-14, 2019

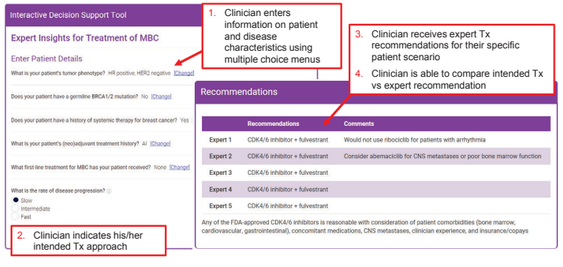
Background

- Endocrine therapy and the recent approvals of CDK4/6 inhibitors have dramatically improved outcomes for patients with hormone receptor–positive (HR+) metastatic breast cancer (MBC)
- To provide healthcare providers (HCPs) with expert guidance on choice of Tx for specific MBC case scenarios, we implemented an **interactive online decision support tool**, in which HCPs input specific patient and tumor characteristics along with their planned Tx approach and then receive expert recommendations
- Here we analyze data from the 2 most recent iterations of this tool capturing Tx trends in the care of HR+ MBC since 2016, variance in HCP planned Tx vs expert recommendations during this period, and the impact of this online tool on practice

Study Components

- Online decision support tools published in Dec 2016 and Sept 2018
  - Faculty (2016): Kimberly Blackwell, MD; Sara Hurvitz, MD; Mohammad Jahanzeb, MD; Kathy D. Miller, MD; and Nicholas Robert, MD
  - Faculty (2018): Sara Hurvitz, MD; Mohammad Jahanzeb, MD; Kathy D. Miller, MD; Ruth O'Regan, MD; and Tiffany Traina, MD
- Each tool included **≈ 500 different MBC case variations** based on specific patientt/tumor characteristics, including disease phenotype, previous therapy, visceral crisis, rate of disease progression, and *BRCA1/2* mutation status (2018 tool)
- HCPs are prompted to enter patient/tumor characteristics and indicate their intended clinical approach
  - Recommendations from the 5 experts are then displayed
  - Users are then asked whether the experts' recommendation confirmed or changed their intended clinical approach
- **The tool is online at: clinicaloptions.com/MBCtool**

MBC Tool Screenshots (2018 Examples)



Results

Tool Participant Demographics

- 2016: 793 HCPs entered 1470 different patient cases between December 2016 and October 2017
- 2018: 692 HCPs entered 1367 different patient cases between September 2018 and October 2019

Year	Region, %	Physicians, %	Hem/Onc or Onc Specialty, %
2016 (n = 793)	US: 18 EUR: 36 E Asia: 9 RoW: 37	81	79
2018 (n = 692)	US: 25 EUR: 23 E Asia: 8 RoW: 44	76	87

Patient Cases Entered by Year and Phenotype

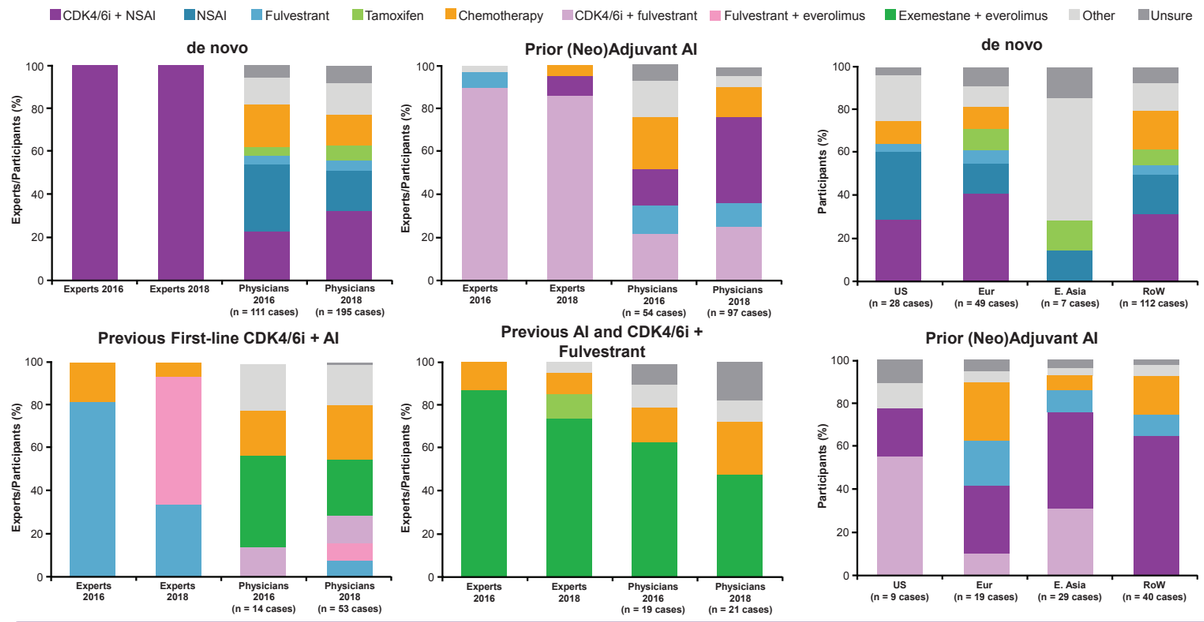
Year	HR+/HER2-, %	HR-/HER2+, %	HR+/HER2+, %	HR-/HER2-, %
2016 (n = 1470)	54	10	14	21
2018 (n = 1367)	54	11	13	22

Clinical Impact of 2018 Tool

Intended Use of Tool (n = 282 cases)	Cases, %
Hypothetical patient case (educational resource)	41
Actual patient case (virtual consultation)	58
Self-Identified Impact (n = 308 cases)	**Cases, %**
Changed treatment plan to match experts ***(among those who initially differed from experts)***	55
Confirmed treatment plan	45

All subsequent presented data analyses limited to cases entered by physicians with an indicated specialty of oncology or hematology/oncology.

Treatment Choice for HR+/HER2- MBC (No Visceral Crisis)



Treatment Choice by Region in 2018 Tool for HR+/HER2- MBC (No Visceral Crisis)

Conclusions

- Substantial variation was evident between oncologists' planned Tx and expert recommendations for HR+/HER2- MBC in different settings
  - In 2016 and 2018, experts mainly recommended a CDK4/6i + NSAI regimen in the de novo setting in contrast to oncologists, though there was a modest increase from 23% to 32% in this recommendation among oncologists over time
  - In 2016 and 2018, experts largely recommended a CDK4/6i + fulvestrant regimen after (neo)adjuvant AI therapy in contrast to ≈ 22%/25% of oncologists
  - Following a first-line CDK4/6i + NSAI regimen, experts primarily recommended fulvestrant ± exemestane which were rarely chosen by oncologists
- Expert recommendations from the 2018 tool led to a change in intended treatment for 55% of cases where HCPs initially chose a Tx plan different from the expert panel indicating this tool can have an impact on patient care
- These findings underscore a need for continuing education as new treatments become available for patients

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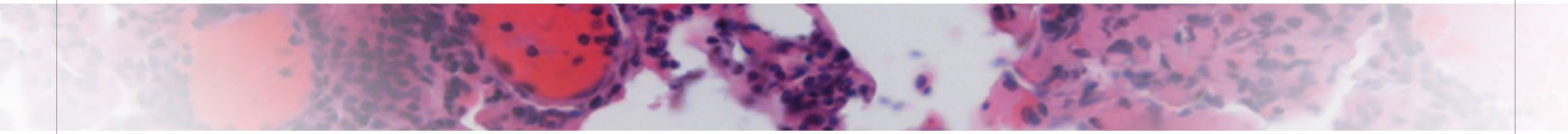

Analysis of Practice Patterns Among Experts and Community Healthcare Providers for the Treatment of Acute Myeloid Leukemia

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Disclosures

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Off Label Disclosure: In this report of results from a treatment decision support tool for AML, some of the drugs selected by the experts are recommended in off-label applications (eg, IDH2 inhibitor enasidenib in frontline AML therapy).

Background

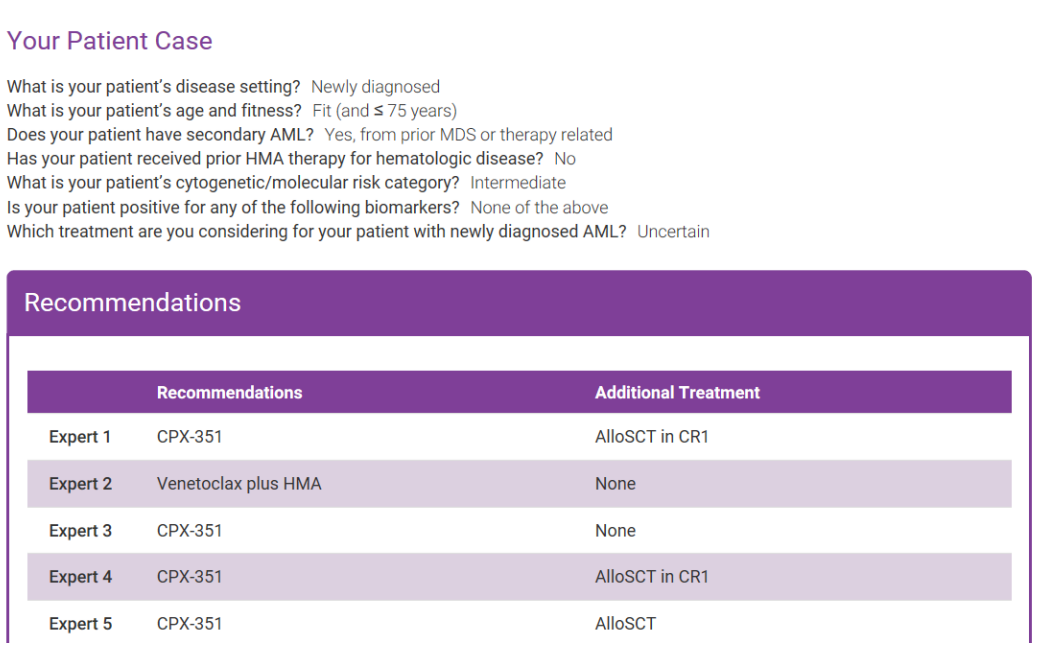
- Acute myeloid leukemia (AML) treatment options have expanded rapidly, with 9 new agents FDA approved since 2017
- This has provided many new strategies for both patients and healthcare providers (HCPs), but it has also introduced new challenges in treatment selection
- To address this, CCO developed an online AML decision support tool designed to provide HCPs with expert guidance for optimal individualized patient treatment selection

AML Tool Development

- 5 experts identified a simplified set of key patient/disease characteristics on which they based treatment recommendations for patients with AML
  - **Experts**: Jeffrey E. Lancet, MD; Farhad Ravandi, MD; B. Douglas Smith, MD; Roland P. Walter, MD, PhD; Eunice S. Wang, MD
  - **Patient/disease characteristics**: disease setting, age and fitness, secondary AML, previous HMAs, cytogenetic/ molecular risk factors, biomarkers, others
- The expert panel provided treatment recommendations in February 2019 for 330 distinct case scenarios in ND (n = 150) and R/R (n = 180) AML

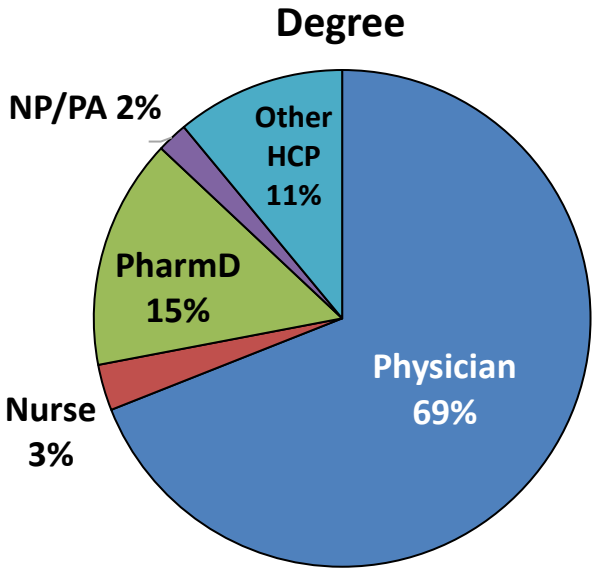
Using the AML Tool

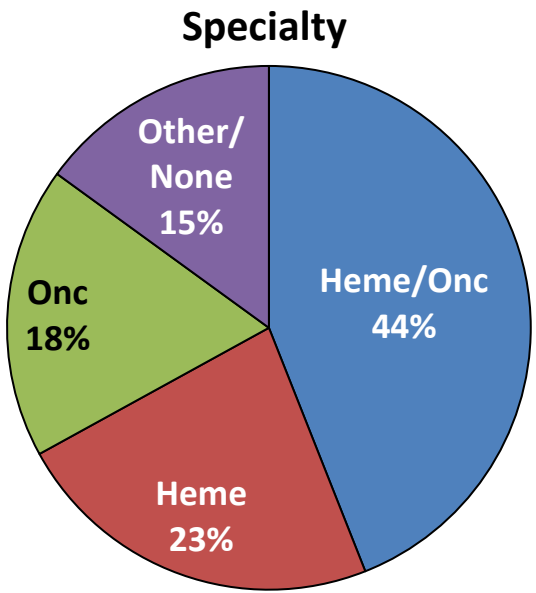
- HCPs are prompted to select defined patient/ disease characteristics from drop-down menus and then are asked to provide their Tx choice
- They then receive expert recommendations for that case scenario

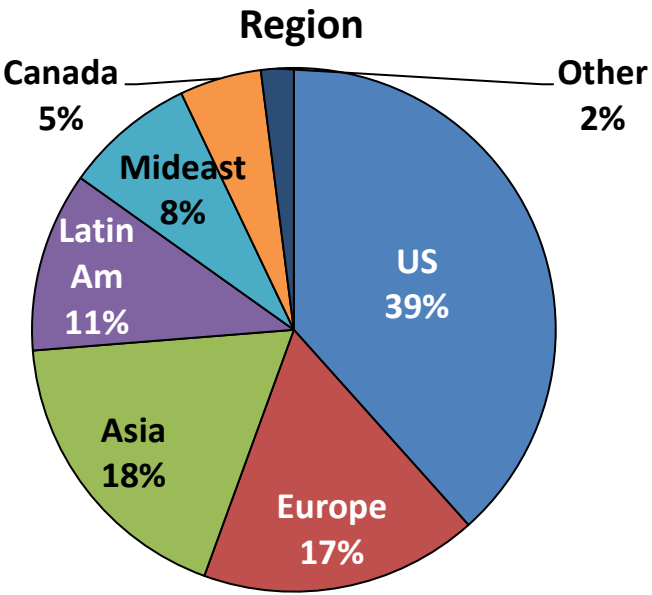


Demographics of AML Tool Participants

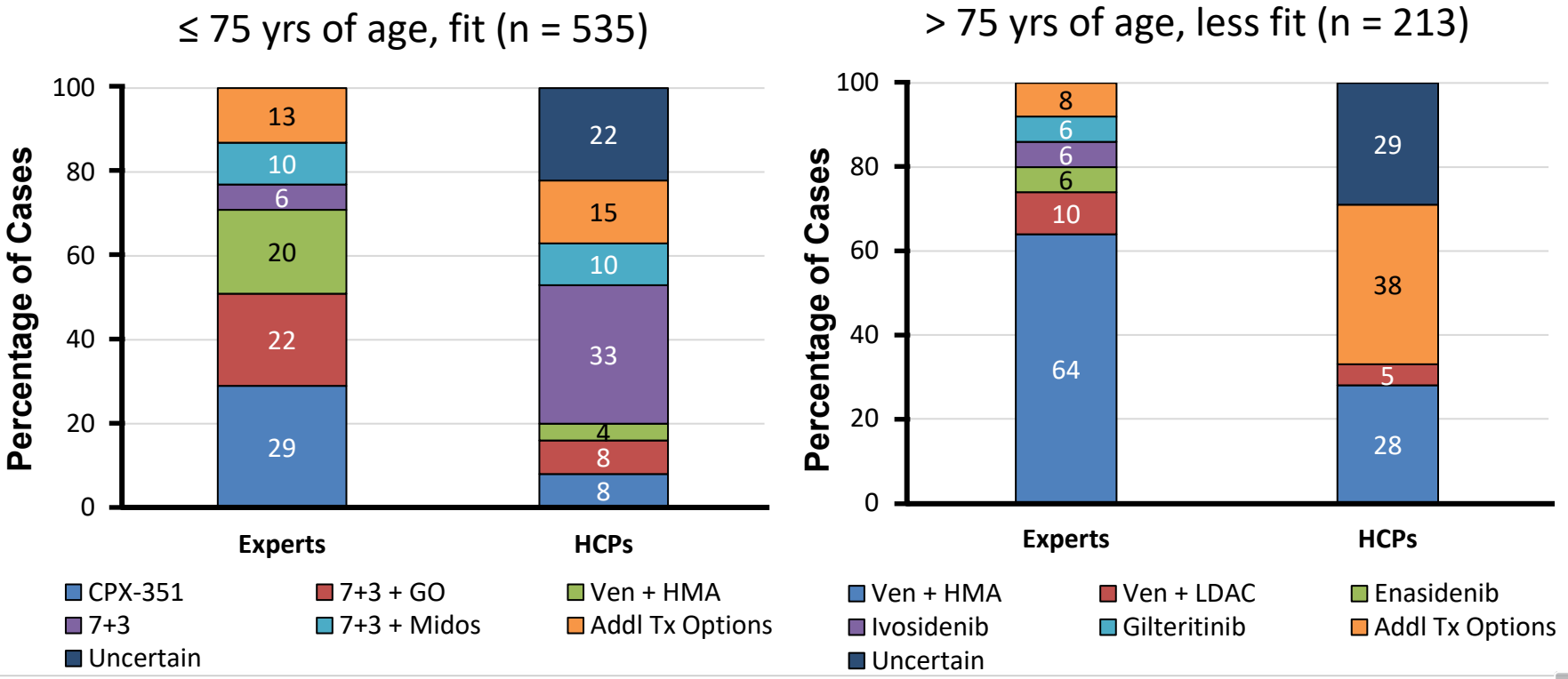
- A total of 417 HCPs entered 934 patient scenarios from June 2019 - July 2020



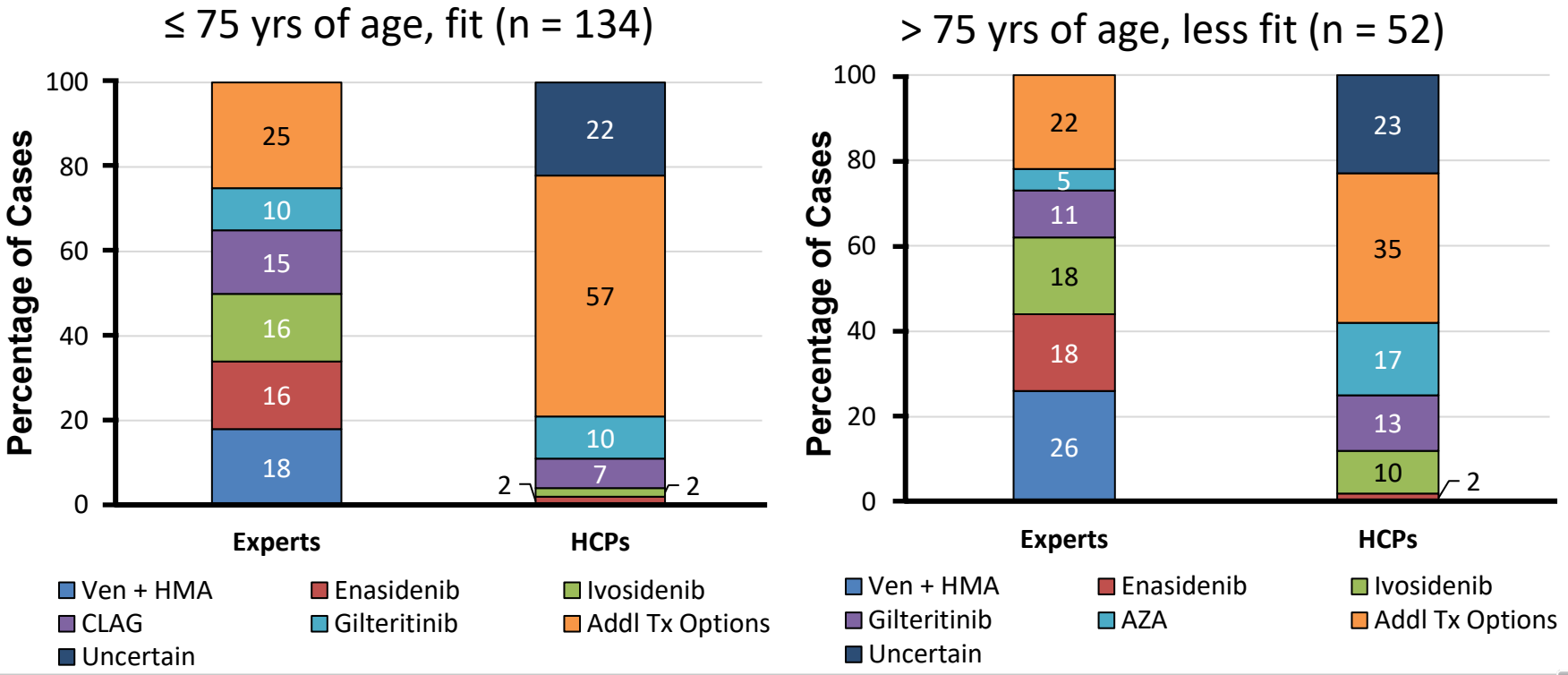




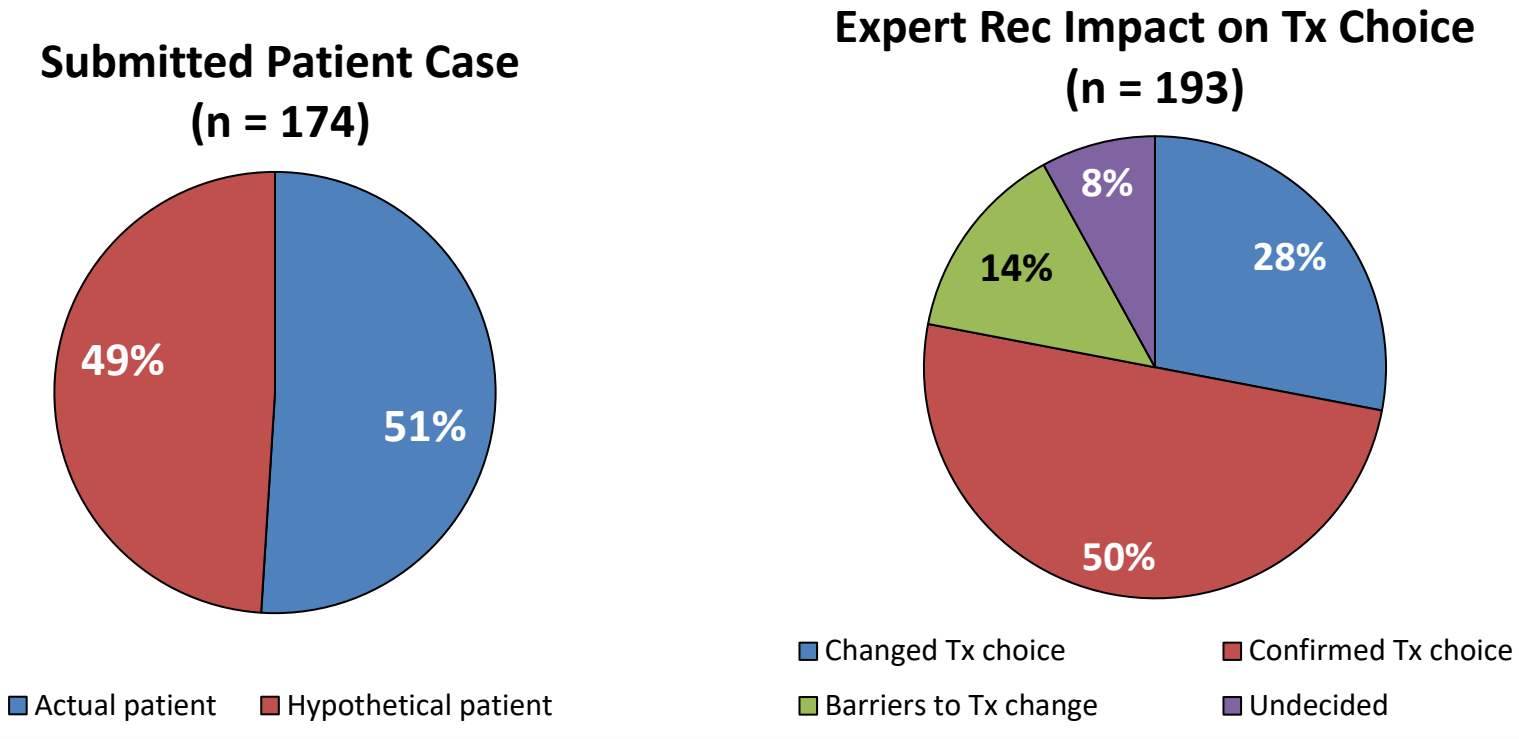
Treatment Recommendations for Cases of ND AML



Treatment Recommendations for Cases of First Relapse AML



Case Disposition and Recommendation Impact



Conclusions

- Data analysis showed expert consensus regarding Tx strategies for AML, including:
  - Venetoclax plus HMAs for older, less fit patients with ND AML
  - Targeted therapies for patients with AML and *FLT3* or *IDH1/2* mutations
- HCP practice patterns differed considerably from the experts for most cases
  - Fit, younger ND AML: CPX-351, 7+3 plus gemtuzumab ozogamicin, or venetoclax + HMA selected by experts in 71% of cases vs 20% for HCPs
  - Older, less fit ND AML: venetoclax plus HMA or LDAC selected by experts in 74% of cases vs 33% for HCPs
  - In first relapse AML cases with FLT3 or IDH1/2 mutations, experts chose targeted therapies in 87% of cases vs 41% for HCPs
- Differences between HCPs and experts suggest continued educational need to increase HCP awareness of best practices in AML

Practice Trends and Attitudes of Medical Oncologists on New Therapies in Urothelial Carcinoma

Kristen M. Rosenthal, PhD[1]; Matt D. Galsky, MD, FASCO[2]; Matthew I. Milowsky, MD[3]; Alexandra Howson, PhD[4]; Timothy A. Quill, PhD[1]; and Kevin Obholz, PhD[1]

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[3]University of North Carolina Department of Medicine, Division of Hematology/Oncology, Chapel Hill, NC; [4]Thistle Editorial, LLC, Snoqualmie, WA

Background

Treatment options for patients with urothelial carcinoma (UC) have dramatically changed over the last 5 years, with the approval of various immune checkpoint inhibitors (ICIs), erdafitinib, and enfortumab vedotin. The goal of this study was to assess the impact and use of new therapeutic developments in clinical practice management of patients with UC as well as identify the current educational needs of healthcare providers who are involved in the care of patients with UC.

Methods

- 2-phase study was designed to determine current practice trends and specific challenges faced by clinicians
  - Phase 1: qualitative telephone interviews (3/25/19-4/5/19)
  - Phase 2: quantitative online survey (3/20/19-5/27/19)
- Participants were recruited via email and their responses were compared with those of experts, guideline recommendations, and regulatory approvals

Conclusions

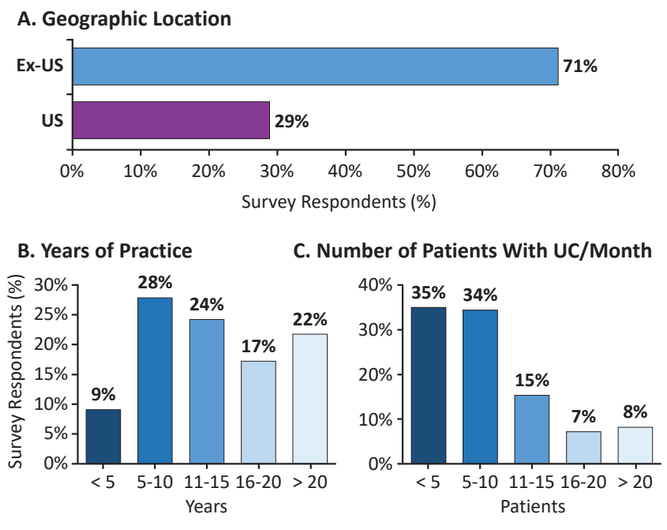
- This study highlights the need for ongoing education on the optimal use of novel treatment strategies for patients with UC
- Only 40% of clinicians use regulatory guidance for appropriate PD-L1 testing
- ~ 50-60% of clinicians correctly selected SoC cisplatin-based CT for eligible patients with mUC
- For cisplatin-ineligible patients, ~ 60% of clinicians indicated use of ICI despite low PD-L1 expression
- 50%-60% of clinicians could identify the target of erdafitinib and ≤ 35% knew the MoA of investigational agents at the time of the survey

Results

Participant Demographics

Specialty, n (%)	Phase I (N = 30)	Phase 2 (N = 491)
Hem/Onc	17 (57)	100 (20)
Oncology	8 (27)	312 (64)
Urology	5 (17)	50 (10)
Other	--	29 (6)
Practice Setting, n (%)		
Academic	11 (37)	137 (28)
Hospital/health system owned	--	143 (29)
Community-based practice	9 (30)	19 (4)
Private practice/physician owned	7 (23)	74 (15)
Community cancer center	3 (10)	109 (22)
Federal government owned	--	6 (1)

Figure 1. Participants From Phase 2 Quantitative Interviews (N = 491)



Use of Immune Checkpoint Inhibitors in Clinical Practice

Figure 2. Use of PD-L1 Biomarker Testing

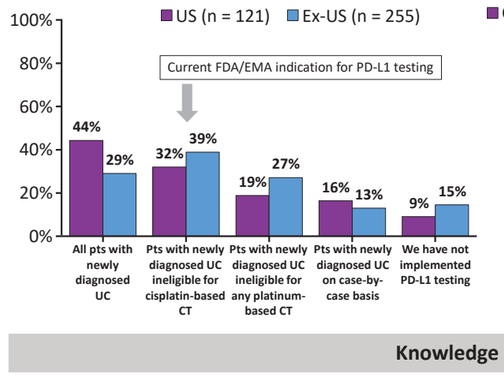
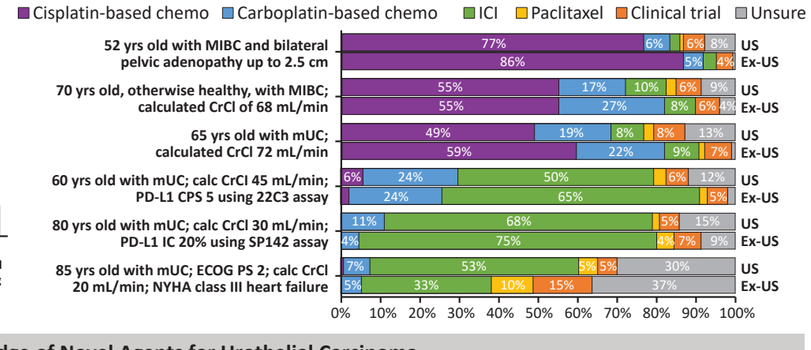


Figure 3. Preferred Tx for Newly Diagnosed UC (US: n = 125; Ex-US: n = 258)



Knowledge of Novel Agents for Urothelial Carcinoma

Figure 4. Identifying Agent Targets/MoA (US: n = 132; Ex-US: n = 289)

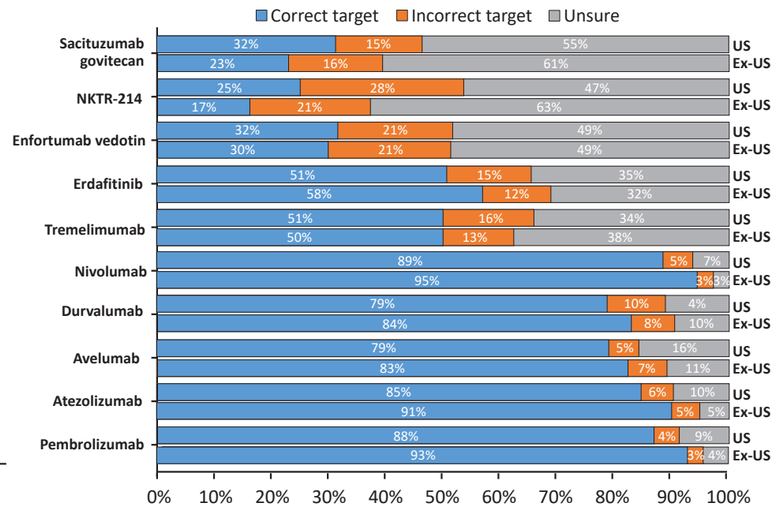
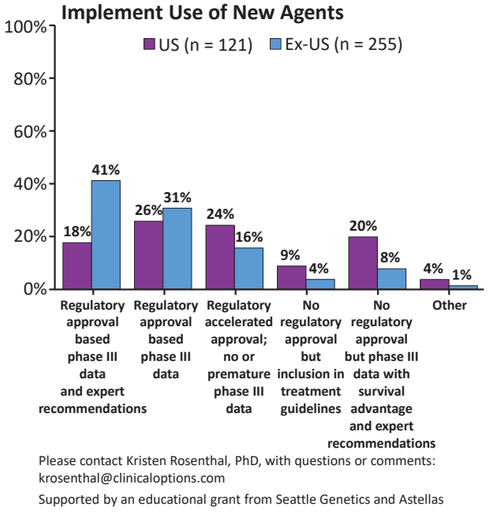


Figure 5. Level of Evidence Needed to Implement Use of New Agents



Please contact Kristen Rosenthal, PhD, with questions or comments: krosenthal@clinicaloptions.com

Supported by an educational grant from Seattle Genetics and Astellas

Practice Gaps and Barriers in Optimal Care Among Healthcare Professionals Treating Patients With Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML): Results of a Two-Phase Qualitative/Quantitative Study

Marie N. Becker, PhD[1]; Alexandra Howson, PhD[2]; Timothy A. Quill, PhD[1]; Naval Daver, MD[3]; and Eytan M. Stein, MD[4]

[1]Clinical Care Options, LLC, Reston VA. [2]Thistle Editorial, LLC, Snoqualmie, WA. [3]The University of Texas MD Anderson Cancer Center, Houston, TX. [4]Memorial Sloan Kettering Cancer Center, New York, NY.

Background

Rapid advances in the understanding of the biology of MDS and AML have led to novel therapeutic interventions that have increased the clinical complexity of decision-making in patient care. This study sought to quantify professional practice gaps and barriers to optimal care among healthcare professionals (HCPs) treating patients with MDS and AML at academic medical centers and/or community cancer centers and clinics globally, with the goal of informing the design of evidence-based education interventions aiming at addressing these gaps.

Methods

- A 2-phase study was designed to determine current practice trends and specific challenges faced by HCPs who care for patients with MDS or AML
  - Phase 1: quantitative online survey (February-May 2021) for both US-based and ex-US–based HCPs
  - Phase 2: qualitative telephone interviews (March-May 2021) US-based solely
- Participants were recruited via email and their responses were compared with those of experts, guideline recommendations, and regulatory approvals
- Data shown are from physicians, pharmacists, and advanced practice nurses

Conclusions

Core practice gaps:

- Evaluation and fitness assessment in MDS and AML
  - HCPs indicated a lower maximum age for transplant eligibility compared with experts and were more likely to select intensive chemotherapy for patients with poor performance status
- Therapy selection for higher-risk MDS
  - Experts are primarily using venetoclax/azacitidine off label for higher-risk MDS; a minority of HCPs selected this option except for patients progressing after HMA therapy
- Therapy selection for newly diagnosed AML
  - 50%-60% of respondents concur with expert recommendations for newly diagnosed older patients without targetable mutations, but there is low concordance with the experts for other case scenarios including for patients with poor performance status and *FLT3* mutation
- Therapy selection in relapsed/refractory AML
  - The lack of a standard approach to relapsed/refractory AML is a clear unmet need leaving HCPs challenged to select optimal approaches for their patients
- Therapy for *TP53*-mutated MDS and AML
  - The lack of familiarity with agents in clinical trials, including those directed at *TP53*-mutant disease, may negatively affect clinical trial referral; many HCPs interviewed noted the challenges in selecting therapy for patients with *TP53* mutations
- Clinical trial referral and knowledge of agents in trial
  - Most HCPs were unable to identify the targets of novel agents currently in clinical trials potentially limiting clinical trial referral and the ability to integrate these agents into practice once approved

This poster and the entire report can be accessed using the QR code at the top of the poster.

COI: Marie N. Becker, PhD has no conflicts of interest to report.
Acknowledgement: Supported by an independent educational grant from Gilead Sciences Inc.

Results

Participant Demographics

Clinical Role, n (%)	Qualitative US Based (n = 30)	Quantitative US Based (n = 263)	Quantitative Ex-US Based (n = 66)
Physician	22 (73)	131 (50)	59 (89)
Nurse practitioner	3 (10)	49 (19)	2 (3)
Pharmacist	5 (17)	68 (26)	4 (6)
Physician assistant	0	15 (6)	1 (2)
Practice Setting, n (%)*			
Academic	13 (43)	51 (32)	12 (33)
Community/hospital/health system owned	10 (30)	61 (38)	19 (53)
Physician owned	7 (23)	42 (26)	4 (11)
Other	0	8 (5)	1 (3)
No response	NA	101	30

*For quantitative survey, percentages are based on n = 162 US participants and n = 36 ex-US who answered the question.

Table 1. Oldest Age at Which HCPs Would Consider Stem Cell Transplant

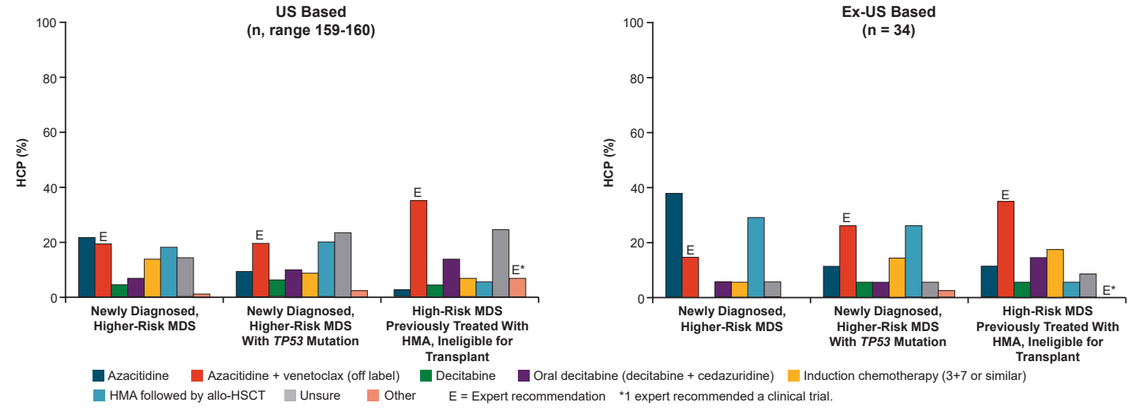
Age at Transplant, %	US (n = 160)	Ex-US (n = 35)
60 yr	6.88	25.71
65 yr	19.38	28.57
70 yr	39.38	34.29
75 yr	24.38	8.57
>75 yr	10.00	2.86

Red box indicates expert recommendation.

Table 2. Ability to Identify Targets of Novel Therapies

Identify Target, %	US (n = 163)			Ex-US (n = 35)		
Agent	Correct	Incorrect	Unsure	Correct	Incorrect	Unsure
Eprenetapopt (APR-246)	31.85	22.93	45.22	26.67	23.33	50.00
Flotetuzumab	21.38	34.59	44.03	38.24	20.58	41.18
IMGN632	15.38	23.08	61.54	9.68	22.58	67.74
Magrolimab	35.44	23.42	41.14	35.48	22.58	41.94
Pevonedistat	21.25	24.38	54.37	12.50	34.37	53.13
Sabatolimab (MBG 453)	17.39	24.85	57.76	12.90	16.13	70.97

Figure 1. Selection of Therapy for Higher-risk MDS



AML

Figure 2. Management of Newly Diagnosed AML

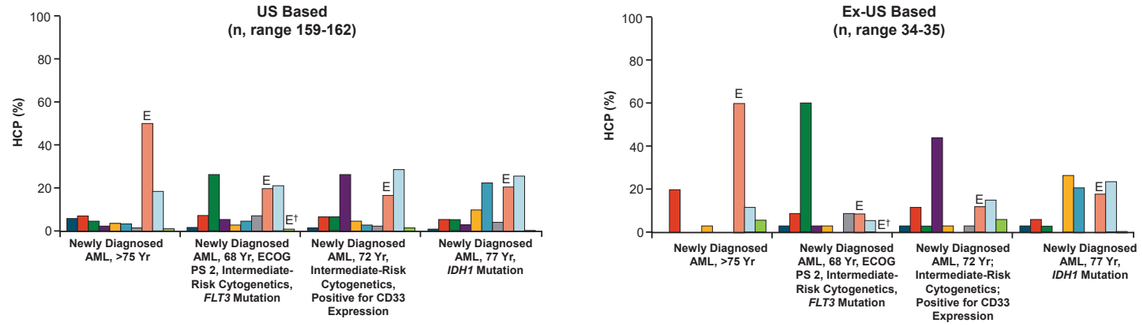
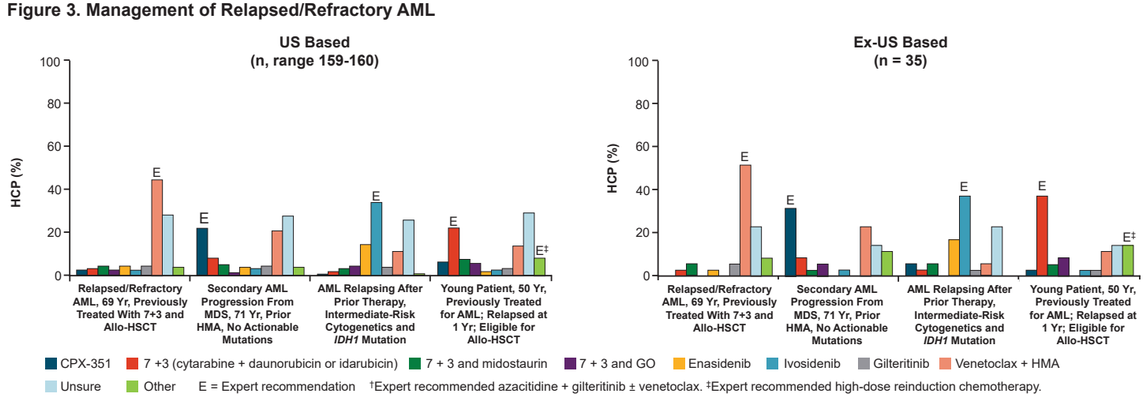


Figure 3. Management of Relapsed/Refractory AML



Suboptimal Clinician Awareness of Appropriate *NTRK* Fusion Testing and TRK Inhibitor Use in Solid Tumors

CLINICAL CARE OPTIONS® ONCOLOGY

Ryan P. Topping, PhD[1]; Krista Marcello[1]; Terrence Fagan[1]; Timothy A. Quill, PhD[1]; Todd M. Bauer, MD[2]; Alexander Drilon, MD[3]; George D. Demetri, MD[4]

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Scan me

Background

Since late 2018, 2 TRK inhibitors—larotrectinib and entrectinib—have been approved by the EMA and FDA for treating patients with advanced solid tumors harboring an *NTRK* fusion and progressive disease or no therapeutic alternatives. Although *NTRK* fusions occur with relatively low frequency in many tumor types, it is recommended that testing for *NTRK* fusions occur as early as possible after a diagnosis of advanced disease in all patients with solid tumors to inform potential use of TRK inhibitors, which have been associated with high response rates (~60%-80%) in basket clinical trials in patients with multiple solid tumor types.

This study evaluated baseline data from a series of educational activities to determine knowledge and competence gaps in oncology healthcare professional (HCP) awareness of expert recommendations on *NTRK* fusion testing and the selection of TRK inhibitor therapy for appropriate patients.

Methods

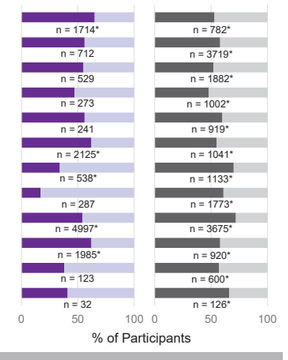
Between April 2018 and August 2021, we conducted multiple expert-led live and online educational activities for HCPs focused on *NTRK* fusion testing and/or TRK inhibitor treatment for varied solid tumors (see Educational Activities below). Each activity included baseline polling questions designed to assess HCP knowledge and practice patterns prior to the education. In this analysis, we assessed HCP responses to these questions to evaluate awareness of expert recommendations on *NTRK* fusion testing and appropriate patients for TRK inhibitor therapy.

Results

Educational Activities and Participant Demographics

Most participants in the educational activities were US-based MDs.

Activity No.	Activity No. and Timing	Focus of Education
1	4.2018-4.2019	*NTRK* testing/TRKi use in solid Ca
2	6.2018-7.2019	Actionable biomarkers in solid Ca
3	5.2019-7.2020	Actionable biomarkers in solid Ca
4	6.2019-7.2020	*NTRK* testing/TRKi use in solid Ca
5	11.2019-1.2021	Novel treatments for GBM
6	1.2020-1.2021	Actionable biomarkers in GI Ca
7	2.2020-3.2021	Treating advanced lung Ca
8	5.2020-8.2021	Actionable biomarkers in solid Ca
9	7.2020-12.2020	*NTRK* testing/TRKi use in solid Ca
10	7.2020-3.2021	Treating advanced head/neck Ca
11	12.2020-4.2021	*NTRK* testing/TRKi use in lung Ca
12	6.2021	*NTRK* testing/TRKi use in solid Ca



*Indicates demographic data only available from entire educational program, including participants who may not have answered a polling question. Nonasterisk n values indicate data available for participants who answered the demographic polling question for that specific activity.

Knowledge of *NTRK* Fusions/TRK Inhibitors

Question	Optimal Response	Correctly Answered (%)	n	Activity†/ Dates
Which of the following is a first-generation TRKi indicated for *NTRK* fusion head and neck cancers?	Larotrectinib	55	20	10/7.2020-3.2021
Which of the following types of CRC is enriched with *NTRK* fusions?	dMMR/MSI-high	57	240	6 + 9/1.2020-1.2021
Which of the following is a selective second-generation TRKi for which clinical trials are currently enrolling patients who have progressed on a first-generation TRKi?	Selitrectinib	19	113	9/7.2020-12.2020

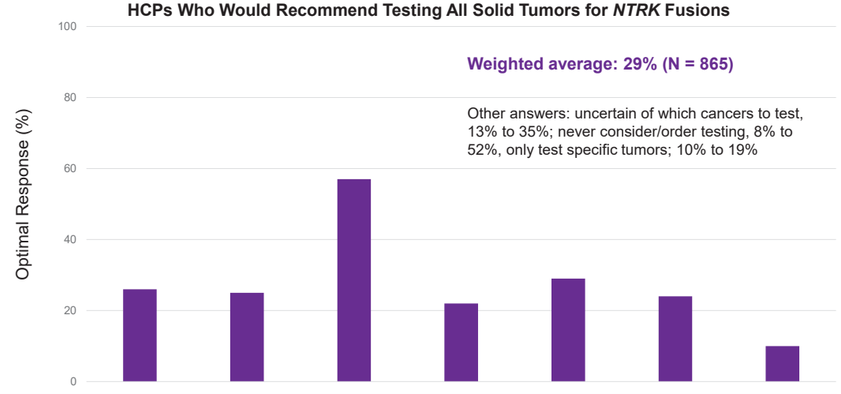
Results

Testing for *NTRK* Fusions

Across educational activities, only 29% of HCPs test all solid tumors for *NTRK* fusions. The percentage of HCPs who test has not improved substantially over time.

Assessment: HCPs were asked 1 of the following:
- In your current practice, for patients with which of the following solid tumors would you consider using broad-based molecular profiling to test for *NTRK* fusions?
- In your current practice, for which cancers do you typically order molecular profiling to test for *NTRK* fusions?

Optimal response: **All solid tumors**



Activity No.†	1	2	3	4	9	11	12
Timing	4.2018-4.2019	6.2018-7.2019	5.2019-7.2020	6.2019-7.2020	7.2020-12.2020	12.2020-3.2021	6.2021
n	182	207	116	148	104	89	21
Focus	NTRK/ solid Ca	Solid Ca biomarkers	Solid Ca biomarkers	NTRK/ solid Ca	NTRK/ solid Ca	NTRK/ lung Ca	NTRK/ solid Ca

†Refers to the Activity Number list in the Educational Activities section.

Conclusions

The rate of broad testing for *NTRK* fusions across patients with solid tumors remains low, and many HCPs lack awareness of when to consider a TRK inhibitor.

Educational activities designed to address these deficiencies would be of clear benefit to HCPs treating patients with advanced solid tumors.

Acknowledgments
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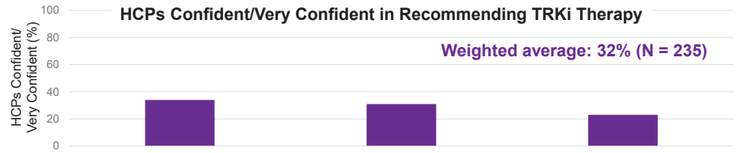
Abbreviations: Ca, cancer; CRC, colorectal cancer; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma; GI, gastrointestinal; i, inhibitor; IHC, immunohistochemistry; MSI, microsatellite instability; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD, progressive disease; PS, performance status; RoW, rest of the world; TMB, tumor mutational burden; TMZ, temozolomide.

Results

Optimal Use of TRK Inhibitors

Many HCPs lack awareness of which patients may benefit from TRK inhibitors.

Assessment: HCPs were asked, "In your current practice, how confident are you in recommending TRK inhibitor therapy for appropriate patients?"

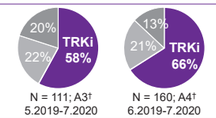


Activity no.†	9	11	12
n	130	83	22

Assessment: HCPs were asked their optimal treatment choice for case patients for whom experts would select a TRK inhibitor (larotrectinib and/or entrectinib).

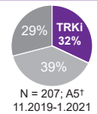
Case — **HCP Treatment Choice** (TRK inhibitor / Other treatment / Uncertain)

- 57-year-old man with swelling under jaw diagnosed with **salivary gland myoepithelial carcinoma**; underwent maximal debulking and adjuvant radiation, but recurrent disease noted 6 months later
- Completed first-line therapy with carboplatin + vinorelbine; at progression, NGS testing revealed an *ETV6-NTRK3* fusion



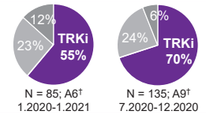
N = 111; A3† 5.2019-7.2020 — N = 160; A4† 6.2019-7.2020

- 35-year-old woman with recurrent *IDH*-mutated **GBM**
- Initial extensive subtotal resection + radiotherapy + TMZ followed by TMZ and tumor-treating fields; asymptomatic radiographic PD during 2 years after initial diagnosis
- NGS (original tissue): *EML4-NTRK3* fusion (intratumoral heterogeneity by IHC)



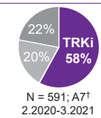
N = 207; A5† 11.2019-1.2021

- 43-year-old woman diagnosed with pT4aN0 **colon cancer**; deferred chemotherapy; right lower quadrant mass later recurred, with carcinomatosis and ascites
- Cancer is dMMR/MSI-high, TMB-high, and *NTRK* fusion positive; pembrolizumab started but PD after 2 months; nivolumab/ipilimumab started but PD again after 2 months



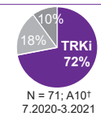
N = 85; A6† 1.2020-1.2021 — N = 135; A9† 7.2020-12.2020

- 50-year-old nonsmoker with metastatic **lung adenocarcinoma**
- *EGFR/ALK/ROS1/BRAF* all negative, PD-L1 <1%; patient received carboplatin, pemetrexed, and pembrolizumab but PD
- NGS panel of original biopsy showed *NTRK* fusion



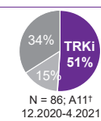
N = 591; A7† 2.2020-3.2021

- 42-year-old woman with metastatic, radioiodine-refractory **papillary thyroid cancer** with multiple lung nodules; rapid disease progression noted on imaging
- Sequencing identified *NTRK3* gene fusion



N = 71; A10† 7.2020-3.2021

- 68-year-old man presents with *EPS15-NTRK1* **NSCLC** with metastases to liver; past medical history: fatigue, cough, hyperlipidemia; ECOG PS 1
- No previous surgery, radiation, or chemotherapy



N = 86; A11† 12.2020-4.2021

Understanding the Educational Needs of Healthcare Providers on Emerging Treatments for MDS & AML

Table of Contents

EXECUTIVE SUMMARY

Background

Advances in the management of MDS and AML have been rapid and have led to significant improvements in clinical outcomes for many patients. However, not all patients are benefiting due to suboptimal treatment decisions stemming from a lack of application of the latest clinical trial data and drug approvals. To provide targeted education that adequately prepares clinicians to confidently and safely use novel treatments in MDS and AML, a clear understanding of the current educational needs of healthcare providers is urgently needed.

Study Goal

The goal of this comprehensive needs assessment was to understand current practice patterns in managing patients with MDS and AML as well as clinician knowledge of emerging therapeutic options for these patients in order to identify the current educational needs of healthcare providers across the United States (US) as well as ex-US clinicians. Clinical Care Options (CCO) and Thistle Editorial, LLC, strategically designed a multi-methods assessment involving an in-depth qualitative exploration and a quantitative survey of the various factors that affect clinical reasoning, current approaches to practice, knowledge of emerging therapy options, and specific challenges faced by US healthcare providers responsible for treatment decisions for patients with MDS and AML.

Design and Methodology

This two-phase, mixed-methods needs assessment study consisted of qualitative telephone interviews (Phase 1) and an online survey (Phase 2). Phase 1 of the study explored attitudinal, motivational, and contextual issues—the intuitive decision-making factors—inherent to clinical reasoning in cancer care as well as gaps in the knowledge, skills, and clinical confidence of US medical oncologists/hematologists and Advanced Practice Providers (Nurse Practitioners or Pharmacists) responsible for the treatment decisions for patients with MDS and AML. Phase 2 (quantitative) examined practice trends and knowledge of emerging investigational treatment options among healthcare professionals within the US and globally.

CLINICAL PRACTICE GAPS AND RECOMMENTATIONS

Narrative Summary

The clinicians we interviewed were all thoughtful about their management of patients with MDS or AML. Although they received a small honorarium, many interviewees also saw the interview as an opportunity for reflection on their clinical practice. Overarchingly, these clinicians viewed MDS and AML as challenging diseases to treat. In particular, they felt they had very little to offer patients with *TP53* mutations or patients with relapsing or refractory disease. Corresponding survey data revealed gaps in knowledge of current best practices and emerging therapies as well as gaps in competence selecting appropriate therapies for patients with MDS or AML.

The practice gaps identified below reinforce the need to understand clinical reasoning as a blend of information processing and skills application that arises from, and is shaped by, contextual factors such as patient preference, institutional pathways and protocols, and therapy availability.

Clinical Practice Gaps and Education Need

Practice Gap #1: Evaluation and Fitness Assessment in MDS/AML

Few healthcare professionals have a clear threshold for determining which patients are eligible for intensive therapy and/or transplant and are using an intuitive or Gestalt-based approach to determine patient fitness. Chronological/biological age features prominently as an heuristic device within fitness assessment. Clinicians are pragmatic about the support context that patients need for transplant to be a realistic option even for medically fit patients. This pragmatism may reinforce their reasoning that "in real life" a majority of patients are not candidates for intensive therapy and/or transplant. Nonetheless, survey results show that many patients who experts consider unfit for high intensity therapy are likely being treated with high intensity therapy in practice. At the same time, many clinicians appear to be avoiding potentially curative allogeneic stem cell transplant in some older patients due to their underestimation of the maximum age for transplant eligibility.

Practice Gap #2: Therapy Selection in Newly Diagnosed High-Risk MDS

A considerable proportion of healthcare professionals are unsure about their primary preferred standard treatment for patients with newly diagnosed, high-risk MDS either with or without a *TP53* mutation. Patients with intermediate fitness pose a particular challenge for clinicians in terms of determining therapeutic direction. There is considerable variation in treatment choice

in the frontline high-risk MDS setting and many clinicians report being unsure which therapy to select.

Practice Gap #3: Therapy Selection in Newly Diagnosed AML
It remains challenging to plan optimal therapeutic strategies for patients who have a poor prognosis, who are older or ineligible for intensive chemotherapy, or who have secondary AML. A surprising number of healthcare professionals offer intensive therapy to newly diagnosed patients with AML and a poor performance status. They also vary in their adoption of venetoclax plus an HMA. Healthcare professionals are not uniformly using bone marrow biopsy to assess response to treatment with venetoclax-based therapies.

Practice Gap #4: Therapy Selection in Relapsing or Refractory AML
Healthcare professionals view relapsing or recurring disease as one of the biggest unmet needs in AML management and vary considerably in their treatment approaches.

Practice Gap #5: *TP53*-Mutated MDS and AML
TP53-mutated MDS and AML represents a clear unmet medical need. Healthcare professionals expressed considerable uncertainty on how best to approach therapy for a patient with *TP53*-mutated MDS and were very divided in their treatment approaches.

Practice Gap #6: Clinical Trial Referral
Healthcare professionals vary in the timing of discussion they have with patients about clinical trials as a potential treatment option and view access to clinical trials as a major challenge in the management of patients with MDS or AML. In addition, clinicians lack knowledge of therapeutic agents currently in clinical trials.

Key Recommendations

This study highlights a global need for education and resource exposure across professional role, specialty, and practice setting in the following areas of clinical knowledge and practice in the treatment of patients with MDS and AML.

Recommendation #1: Evaluation and Fitness Assessment in MDS/AML
Clinicians require education on how to incorporate multidimensional fitness tools that uncover vulnerabilities that are not detected in routine clinical practice, as well as how to optimally incorporate cytogenetics and mutational profiles as part of patient evaluation and frontline MDS and AML treatment decisions.

Recommendation #2: Therapy Selection in Patients with Newly Diagnosed High-Risk MDS
Clinicians need guidance on the appropriate therapeutic strategy for patients with newly diagnosed high-risk MDS, as well as access to expert perspectives on determining therapeutic direction for patients with intermediate fitness.

Recommendation #3: Therapy Selection in Patients with Newly Diagnosed AML
Clinicians need guidance on the appropriate use of venetoclax plus HMA for patients with newly diagnosed high-risk AML as well as on the timing of response assessment and optimal duration of therapy following achievement of complete remission.

Recommendation #4: Therapy Selection in Relapsing or Refractory AML
Clinicians need access to expert perspectives on how to optimize therapeutic strategies in relapsed/refractory disease settings as well as access to confidence-building case scenarios.

Recommendation #5: *TP53*-Mutated MDS and AML
Clinicians need access to expert perspectives on how to optimize therapeutic strategies for patients with *TP53*-mutated disease including increased awareness of the targets and mechanisms of action of newly approved or investigational therapies.

Recommendation #6: Clinical Trial Referral
Direct clinicians to resources that increase awareness of and ability to access available clinical trials as part of their routine approach to managing patients with MDS or AML.

Study Design

Following a review of the literature and CCO internal data, this two-phase, mixed-methods needs assessment study was designed to include qualitative telephone interviews (Phase 1) and an online survey (Phase 2).

Qualitative Phase

Clinical practice involves interpretative practice and clinical reasoning is not considered simply a linear series of internal, cognitive decisions. Rather, the reasoning process, which involves both cognitive evaluation of patients (information processing) and the practical application of scientific knowledge and skills,[1] emerges dynamically from the specifics of the situation. Both of these reasoning processes (information processes and skills application) occur in an iterative fashion that is shaped by the range of contextual factors at play (e.g., physician, patient, setting, encounter factors).[2]

Phase 1 of the study explored intuitive decision-making factors—attitudinal, motivational, and contextual issues—inherent to clinical reasoning in cancer care as well as gaps in the knowledge, skills, and clinical confidence of US medical oncologists/hematologists and advanced practice providers responsible for the treatment decisions for patients with MDS and AML. Semi-structured interviews were designed to explore intuitive decision-making factors influencing clinical reasoning.[3] We conducted a series of confidential, 45- to 60-minute telephone interviews, directed by an interview topic guide based on literature review, expert input, and synthesis. Interviews were transcribed verbatim and imported into NVivo 12 for Mac (*QSR International*), a software package designed to support the systematic analysis of unstructured textual data.

Analysis

Analysis was based on an open-ended process of constant comparison that generates themes, descriptive patterns, and hypotheses as an ongoing, iterative process.[4] This approach included 4 components:

1. Data immersion and familiarization
2. Descriptive coding and node generation
3. Thematic coding and analysis
4. Subgroup analysis by demographic and other relevant attributes

The transcript content was initially coded into descriptive categories, or “nodes,” that were tagged to sections of text. Following descriptive node generation, a second round of coding identified potential topics of relevance to decision-making processes. Indicators of themes included words, phrases or segments of text that were used in a similar fashion by respondents across or within interviews, and that pointed to an emerging idea or concept. Qualitative

findings were also examined for educationally significant differences among subgroups (i.e., practice setting, specialty, designation) and reported where relevant. The conclusions for the overall group are, for the most part, relevant across all subgroups.

Quantitative Phase

We fielded an in-depth quantitative online survey to identify practice trends concerning integrating new agents and therapeutic advances in the care of patients with MDS and AML, sources of information consulted for best practices and/or education, gaps in knowledge, competence, and performance, and barriers to the adoption of new treatment options.

Experts (Naval G. Daver, MD, Associate Professor, MD Anderson Cancer Center, Houston TX and Eytan M. Stein, MD, Hematologic Oncologist, Memorial Sloan Kettering Cancer Center, New York, NY) worked with educational and survey design/assessment experts to develop case scenarios and clinical questions to assess gaps in optimal patient management, trends in care, knowledge of clinical trials and investigational agents, and self-identified barriers to optimal care.

The data analysis included in this report is from US and global healthcare providers who indicated that they managed patients with MDS or AML and identified themselves as physicians, physician assistants, nurse practitioners, or pharmacists. The survey was designed such that no questions were required resulting in a varying number of participant responses for each question (see Appendix).

Recruitment

Oncology clinicians treating MDS and AML were recruited to complete a 10- to 15-minute online survey. The study design included informed consent and measures to ensure protection and confidentiality for participants. Participants were offered an ethically acceptable level of compensation (ie, fair market value, but not enough to create coercion) to increase the number of participants and improve the statistical power as well as the likelihood that our study cohort is representative of the general US oncology specialist healthcare provider population as well as ex-US clinicians.

Invitations to participate in both phases of the study were sent through email to a list of CCO members. CCO Oncology membership includes more than 163,000 clinicians worldwide, including more than 26,000 physicians in the United States, of whom more than 16,000 define themselves as having a specialized interest in medical oncology or hematology/oncology. Multiple targeted emails were sent to each group in an effort to maximize participation.

FINDINGS

Participant Characteristics

Demographic Characteristics of Participants

The quantitative survey was conducted between February and May 2021. A total of 718 individuals responded and 405 indicated that they treat patients with MDS or AML. The responses were filtered for physicians, physician assistants, and Advanced Practice Providers, and yielding 263 US-based participants and 66 ex-US-based participants (**Table 1**). We conducted qualitative interviews between March and May 2021. For the qualitative phase, we recruited 30 clinicians from those completing surveys who described themselves as practicing in US academic centers, community cancer centers, private practice, or community-based settings (**Table 1**). A majority of interview participants were physicians with a decision-making role with regards to treatment; 8 participants were Advanced Practice Providers.

Table 1. Demographic Characteristics of Participants

	Qualitative (n=30)		Quantitative US (n=263)		Quantitative ex-US (n=66)	
	n	%	n	%	n	%
Position						
Physician	22	73.33	131	49.8	59	89.4
Nurse Practitioner	3	10	49	18.6	2	3.0
Pharmacist	5	16.66	68	25.9	4	6.1
Physician Assistant	0	0	15	5.7	1	1.5
Years of practice						
<5			37	14.1	5	7.6
5-10	11	36.66	69	26.2	9	13.6
11-15	5	16.66	39	14.8	7	10.6
16-20	7	23.33	40	15.2	6	9.1
>20	7	23.33	78	29.7	39	59.1
Practice setting*						
Academic	13	43.33	51	31.5	12	33.3
Community/hospital/ health system owned	10	30	61	37.7	19	52.8
Physician owned	7	23.33	42	25.9	4	11.1
Other	0	0	8	4.9	1	2.8
No response	0	0	101	--	30	--
MDS/AML Patients per Month*						

< 5	4	13.33	44	27.2	10	27.8
5-10	7	23.33	56	34.6	12	33.3
11-15	6	20	25	15.4	5	13.9
16-20	3	10	17	10.5	4	11.1
> 20	10	33.33	20	12.4	5	13.9
No response	0	0	101	--	30	--

*For quantitative survey percentages are based on n = 162 US participants and n = 36 ex-US who answered the question.

Practice Gap #1: Evaluation and Fitness Assessment in MDS/AML

Few clinicians have a clear threshold for determining which patients are eligible for intensive therapy and/or transplant evaluation and are using an intuitive or Gestalt-based approach to determine patient fitness. Chronological/biological age features prominently as an heuristic device within fitness assessment. Although lack of access to transplant centers is likely a barrier to whether medically fit patients with newly diagnosed high-risk MDS are evaluated for intensive therapy/transplant, clinicians are pragmatic about the support context that patients need for transplant to be a realistic option even for medically fit patients. This pragmatism may reinforce their reasoning that "in real life" a majority of patients are not candidates for intensive therapy and/or transplant. Nonetheless, survey results show that many patients with AML are receiving high intensity therapy who are not fit for such therapy.

Most interviewed clinicians are using the revised international prognostic scoring system (IPSS-R) or the original IPSS as tools to classify prognostic risk.[5] They described using bone marrow biopsy as a diagnostic gold standard in their evaluation of patients with suspected MDS or AML, especially for previously healthy patients who suddenly present with cytopenias or present with unexplained cytopenias (**Appendix Table 1**). Some clinicians used age/fitness as the threshold for bone marrow biopsy (**Appendix Figure 1**).

Most interviewed clinicians incorporate cytogenetics and mutational profiles as a routine component of fitness assessment, evaluation, and risk stratification in both MDS and AML (**Appendix Table 1**). Pharmacists and nurse practitioners were less certain about how or whether these parameters were included in patient evaluation. In general, frailty frameworks and clinical thinking about frailty are not well-aligned. Although few clinicians provided definitions of frailty, some are using a frailty index, Eastern Cooperative Oncology Group (ECOG), or the Charlson Comorbidity Index (CCI) as a screening tool for frailty in the MDS and AML settings.

Gestalt Assessment

Clinicians are aware of, and sometimes familiar with fitness assessment tools, but generally described taking an intuitive reasoning approach to fitness determination—taking a gestalt view, using clinical or subjective judgment, interpreting qualitative patient characteristics. They

viewed themselves as good at evaluating patients in the clinic and having developed a practiced eye for "fitness" (**Appendix Table 2**).

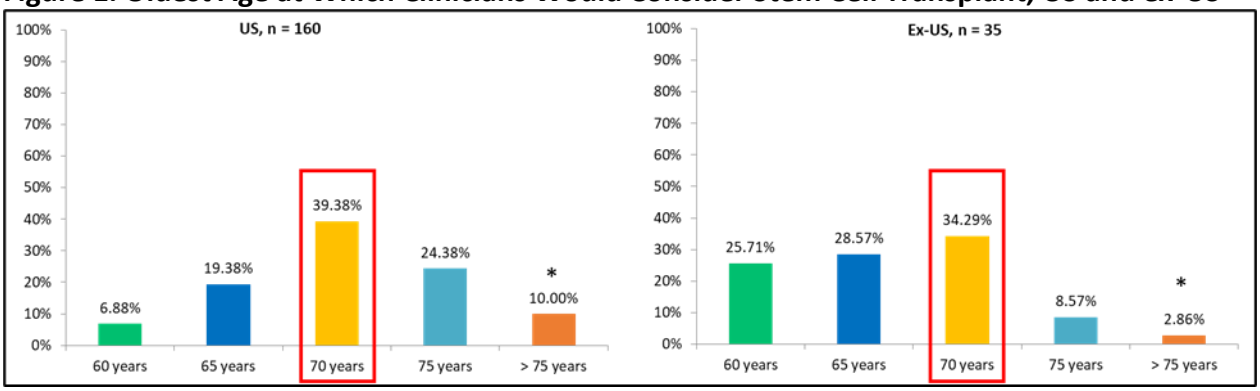
A small group of clinicians (n=5) in either academic or large health systems had access to a colleague (e.g., health psychologist) or training in administering a comprehensive geriatric assessment such as the CCI or Get Up and Go. They viewed formal assessment as crucial for determining whether the patient vulnerabilities that could be seen via an "eyeball test" preceded or were a result of disease onset. Most experienced clinicians did not "believe in these formal assessments;" viewed them as research versus clinical practice tools; or trusted their own tacit knowledge/assessment expertise as a foundation for determining eligibility for intensive induction chemotherapy. They also referred to patient willingness to undergo transplant as a confounding variable in their fitness determination.

Regardless of the chronological age that clinicians identified in the survey as the oldest age for stem cell transplant, (70 years, for a majority of those interviewed), they struggle with assessing fitness in the gray areas between what they view as the "extremes" of age and other characteristics (**Appendix Figure 2**).

Transplant Evaluation for Medically Fit Patients with High-Risk MDS

Survey responses indicate that a majority of oncology clinicians believe that patients should be 70 or younger to have a successful allogeneic stem cell transplant (**Figure 1**). Our 2 experts agreed that patients over 75 years of age can be eligible for transplant (noted by asterisk).

Figure 1. Oldest Age at Which Clinicians Would Consider Stem Cell Transplant, US and ex-US



The clinicians we interviewed reflected the distribution seen in the survey. One third of the interviewed clinicians believe that patients aged 70 or older could have a successful allogeneic stem cell transplant, the majority of whom practiced in academic settings.

Just over one half of interviewed clinicians (all with established access to transplant centers) said that their first consideration would be to evaluate medically-fit patients as potential candidates for transplant based on chronological/biological age and factors such as performance status, comorbidities, and patient preference. Yet clinicians lack a clear threshold

for determining which patients are eligible for intensive therapy and/or transplant evaluation. The general trend was for clinicians to consider a range of criteria in the scenario of patients with high- or intermediate-risk MDS; they are likely applying different weightings to these criteria. Chronological age, cytogenetics, fitness or frailty, donor availability, patient preference, transfusion burden, and local availability of formulary medications all played into decision-making about therapy selection for these patients.

There was a strong view that treatment for MDS patients was "*damned if you do and damned if you don't*." They emphasized the importance of clinical judgment here—gut feelings, tacit knowledge—as the basis of their determination about a patient's potential transplant eligibility (**Appendix Table 2**).

> I think most clinicians, especially in the community, are probably just assessing patients based on their age, usually over 70 or so, and fitness. And so, I think those are – you know, and, also, whether or not they might be fit for an allogeneic stem cell transplant. And the age for that is roughly less than 75. Some centers may be even less than 70. So, I think those are the factors that go into consideration. [Physician, Academic Setting]

Although most clinicians said they did not think about chronological/biological age in terms of a hard cut-off, chronological/biological age still featured prominently in how clinicians described their approaches to evaluating and managing patients with newly diagnosed high-risk MDS. For some, age *was* the primary organizing principle around which decision-making occurred and appeared to operate as an heuristic shortcut in clinical decision-making. Other factors included fitness, tolerance of therapy, and patient preference (**Appendix Table 3**).

Barriers to Transplant and Intensive Chemotherapy

Clinicians suggested the following as potential barriers to evaluation for transplant and intensive chemotherapy:

- The importance of getting patients to remission prior to transplant but the challenges in doing so.
- Academic clinicians assumed that community clinicians were using chronological age to assess patient fitness for intensive therapy and transplant and not referring patients for transplant.
- Clinicians are using chronological age as an heuristic cutoff.
- Lack of access to transplant centers.

Clinicians were also pragmatic about the support context that needed to be in place for transplant to be a realistic option even for medically fit patients with high-risk MDS. They factored social, emotional, material support, likely access to transport and financial support into their decision-making. This pragmatism may color the approach to fitness assessment and reinforce the reasoning that "in real life" a majority of patients are not candidates for intensive induction chemotherapy therapy (**Appendix Table 2**).

> In real life, though, a majority of patients are not candidates, so that means that those patients will be receiving treatments with us and eventually at the end of the day that will be a hypomethylating agent plus/minus venetoclax. [Physician, Hospital/Health System]

Practice Gap #2: Therapy Selection in Newly Diagnosed High-Risk MDS

Many hematologists are uncomfortable managing patients with high-risk MDS and there is considerable variation in how clinicians are using HMAs in practice in the frontline high-risk MDS setting. Survey and interview data show that a considerable proportion of US and ex-US clinicians are "unsure" about their primary preferred standard treatment for patients with newly diagnosed MDS and are selecting suboptimal therapies for these patients. Patients with intermediate fitness pose a particular challenge for clinicians in terms of determining therapeutic direction.

Therapy Selection in Specific Clinical Scenarios

Although there is no consensus concerning the optimal management of patients with newly diagnosed MDS who are candidates for intensive therapy, current clinical evidence suggests that at diagnosis, patients who are considered medically fit should be evaluated for transplant, intensive induction chemotherapy, or clinical trial eligibility as well as for the presence of prognostic genetic features. Therapeutic strategies for patients with intermediate fitness and/or who are not candidates for intensive therapy include hypomethylating agents (HMAs), erythropoiesis-stimulating agents, immunosuppressive therapies, and lenalidomide. The HMAs azacitidine and decitabine have been used for over a decade in MDS treatment and lead to a modest survival benefit, although response rates are around 35-50% and responses are mostly transient.[6,7] For HMA-refractory MDS patients the prognosis is poor.[8]

Venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine is FDA-approved for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. The combination of venetoclax and azacitidine has demonstrated efficacy in MDS, but does not yet have regulatory approval.[9,10] Survey data show that many US but not ex-US clinicians have already shifted to azacitidine plus venetoclax off-label for frontline high-risk MDS including for patients with a *TP53* mutation. This is consistent with expert recommendations. Clinician survey selections diverge from expert recommendations (denoted by asterisk) in all three case scenarios surveyed (**Figures 2 and 3**). In patients with high-risk MDS previously treated with HMA, many clinicians opted for another HMA, either decitabine or oral decitabine (decitabine plus cedazuridine). Expert faculty were surprised that so many clinicians (US 13.84%, n=160; ex-US 14.71%, n=34) were switching to oral decitabine after HMA-failure (**Figures 2, 3, red arrow**). Additionally, as many as 25% of US-based clinicians were unsure of therapy selection for patients with MDS (**Appendix Figures 3 and 4**).

Figure 2. Primary Preferred Standard Treatment Recommendation for Clinical Scenarios of Patients with MDS, US (n, range 159-160)

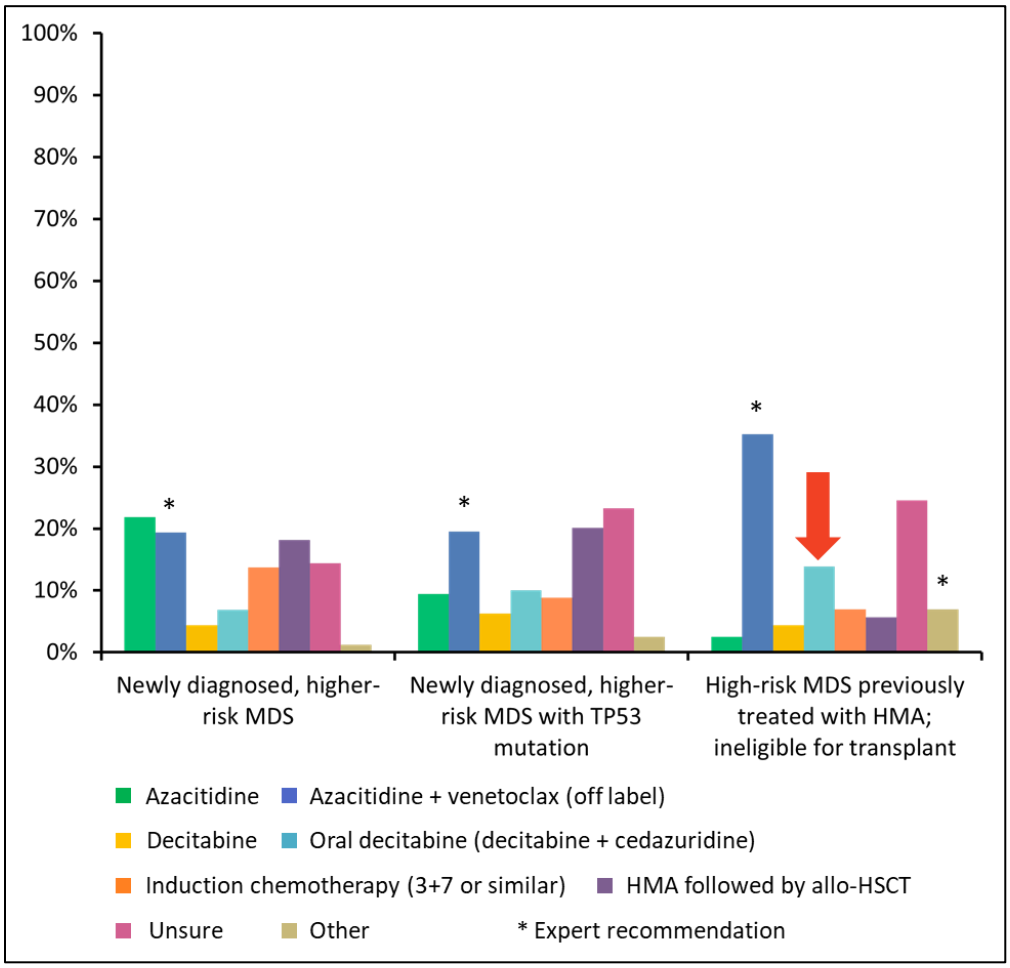
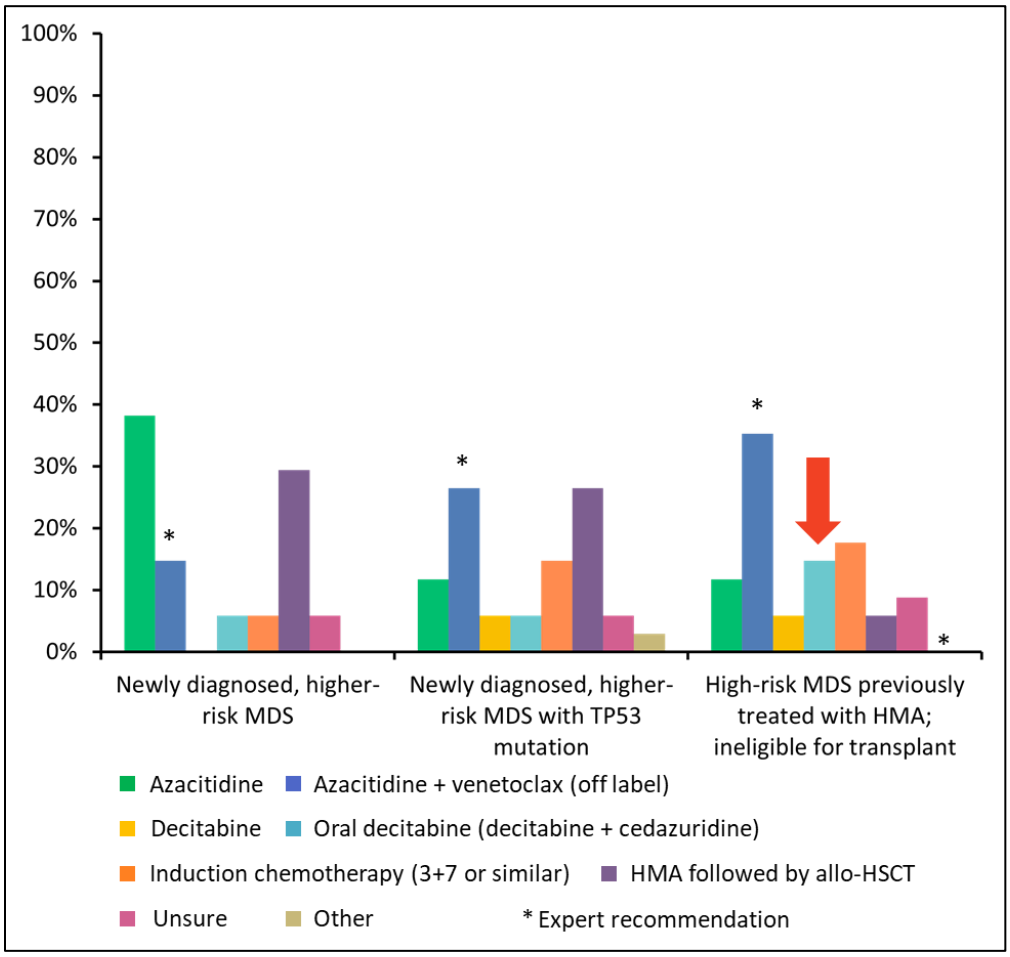


Figure 3. Primary Preferred Standard Treatment Recommendation for Clinical Scenarios of Patients with MDS, ex-US (n = 34)



Interviewed clinicians described using either a single agent HMA and adding venetoclax following ineffective response or using combination HMA and venetoclax from the outset for patients they described as frail, transforming, "close to leukemia," or requiring considerable supportive therapy.

> *Usually you can do like azacitidine or decitabine plus or minus venetoclax. So I would say those are kind of like our recommendations. So I would say a hypomethylating agent plus or minus venetoclax is kind of our go-to. Certainly a hypomethylating agent for sure. [Physician, Academic Setting]*

> *If they are frail and older, then my first-to-go option is using a combination of venetoclax and azacitidine. [Physician, Hospital/Health System]*

> *I do add venetoclax. I don't know if you're aware of the data venetoclax 400 mg day 1 to 14, not the whole 21- or 28-day cycle, just day 1 to 14. So that's what I've been doing*

even before that because of my training. And that's what I do – hypomethylating agent and venetoclax. [Physician, Hospital/Health System]

Almost two thirds of interviewed clinicians (n=18) viewed transplant as optimal for patients with newly diagnosed high-risk MDS but seldom categorized patients as sufficiently fit for transplant evaluation. Few clinicians recommended intensive induction chemotherapy for patients with a new diagnosis of high-risk MDS. The trend was to opt for "gentler" therapies, such as HMAs. Almost 14% of US-based clinicians surveyed did select induction chemotherapy for newly diagnosed high-risk patients without *TP53* mutations.

We do not give 7 + 3 to MDS patients anyway. Even when you are claiming somebody is high risk, ***our options still do not involve 7 + 3****. The question is what do you call aggressive. In my world****, there is no aggressive chemotherapy that we give for MDS****. Simple as that, right? [Physician, Hospital/Health System]*

So higher risk, which includes both intermediate and high-risk MDS, is generally approached with the use of hypomethylating agents. ***That's kind of the backbone of therapy****. [Physician, Academic]*

For those who are high risk and not transplant eligible, the most common thing is hypomethylating agents. I almost never use intensive induction therapy for those people, because the goals really for them are mostly palliative. [Physician, Hospital/Health System]

Newly Diagnosed Low-Risk MDS

Although not all clinicians discussed their approach to managing patients with low-risk MDS, those who did so mentioned using lower intensity agents that are consistent with current guideline recommendations for patients stratified as having symptomatic low-risk MDS. Such approaches include lenalidomide for patients with 5q deletion, observation, growth factor support, supportive therapy, darbepoetin alfa, luspatercept, transfusions, erythropoietin (EPO), azacitidine or decitabine (**Appendix Table 4**).

Low-risk patients can actually do very well with institution of nothing more than supportive therapy, Aranesp, luspatercept, transfusions. [Physician, Hospital/Health System]

Targetable Mutations

Ivosidenib and enasidenib are approved by the FDA for treating *IDH1* or *IDH2* mutations (respectively) in patients with relapsed or refractory AML.[11,12] Overall, clinicians we interviewed were reserving these therapies for patients with diagnosed AML versus for patients with MDS. Both ivosidenib in *IDH1*-mutated MDS or enasidenib for *IDH2*-mutated MDS have shown efficacy in early phase studies.[13,14] A small group of clinicians in academic and hospital/health system settings spoke of using these options off-label based on "emerging data," although the role of IDH inhibitors is not yet well-defined in the high-risk MDS setting.

> *We have had patients who have been found to have IDH1 and IDH2 mutations, and we have given them these targeted therapies. We have had success with that also. [Physician, Hospital/Health System]*

> *If a patient does have an IDH mutation or a FLT3 mutation that comes back, we may consider using directed therapy to that, plus or minus a hypomethylating agent. I do have a conversation with patients that the data for doing that is not as robust as with the prior option, considering that the venetoclax combination does have Phase III trial data to back it up. I think that they [IDH inhibitors] might be slightly probably more well-tolerated medications, at least initially. I do think that* ***first cycle of venetoclax is actually quite difficult for a lot of older patients****. It is definitely a conversation to have. [Pharmacist, Hospital/Health System]*

> *If it's someone who is older, if they have a higher risk, if they have certain mutations that we can possibly target, then that might be something that we would treat here, start on a hypomethylating agent. If we can do some of the orals like Bcl-2 inhibitors, or again, they have those mutations and the IDH mutations, then we can target those. [Pharmacist, Academic]*

Assessment of Response in MDS

Most interviewed clinicians consider evidence of blast count recovery as "an important metric," "easy to do," and a "simple" method for assessing response to HMA treatment. Most clinicians said they would repeat bone marrow biopsy in the presence of cytopenias or changes in circulating blast counts, "after several courses of hypomethylating agent therapy," "after about 2 to 3 cycles" of HMA therapy, or after "a couple cycles of treatment." One third of interviewed clinicians considered patient reported outcomes and reduction in transfusion burden as important, if not more important, than clinical parameters (**Appendix Table 5**).

> *If we had a positive response, I would just follow the counts. I would not repeat a bone marrow biopsy unless I saw something going, you know, the wrong way, such as a cytopenia that's getting much worse. [Physician, Hospital/Health System]*

That they have palliation of their symptoms. That's success. [Physician, Hospital/Health System]

Supportive Therapy/Care

In MDS, clinicians described supportive care or therapy in two main ways.

Symptom Management

Supportive care included therapies to manage symptoms associated with MDS in ways that are consistent with current guidance, including transfusions, erythropoiesis stimulating agents, and antibiotic therapy for infection prophylaxis. Over half of surveyed US-based clinicians (n=160) reported not using growth factors in patients with either standard induction chemotherapy or venetoclax plus HMA therapy. These findings were reflected in interviews. Some clinicians were using luspatercept, which was FDA approved in 2020 for treating anemia in patients with very low to intermediate-risk MDS with ring sideroblasts who require RBC transfusions (*If you have ring sideroblasts, then you know that luspatercept is an option*). Other clinicians felt that growth factors were controversial in the high-risk MDS setting and did not routinely provide G-CSF support.

Palliative Care

One third of interviewed clinicians also included palliative care in their definition of supportive care or therapy. They described consulting the palliative care service, palliative social workers, nurse practitioners, nurse navigators or psychologists to ask for help in supportive care, supportive care with transfusions, or hospice care and "just being comfortable."

Supportive care is a very important component of any malignancy treatment, more so in these folks because they tend to be sicker, and they tend to be more transfusion dependent. Supportive care is something that I start or attempt to start the day 1 of my clinic visit with them. I involve oncology social work. I involve financial assistance if needed. There is so much that goes on that is to be done from a supportive care standpoint. We have already talked about some of those things. It could be just transfusions. There could be pain management. There could be oxygen treatments.[Physician, Hospital/Health System]

Some clinicians debated the benefit of transfusions as part of the supportive therapy rubric, viewing them as overused in myeloid malignancies, especially at the end-of-life. They pointed to the side effects and inconvenience associated with transfusion as a rationale for reducing use in the palliative setting and viewed transfusion are largely symbolic, as two academic physicians noted:

That's just basically our physicians' defensive mechanism. You can't treat the patient, there is no cure, and you don't want to go to hospice, at least not yet. Then you're basically just providing transfusion as a symbol. A symbol of supportive care and a

symbol of our physicians' things we can offer to the patient. [Physician, Academic Setting]

Usually you can do like azacitidine or decitabine plus or minus venetoclax. So I would say those are kind of like our recommendations. So I would say a hypomethylating agent plus or minus venetoclax is kind of our go-to. Certainly a hypomethylating agent for sure. You look and see what is kind of their quality of life. I always kind of do it…if they're requiring frequent transfusions and their numbers are really low, then that would tip me off. Because any of the agents that you're doing in MDS, you're really trying to help…you're not going to cure them. So you're really just trying to help them from a palliative perspective. So if they have like high transfusion needs, then I try to give an agent to just try to spare them…like their frequent transfusions. [Physician, Academic Setting]

These clinicians described palliative care as supportive therapy for patients who no longer responded to therapy and many shared stories about particular patients who requested—implicitly or explicitly—supportive care.

I have one patient that has end-stage congestive heart failure, who is 86, and the family is very burdened by so many things that he has. So transfusing him is very difficult because every time you transfused him, he tilted into acute heart failure exacerbation. So it's very difficult. The transfusion has to be almost six hours, one bottle of cells. We tried to give him EPO, but with the EPO, it ended up increasing his blood pressure, because that's the EPO analogs increase the blood pressure. So ***it's such a tough situation that the patient and the family decided just to hold up on anything****. They didn't want to do anything subcutaneous. They didn't want to come into the inpatient centers, especially because with HMA, you can have more cytopenias in the beginning before they get better. [Physician, Hospital/Health System]*

I have a lot of little old ladies that are at the end of their lives, and half their kids are dead already, and all their friends are dead, and they've been without a husband for 40 years. And they wake up and their backs are sore, and their knees are sore, and they've got cataracts, and they can't hear. And they're the ones who are like let's treat this if it makes me feel better, but ***I don't want to be sick with chemo to get an extra 6 months or an extra year. Or can we just do supportive care?*** *They gave me a transfusion, and I felt so much better. Can't we just do that again? [Physician, Physician-Owned/Private Practice]*

Practice Gap #3: Therapy Selection in Patients with Newly Diagnosed Patients with AML

It remains challenging to plan optimal therapeutic strategies for patients who have a poor prognosis, who are older or ineligible for intensive chemotherapy, or who have secondary AML. A surprising number of healthcare professionals offer intensive therapy to newly diagnosed patients with AML with poor performance status. They also vary in their adoption of venetoclax plus HMA.

Eligible for Intensive Induction Chemotherapy

Remission induction chemotherapy (e.g., 7 + 3, CPX-351) is considered the standard therapeutic option for medically-fit patients diagnosed with AML. The emergence of newer treatment options for patients with newly diagnosed AML now requires that clinicians determine whether intensive induction chemotherapy is the optimal option for these patients, and, if so, if they are sufficiently "fit" to withstand this treatment approach.

Interviewed clinicians were mostly using 7+3 as their chemotherapy approach for medically fit patients. Clinicians described using either low-dose cytarabine or daunorubicin and cytarabine for patients with low-risk AML, secondary AML, or as consolidation. Some clinicians expressed reservations about using CPX-351 (liposomal daunorubicin and cytarabine) for patients eligible for intensive induction therapy ("*I know there's some data, but it's not quite prime time yet in terms of using the Vyxeos"*) (**Appendix Table 6**). Again, chronological age factored into decisions about fitness.

Ineligible for Intensive Induction Chemotherapy

Inappropriate Selection of Intensive Therapy

FDA-approved options for patients with newly-diagnosed AML who are medically-unfit, but not frail include venetoclax in combination with azacytidine, decitabine, or low-dose cytarabine and for newly diagnosed patients with an *IDH1* mutation, ivosidenib. Midostaurin in combination with cytarabine plus daunorubicin is approved for newly diagnosed patients with *FLT3* mutations. One of our case scenarios was a patient newly diagnosed with *FLT3*-mutated AML and an ECOG PS of 2. Expert faculty noted among those surveyed (**Figure 4a, 4b, red arrow**) that a relatively large number of clinicians, especially non-US clinicians, inappropriately selected intensive chemotherapy plus midostaurin in this scenario (US=26%; ex-US=60%). In the case of the 77-year-old patient with newly diagnosed AML and an *IDH1* mutation our experts selected venetoclax plus HMA therapy over targeted therapy with ivosidenib. Among the survey population, a similar proportion of clinicians are using single agent ivosidenib versus the

preferred approach of venetoclax plus HMA therapy (blue arrow, US=22.64% versus 20.75%; ex-US 20.59% versus 17.65%). Of note, among ex-US clinicians there appears to be confusion between ivosidenib which targeted *IDH1* and enasidenib which targets *IDH2*.

Figure 4a. Primary Preferred Treatment Recommendations for Newly Diagnosed AML Clinical Scenarios, US (n, range 159-162)

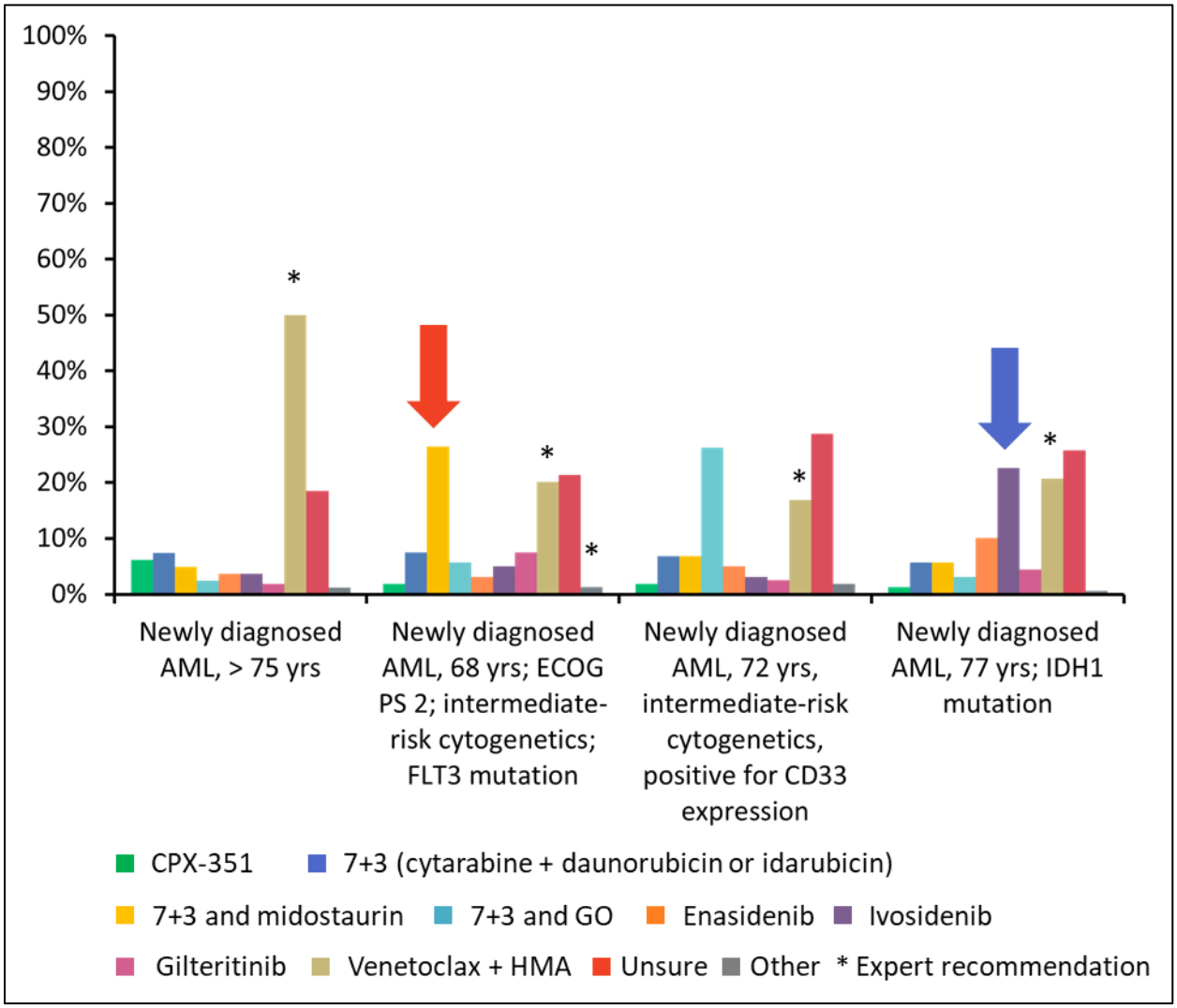
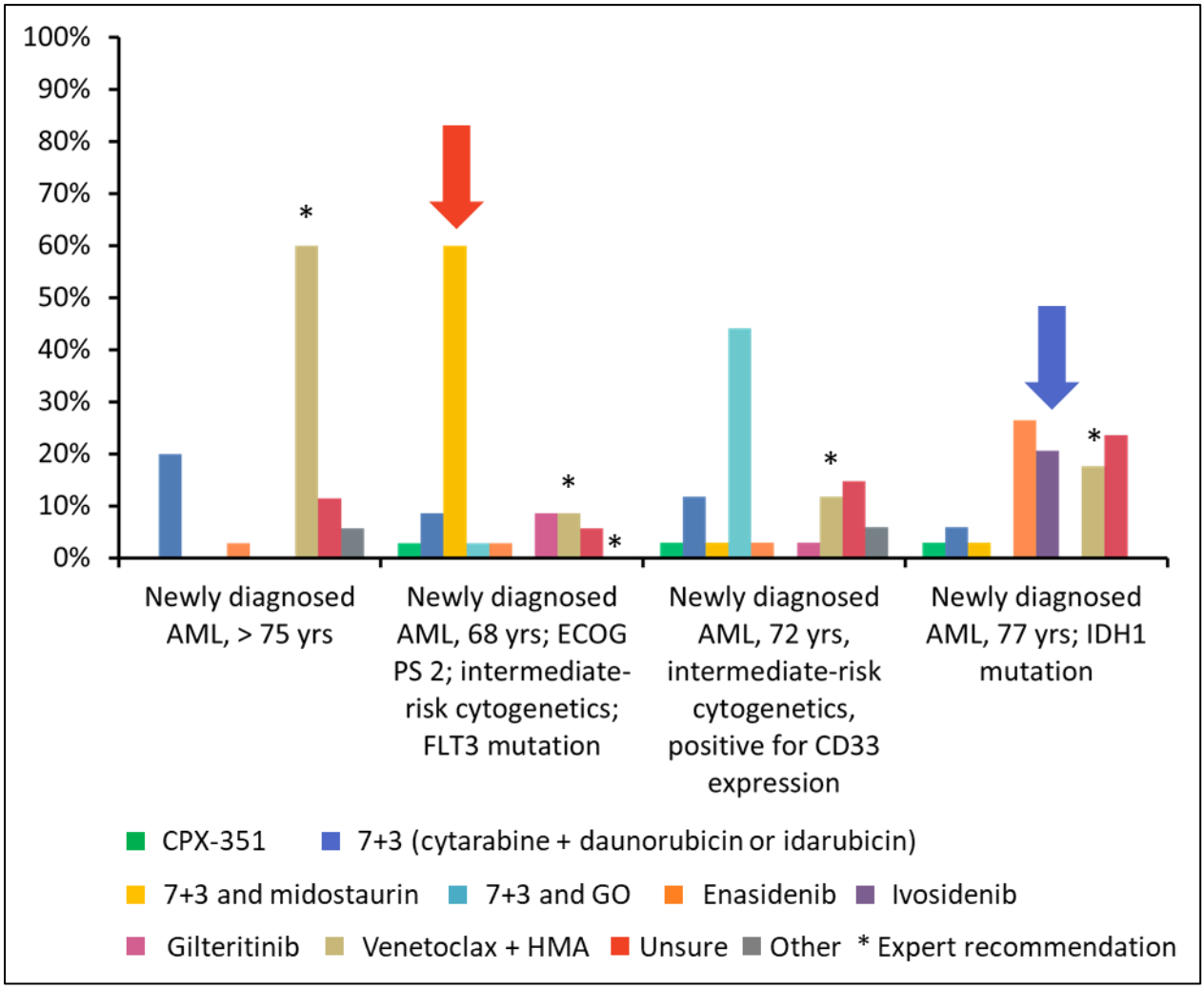


Figure 4b. Primary Preferred Treatment Recommendations for Newly Diagnosed AML Clinical Scenarios, ex-US (n, range 34-35)



Factors Influencing Therapy in Newly Diagnosed AML

Clinicians identified favorable cytogenetics, age, fitness, performance status, comorbidities, the presence of *IDH* or *FLT3* mutations, ease of administration, efficacy, and patient preference or willingness to receive or comply with treatment as key factors that influence their treatment recommendations for newly diagnosed AML. Many clinicians described fitness as the key decision point in terms of whether a patient is eligible for venetoclax plus azacitidine versus 7+3 or CPX-351; gave examples of what they defined as fitness; and emphasized the importance of testing for *IDH* and *FLT3* mutations as factors in selecting therapy. Clinicians typically referred to a similar range of characteristics, including chronological age, that they felt differentiated patients at extreme ends of the fitness spectrum (**Appendix Table 7**).

Age

And a lot of the people that I treat if they're close to 68, close to 70, they're not going to be really candidates for…not only are they not a candidate for a transplant, but they're not a candidate for intense treatment options. So then I already know that that's not a great option for them. So I start to steer to the more lower intensity right away. ***So I use age as another factor, too, pretty big factor****. [Physician, Academic Setting]*

Efficacy

The nice thing about venetoclax plus, let's say aza, is that ***it's effective for any patient with AML. So it doesn't make a difference what their baseline findings are****. They are likely to respond. The categorization may imply how long they're likely to respond more so than whether they will respond. So that's the good news. [Physician, Physician-Owned/Private Practice]*

Variations in the Adoption of HMA plus Venetoclax

As expected, there was very little signal concerning use of 7+3 for patients ineligible for intensive therapy in the interview data; however, there was variation in the adoption of HMA plus venetoclax. Over half of interviewed clinicians described either clinical trial, if available, or azacytidine plus venetoclax as their current standard of care for "older patients," patients over 75 years, or for medically unfit patients. These clinicians are also looking for mutations to treat (*IDH1, IDH2, FLT3*). The remaining clinicians were slowly moving toward adoption of HMA plus venetoclax and away from other options or using existing therapies on occasion (e.g., low-dose cytarabine). Hesitancy about adopting HMA plus venetoclax was linked to the challenge of myelosuppression or cytopenia management, formulary availability, some attachment to 7+3, and questions about whether venetoclax combined with an HMA is less intense than chemotherapy (**Appendix Tables 8 and 9**).

Standard of Care

If they are truly an AML without any actionable mutation, no IDH, and no FLT3 mutation, our standard here is venetoclax with decitabine or venetoclax with azacitidine. If they have one of the targetable mutations like a FLT3 mutation, then that's something you can add to therapy. If they have IDH1 or 2 mutations, there are drugs that are approved for that. [Physician, Academic Setting]

7+3

My only choice here is can I give the patient 7 + 3 or not. That's my first decision. ***If I can get this patient through 7 + 3, that is my go-to drug****. Of course, even if I find a mutation in a patient who is getting 7 + 3, because the molecular studies will take two more weeks to come back, and I cannot wait that long sometimes. [Physician, Hospital/Health System]*

Venetoclax Schedule and Dosing

Toxicities (clinicians noted cytopenias, neutropenia, gastrointestinal toxicity, tumor lysis syndrome), disease progression, or drug-drug interaction between venetoclax and antifungal medications were the most common reasons that clinicians reported for interrupting venetoclax when treating patients with AML. Not all clinicians had seen toxicities with venetoclax and an HMA agent; clinicians who had seen toxicities stopped the venetoclax dose and continued the HMA or lowered the dose of the HMA and maintained the venetoclax. Clinicians noted that side effects from both agents overlapped, making it difficult to identify a toxicity mitigation strategy. They also felt that the administration and dosing schedule described in venetoclax trials were not optimal in clinical practice and often opted for other schedules (**Appendix Table 10**).

Clinicians held a variety of viewpoints on the synergy between venetoclax and HMA therapy, including the following:

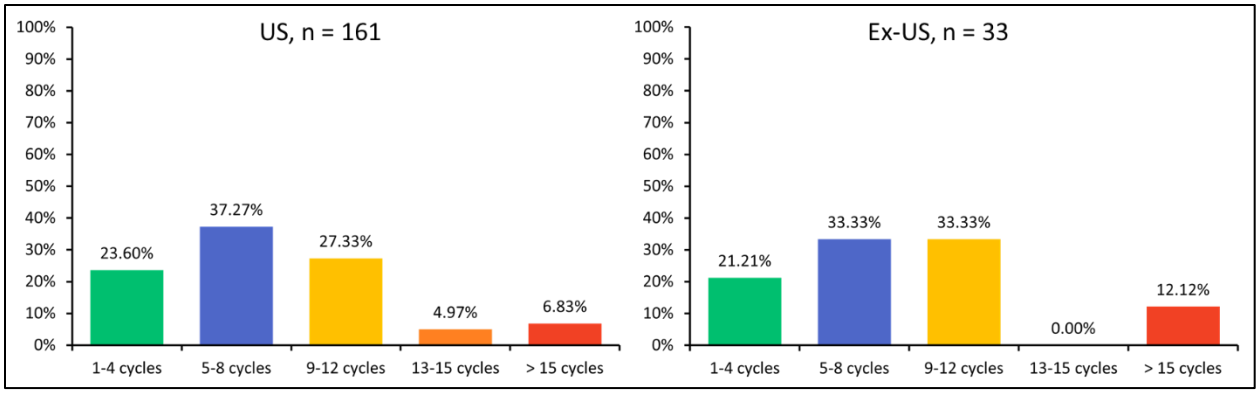
- The efficacy data was stronger for HMAs than venetoclax
- HMAs, either by themselves or in combination, require an extended period of administration to get the full benefit
- Most of the side effects from both agents overlap; therefore, they might stop both agents in the presence of toxicities
- Clinicians questioned continuous dosing and noted that in practice their preference was often to stop venetoclax at day 15 or 21
- Many simply felt uncertain about best practice when using venetoclax and an HMA.

Assessing Treatment Response with Venetoclax

Clinicians vary in therapy duration following complete remission for patients treated with venetoclax plus HMA and are not uniformly using bone marrow biopsy to assess response to treatment with venetoclax-based therapies.

Experts vary in the number of cycles they recommend for patients after achieving complete remission (9-12 or >15 cycles) (**Figure 5**). Similarly, surveyed clinicians also reported variable durations with most recommending fewer cycles than our expert faculty.

Figure 5. Duration of Therapy Following Complete Remission for Patients Treated with Venetoclax Plus HMA Therapy, US and ex-US



Venetoclax-based therapies are associated with rapid responses. Assessment for response is recommended after the first cycle of therapy (around day 28). Venetoclax is associated with significant myelosuppression; therefore, end of cycle bone marrow assessment is important to assess disease status and guide duration of therapy, dose modifications and future cycles.[15] For venetoclax in combination with either low-dose cytarabine (LDAC) or HMA, a bone marrow assessment after the first cycle of treatment is critical to determine dosing and timing of subsequent cycles because most patients will achieve their best response after 1 cycle.

Clinicians were assessing response on a monthly basis using decreasing blast percentages, hematopoiesis improvement, CBC, LDH levels, and coagulation studies. Clinicians who were using bone marrow assessment typically did so after the first cycle and repeated bone marrow biopsy after the third or fourth cycle. Some argued for bone marrow assessment after 2 cycles of treatment. Not all clinicians were using bone marrow for assessment (**Appendix Table 11**).

After 1 Cycle

AML disease is pretty aggressive and much faster growing. You're ready to perform a bone marrow biopsy after induction or after 1 cycle of treatment just to see where the response is. The quality of life is important. Untreated AML will give you very poor quality of life in a very short period of time. It is not just related to the anemia and the thrombocytopenia. It's mostly also related to the infections and other things. [Physician, Academic Setting]

After 2-3 Cycles

I usually see them weekly with a CBC. So, you know, that's a treatment assessment already. And if things are going well, I'll wait probably a month or two for a bone marrow. [Physician, Hospital/Health System]

No Rush to do Bone Marrow Biopsy

The longer you can wait, the better. There's no rush in doing so. It's just if cell counts are good, reasonable, and/or the patient's doing well, no urgency to do a bone marrow evaluation just to see if they're in CR or not. If they're not a transplant candidate, then there's no urgency in getting an evaluation. So you can wait months and months. There's no rush. [Physician, Physician-Owned/Private Practice]

Practice Gap #4: Relapsing or Recurring AML

Clinicians view relapsing or recurring disease as one of the biggest unmet needs in AML management and vary in their approaches.

Relapsing or recurring disease represents a significant unmet need in AML management. Overall, approximately 28% of surveyed US clinicians and 19% of non-US clinicians were "unsure" about their preferred treatment recommendations for patients with relapsed or recurring AML (**Figure 6a, 6b).** Secondary AML is particularly difficult to treat. Both faculty experts indicated they would use CPX-351 in our case scenario. Many survey respondents also chose CPX-351 (US n=22.01%; ex-US n=31.43%) but venetoclax plus HMA (US n=20.75%; ex-US n=22.86%) was also highly selected.

Figure 6a. Primary Preferred Treatment Recommendations for R/R AML Multiple Clinical Scenarios, US (n, range 159-160)

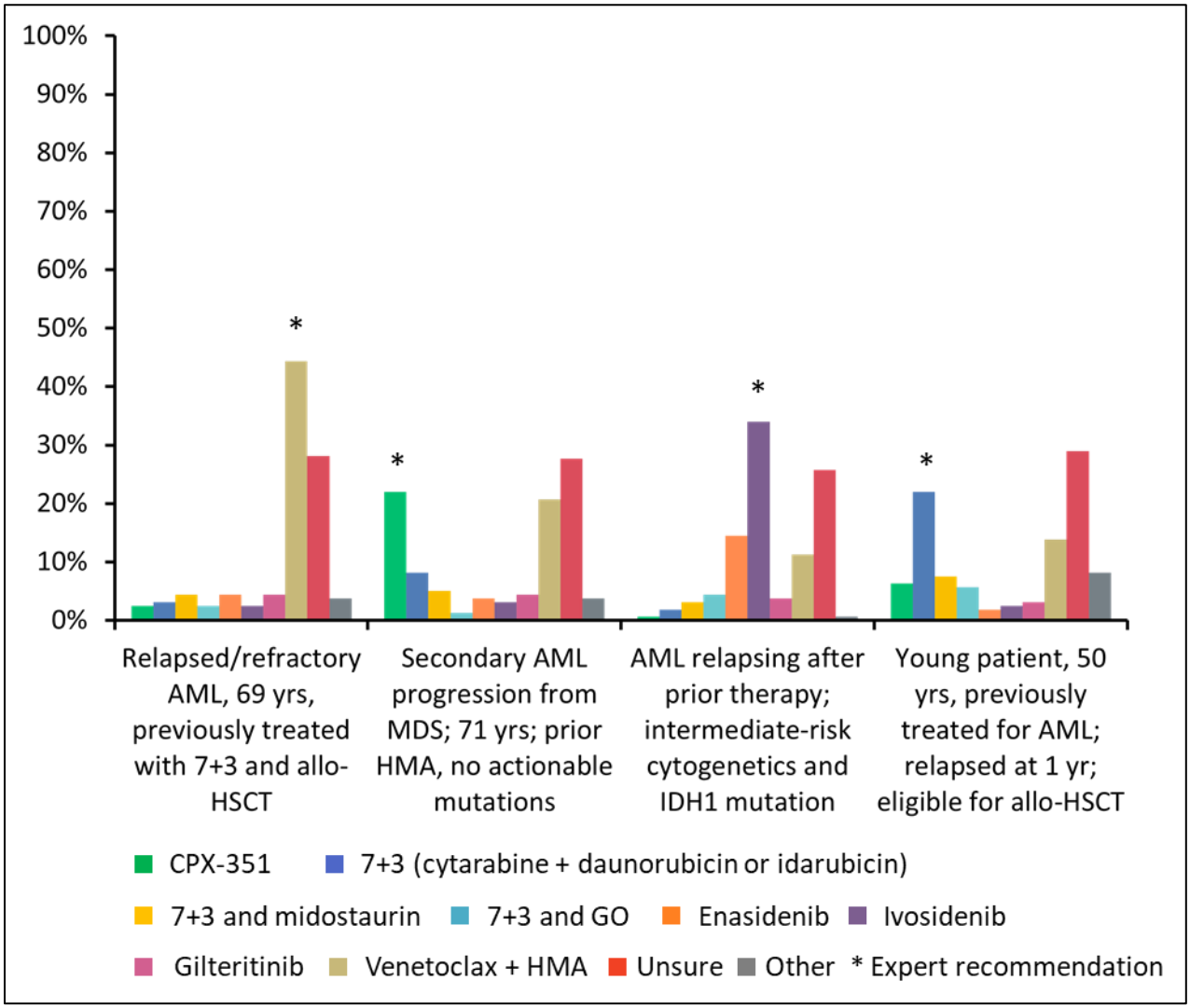
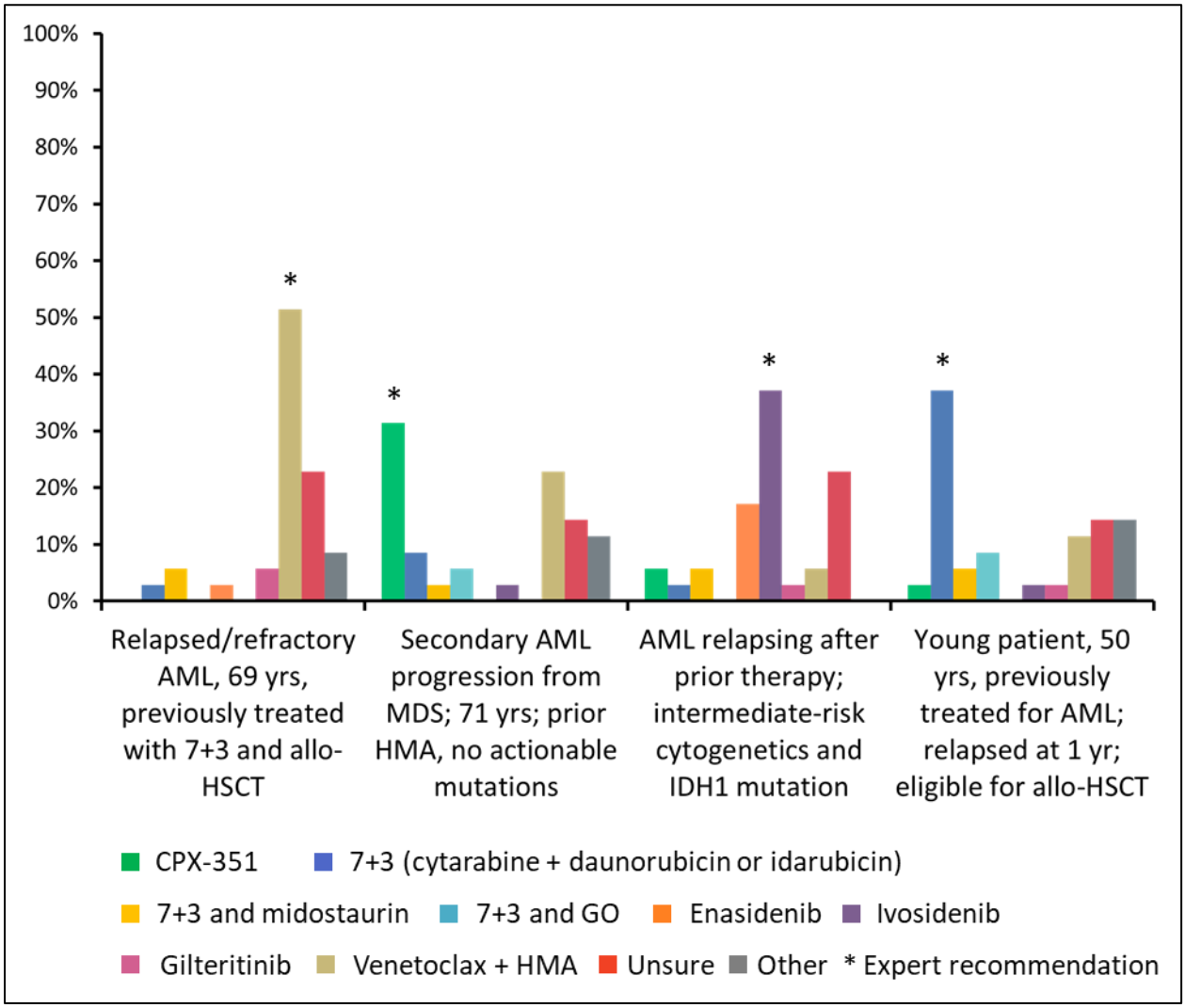


Figure 6b. Primary Preferred Treatment Recommendations for R/R AML Multiple Clinical Scenarios, ex-US (n = 35)



Interviewed clinicians viewed management options were "similar to frail patients" with "no good outcomes" in which patients were often unlikely to make it to the next line of treatment. Said one physician, "*It's a nightmare. So it's not easy*."

Cytogenetics and mutations featured prominently in decision-making with *IDH1/2* inhibitors either as single agents or in combination with HMA or gilteritinib for patients with *FLT3* mutations most frequently mentioned. Otherwise, clinicians were trying whichever options were available in their practice setting with the goal of transplant if patients were eligible and, if not eligible for transplant, then best supportive care. The following comments illustrate the depth of challenges that clinicians face in relapsed or refractory settings.

*And **really talking to the patient in detail about how this is really bad,** and if we're not making improvements soon and we can't get you to a transplant if they're transplant eligible or some other kind of clinical trial protocol, really **talking to them about getting their affairs in order** and we really need to think about palliative care and hospice. [Physician, Hospital/Health System]*

*You kind of look at their cytogenetics and see if there's something that you can maybe target. If you cannot target it, then you just try another induction chemotherapy and pray. **Pray it works**. There's a lot of papers out there that say you can do one versus the other, but in all of my time – even when I was a fellow **– there's no rhythm or reason why one works versus another. So everybody has a style, but nobody really knows**. [Physician, Academic Setting]*

*We would get them to transplant if they're eligible for transplant. If they're not eligible for transplant, then it could become that **we just do best supportive care**. [NP, Physician-Owned/Private Practice]*

The following strategies were noted for treating patients with relapsing or recurring disease. **Table 2**).

Table 2. Reported Strategies for Treating Patients with Relapsing or Recurring AML

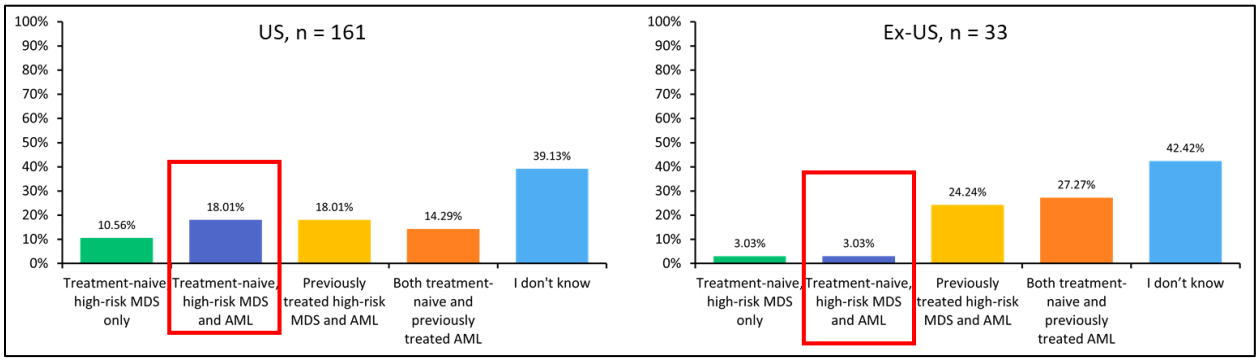
Clinical trials (experimental agents, CAR T-cell)	HMA (decitabine or azacitidine) with venetoclax
Re-induction for primary refractory patients who had never responded to induction regardless of their cytogenetic-risk profile	Reinduction with 5+2, 7+3, low-dose Ara-C, high-dose Ara-C, FLAG-Ida
Second-line therapy like cytarabine or FLAG for transplant-naïve patients who are eligible at relapse to get them to transplant.	Salvage chemotherapy with a different agent (e.g. MEC, FLAG, CLAG-M) to put patients into second remission and try for transplant
Oral azacitidine for patients who have achieved at least remission after the first induction	Off-label glasdegib Gilterinib, enasidenib, ivosidenib, gemtuzumab ozogamicin, high dose lenalidomide

Practice Gap #5: *TP53*-Mutated MDS and AML

***TP53*-mutated MDS and AML represent a clear unmet medical need. Clinicians expressed considerable uncertainty on how best to approach therapy for a patient with *TP53*-mutated AML and were very divided in their approaches.**

TP53-mutated AML is a chemoresistant disease subtype that reduces the effectiveness of intensive chemotherapy such as 7 + 3.[16] Patients with the *TP53* mutation are also frequently older, less fit with more comorbidities, and experience a higher risk of treatment-related adverse events and treatment-related mortality.[17,18] Venetoclax/HMA or decitabine monotherapy are considered less toxic options for these patients than intensive induction chemotherapy.[19] Two novel agents have recently shown some efficacy in patients with *TP53*-mutant disease. Eprenetapopt (APR-246) is a P53-stabilizing agent that in combination with azacitidine numerically, but not significantly, improved complete response rate in a phase III trial for TP53-mutant MDS.[20] In early phase trials, the anti-CD47 antibody magrolimab plus azacitidine demonstrated durable responses in both MDS and AML and especially in TP53-mutant disease.[21,22] A phase III trial of magrolimab plus azacitidine vs placebo plus azacitidine for MDS is currently enrolling (NCT04313881). Despite these favorable results with magrolimab, the majority of survey respondents were unfamiliar with this recent evidence. (**Figure 7**)

Figure 7. Clinician Awareness of Magrolimab Activity in Select Patient Populations, US and ex-US

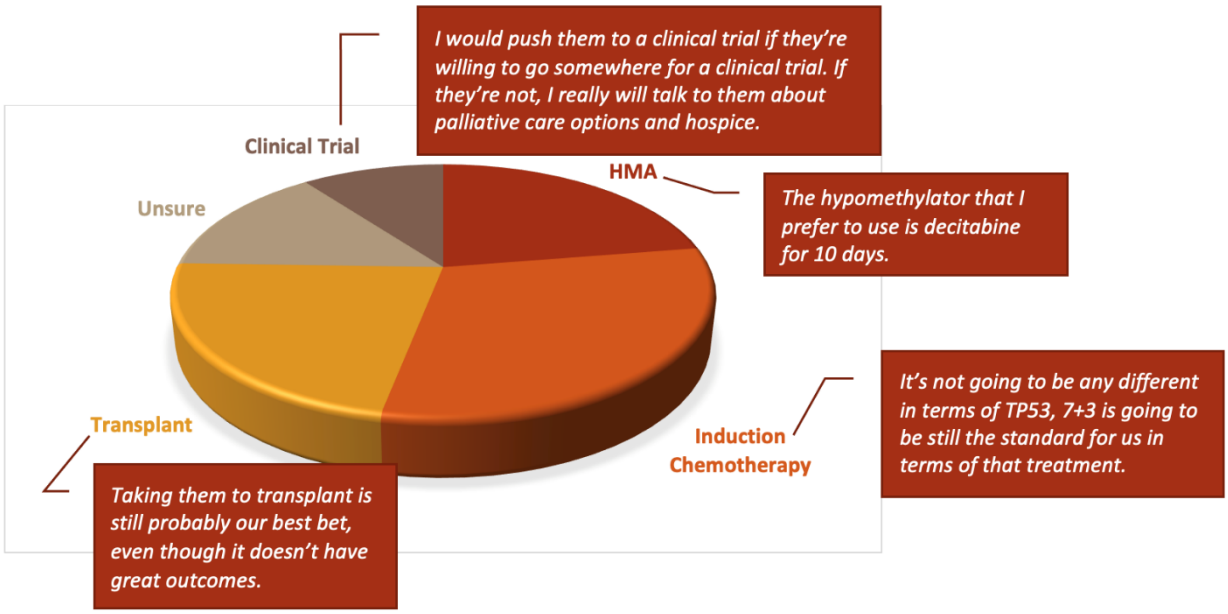


Some interviewed clinicians had not treated patients with high-risk MDS and *TP53* mutations but most of those with some experience of managing these patients said that the presence of *TP53* mutations would not change their overall approach. Most experts believe venetoclax adds little, if any, benefit to patients with *TP53*-mutated MDS. Clinicians described *TP53* mutations as "the worst of the worst" and used a similar, or "more aggressive" strategy as for high-risk MDS patients without *TP53* mutations, including transplant eligibility evaluation depending on the *TP53* mutation burden, clinical trial availability, or hypomethylating agents with or without venetoclax based on data in the AML setting (**Appendix Table 12**). Decitabine was the preferred HMA for some clinicians for patients with *TP53* mutations. Echoing the survey results, few clinicians were aware of the activity of magrolimab in particular patient populations. Clinicians aware of this agent (all in academic settings) were impressed with what they knew of the

available clinical data. These findings highlight the dire unmet need for new effective agents to treat patients with *TP53*-mutated MDS.

Clinicians expressed considerable uncertainty on how best to approach therapy for a patient with TP53-mutated AML and were very divided in their approaches (**Figure 8**).

Figure 8. Reported Therapeutic Approaches for Patients with *TP53*-mutated AML



They felt nothing works in this setting and many viewed transplant as the main goal. A small handful said that clinical trial would be their first consideration (only two specifically mentioned investigational agent magrolimab in this setting), and if unavailable, an HMA with venetoclax, which just over one third overall said they would likely choose. Almost one half said they would opt for induction chemotherapy (with or without transplant) noting 7+3, CFAR (fludarabine, alemtuzumab, rituximab), gemtuzumab, and CLAG (cladribine, mitoxantrone, and cytarabine). Age and fitness were key factors in determining therapeutic direction. Many said they would add midostaurin for patients with *FLT3* mutations or an IDH inhibitor in the setting of an IDH mutation to whichever regimen the patient was receiving (**Appendix Table 13**).

Practice Gap #6: Clinical Trial Referral

Clinicians vary in the timing of clinical trial discussion and the estimated percentage of patients that clinicians said they were able to refer for clinical trials is low. Clinicians themselves view access to clinical trials as a major challenge in the management of patients with MDS or AML. In addition, clinicians lack knowledge of therapeutic agents currently in clinical trials.

In MDS and AML, often there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with MDS and AML and to promote discovery of new therapies. Yet discussion of clinical trials with patients was highly variable. Among US-based clinicians 12% report they "Never" discussing clinical trials and among non-US based clinicians approximately 31% responded "Never" (**Figures 9a and 9b**).

Figure 9a. Frequency of Discussing Clinical Trials in Newly Diagnosed MDS/AML, US and ex-US

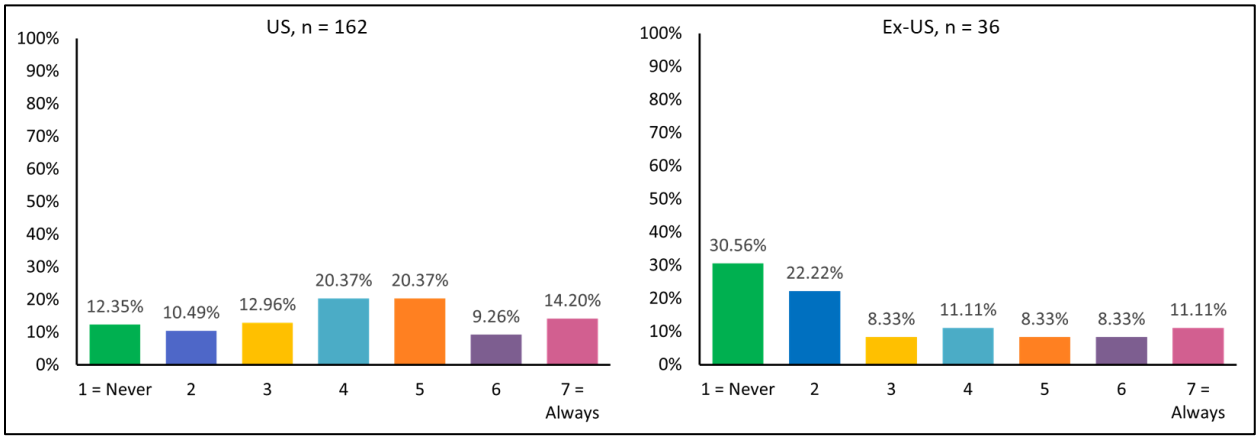
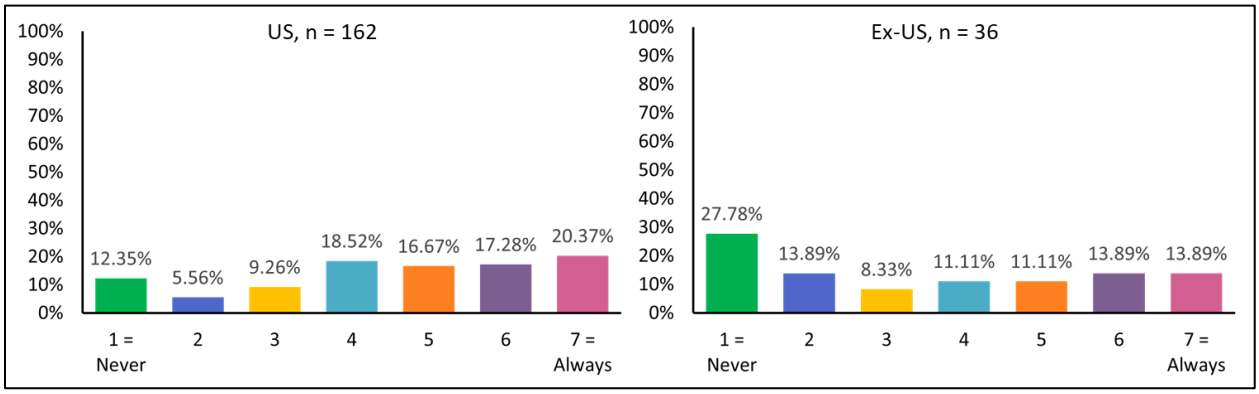


Figure 9b. Frequency of Discussing Clinical Trials in Relapsed/Refractory MDS/AML, US and ex-US



Many clinicians are also unfamiliar with the activity or mechanism of action of agents in clinical trials (**Appendix Figures 5 and 6**). In particular, just 35% of US and non-US respondents were

able to correctly identify the target of magrolimab as CD47. This lack of awareness of mechanism of action is not limited to unapproved agents. Ivosidenib which targets IDH1 and enasidenib which targets IDH2 were often confused and only correctly identified 36-45% of the time.

The picture from interviews of how and at what point in the disease process that clinicians discuss clinical trials varied across healthcare setting.

At Diagnosis and Beyond

Just under half of clinicians in academic or hospital/health system settings said they discussed clinical trials as an option for patients at diagnosis of MDS or AML and beyond. These findings align with the responses this group of clinicians gave to survey questions about how often they discussed clinical trials with patients (i.e., at diagnosis and in the relapsed/refractory setting). These clinicians described having good access to clinical trials at their own institutions and the ability to talk with colleagues about potentially open trials.

At Relapse or Refractory Disease

Approximately 25% of interviewed clinicians reserved discussion about clinical trials as an option for patients with relapsed or refractory disease. Although they too, felt they had good access to clinical trials at other institutions, distance from the clinical trial was a frequently noted barrier to patient interest in participating in a clinical trial. The remaining clinicians—all in physician owned/private practice settings—felt they had considerably less access to clinical trials as an option for their MDS and AML patients or felt that their patients would be reluctant to participate in a trial, again, as a result, in the clinicians' eyes, of distance from the trial center or lack of social and material support (**Appendix Table 14**).

> *Unfortunately, with me being in a very rural setting away from civilization sort of, and patient are in a low socioeconomic status, especially when they have AML, they are really, really reluctant to go anywhere. The only thing I can convince them is to go for a transplant. But to talk about clinical trial will be hard. [Physician, Physician-Owned/Private Practice]*

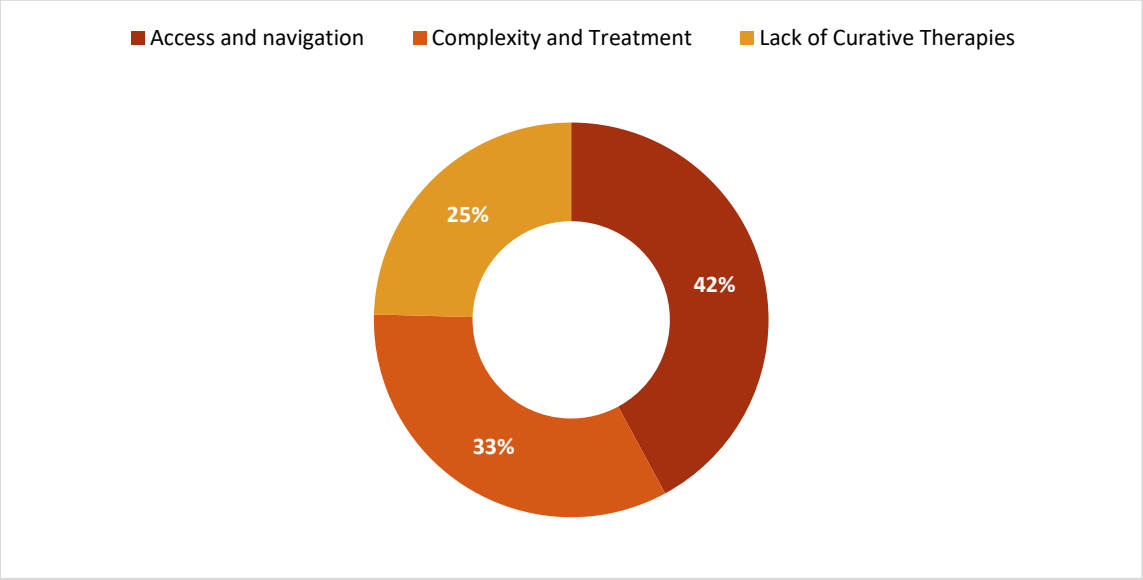
> *In certain situations we may consider induction chemotherapy, but a lot of patients don't want to be admitted to the hospital to get induction chemotherapy, or don't want that intensive therapy in a non-transplant setting in a non-curative setting for MDS. I will highly involve the patient in letting them know these are a couple of the different options that you can use, what would you like us to try. [Physician, Hospital/Health System]*

However, even clinicians who felt they had good access to clinical trials in their own or other institutions, or had a clinical trial coordinator, identified clinical trial access as a major challenge in the management of patients with MDS or AML.

Main Clinical Challenges in the Optimal Treatment of Patients with MDS or AML

The top 3 clinical challenges that interview participants identified as barriers to optimal treatment and patient management were access and navigation to therapies; the complexity of treatment; and the lack of effective therapies (**Figure 10**). Clinicians across different practice settings shared these challenges.

Figure 10. Top 3 Reported Clinical Challenges



APPENDIX

MDS/AML Survey

1. Do you currently treat patients with either MDS or AML?
   A. Yes
   B. No [If selected send directly to “thank you” screen]

2. Which of the following most accurately identifies your role on the healthcare team?
   A. Physician
   B. Nurse practitioner
   C. Nurse navigator
   D. Physician assistant
   E. Pharmacist
   F. Allied health professional
   G. Other (please specify)

3. For how many years have you been practicing medicine?
   A. < 5
   B. 5-10
   C. 11-15
   D. 16-20
   E. > 20

4. Please indicate where you currently practice medicine.
   A. United States
   B. Outside the United States

5. Approximately how many patients with MDS or AML do you provide care for in a typical month (including newly diagnosed, actively managed, and follow-up patients)?
   A. < 5
   B. 5-10
   C. 11-15
   D. 16-20
   E. > 20

6. Which of the following best describes your primary practice setting?
   A. Academic
   B. Hospital/health system owned

C. Physician owned/private practice
D. Other (please specify)

7. Which of the following best describes your specialty?
   A. Medical oncology
   B. Hematology/oncology
   C. Radiation oncology
   D. Primary care
   E. Nursing
   F. Pharmacy

8. How often do you discuss clinical trial participation with your patients with newly diagnosed MDS or AML?

   (Never to Always 7-point Likert scale)

9. How often do you discuss clinical trial participation with your patients with relapsed/refractory MDS or AML?

   (Never to Always 7-point Likert scale)

10. From memory, try to match the following agents to their target or mechanism of action (please do not look it up)

Agent	Bcl-2	Bispecific antibody to CD123 and CD3	CD123	CD33	CD47	FLT3	Hedgehog Pathway inhibitor	IDH1	IDH2	NEDD8-activating enzyme	p53	TIM-3	Unsure
Enasidenib *(IDHIFA)*													
Eprenetapopt (APR-246)													
Flotetuzumab													
Gemtuzumab ozogamicin *(MYLOTARG)*													
Gilteritinib *(XOSPATA)*													
Glasdegib *(DAURISMO)*													
IMGN632													
Ivosidenib *(TIBSOVO)*													
Magrolimab													
Midostaurin *(RYDAPT)*													
Pevonedistat													
Sabatolimab (MBG 453)													
Venetoclax *(VENCLEXTA)*													

11. Magrolimab has shown encouraging activity in which of the following patient population(s)?
    A. Treatment naïve high-risk MDS only
    B. Treatment naïve high-risk MDS and AML
    C. Previously treated high-risk MDS and AML
    D. Both treatment naïve and previously treated AML patients

12. At what stage do you consider there to be sufficient evidence for you to be comfortable using a new/novel agent to treat your newly diagnosed patients with MDS or AML?
    A. Regulatory approval based on phase III data and expert recommendation
    B. Regulatory approval based on phase III data
    C. Regulatory approval based on phase II or premature phase III data
    D. No regulatory approval but inclusion in treatment guidelines based on clinical data
    E. No regulatory approval but phase III data demonstrating a survival advantage and expert recommendation
    F. Other (please specify)

13. Are you sufficiently familiar with the investigational agent magrolimab to use it in your practice if approved by your regional regulatory agency (FDA, EMA, etc)?
    A. Yes
    B. No

14. How confident are you in your ability to appropriately use the recently approved oral decitabine (decitabine + cedazuridine) for patients with MDS? (*7 pt Likert scale*)

15. For each of the following clinical scenarios of patients with MDS please indicate your primary preferred standard treatment recommendation in your practice.

(Use matching question format; answers may be used more than once; each case can only have 1 answer)

Clinical Characteristics at Presentation	**Azacitidine**	**Azacitidine + Venetoclax** (*off label*)	**Decitabine**	**Oral decitabine** (decitabine + cedazuridine)	**Induction chemotherapy (3+7 or similar)**	**HMA followed by allo-HSCT**	**Unsure**	**Other**
Newly diagnosed, higher-risk MDS								
Newly diagnosed, higher-risk MDS with TP53 mutation								
High-risk MDS previously treated with HMA; ineligible for transplant								

16. For each of the following clinical scenarios of patients with AML please indicate your primary preferred standard treatment recommendation in your practice.

(Use matching question format; answers may be used more than once; each case can only have 1 answer)

Clinical Characteristics at Presentation	CPX-351	7 + 3 (cytarabine + daunorubicin or idarubicin)	7+3 and midostaurin	7+3 and GO	Enasidenib	Ivosidenib	Gilteritinib	Venetoclax + HMA	Unsure	Other
Newly diagnosed AML, > 75 yr										
Newly diagnosed AML, 68 yr; ECOG PS 2; intermediate risk cytogenetics; *FLT3* mutation										
Newly diagnosed AML, 72 yr, intermediate risk cytogenetics, positive for CD33 expression										
Newly diagnosed AML, 77 yr; IDH1 mutation										
Relapsed/refractory AML, 69 yr, previously treated with 7 + 3 and allo SCT										
Secondary AML progression from MDS; 71										

17. In your practice, for patients treated with venetoclax plus HMA therapy who achieve a complete remission, how long do they routinely stay on the combination regimen after reaching a CR?
    A. 1-4 cycles
    B. 5-8 cycles
    C. 9-12 cycles
    D. 13-15 cycles
    E. More than 15 cycles

18. Do you routinely use growth factors with standard induction chemotherapy?
    A. Yes
    B. No

19. Do you routinely use growth factors with venetoclax plus HMA therapy?
    A. Yes
    B. No

20. What is the oldest age of a patient you would consider for stem cell transplant?
    A. ≤ 60
    B. ≤ 65
    C. ≤ 70
    D. ≤ 75
    E. > 75

21. What educational method or approach do you prefer when learning about managing your patients with MDS or AML? (*multiple selections allowed*)
    A. Live meeting/webinar
    B. On-demand webcast
    C. Online short video
    D. Online text
    E. Downloadable slides
    F. Podcast
    G. Live Q&A with an expert
    H. Other (please specify)

22. If you would like to participate in a 45-minute qualitative survey, please enter your email address. (Only for US-based clinicians)

TABLES

Table 1. Cytogenetics, Mutation Profiles, and Patient Preferences in MDS and AML

Bone Marrow Biopsy for Unexplained Cytopenias
If you see a cytopenia that you cannot explain, I'm very trigger happy with bone marrow biopsies. [Physician, Hospital/Health System]
If they have MDS, their erythropoietin level is high most of the time. Essentially, they require bone marrow biopsy. That's a gold standard for diagnosis of MDS. [Physician, Physician-Owned/Private Practice]
MDS is one of the somewhat rare hematologic conditions where you really can't make a diagnosis without a bone marrow biopsy. [Physician, Academic Setting]
It's almost expected that you will have a bone marrow evaluation. It'd be very unusual not to do bone marrow evaluation. It's obviously not a difficult procedure to undergo. It's not too difficult to convince a patient that they need it. Bone marrow evaluation for diagnostic purposes is essentially a must, as far as I'm concerned. [Physician, Physician-Owned/Private Practice]
Ultimately, we would need to do a bone marrow biopsy if the patient didn't have any obvious explanations for their abnormal blood counts. So if they had unexplained cytopenias, I often will simultaneously do a genetic test, where we look for mutations that are associated with MDS. And, in fact, in some patients we often get that information back before we even do the biopsy. [Physician, Academic Setting]
***We do bone marrow biopsies at diagnosis. Only for the very older patients, you'd not**. But for almost everybody it's a bone marrow biopsy to calculate the blasts percentage. Very, very rarely in a very older patient, but almost everybody gets it. [Physician, Academic Setting]*
Cytogenetics, Mutational profile, and Patient Preferences
I'm looking to see if a patient has any mutations for targetable therapy. If a patient has IDH mutations, that would be one thing. And also, if the patient's fit enough to do an allogeneic transplant. [Pharmacist, Hospital/Health System]
We do screen for p53 mutations. There are certain cytogenetic abnormalities, like loss of chromosome 5 and 7, that correlate with p53 mutation, which primarily fits into a higher risk or high-risk category. [Physician, Academic]
We'll do a bone marrow biopsy, and from there we'll send off both conventional studies – FISH, cytogenetics, and also next-gen sequencing for both prognosis and treatment decisions.[*Physican, Academic Setting*
In AML, we've had so many new therapies, just flooded in terms of lots more options. So kind of looking first to determine patient's risk status, the cytogenetics and molecular abnormalities that we're looking at to determine if they're favorable risk status, or if they're poor versus intermediate. And that's one thing to look at. And also, we want to see the targets. Does the patient have a FLT3 mutation? Does the patient have an IDH mutation? And lastly, also looking at the patient's fitness level as well, to help kind of determine which route to go. [Pharmacist, Hospital/Health System]
All these patients would receive bone marrow biopsy, including next-generation sequencing and cytogenetics, and these patients would be risk stratified based on their cytogenetics and molecular makeup into favorable, intermediate, or high-risk patients. [Physician, Academic Setting]
Once you assess all the performance status, they usually get a bone marrow biopsy. And in the bone marrow biopsy, you can see is it just MDS, is it MDS almost about to convert to leukemia? We can send cytogenetic markers to see is there a 5q deletion where you can maybe use lenalidomide or Revlimid; if not, they have complex cytogenetics, or do they have an IDH1 mutation? You can see,

based on the cytogenetics, what are potential treatment options for them. [Physician, Academic Setting]
If I have somebody who's younger, who's fit, who I think might benefit from a transplant who may have MDS, then I will actually proceed with the bone marrow biopsy initially, check cytogenetics, check all of the next-generation sequencing for all of the mutations. And then get them up to a consultation at one of our transplant centers, and then make decisions based on therapy based on whether somebody thinks that they're going to transplant them early, or if we're just going to wait it out and see how things go. [Physician, Hospital/Health System]
Patient Willingness to Receive Transplant
*I have a lot of little old ladies that are at the end of their lives, and half their kids are dead already, and all their friends are dead, and they've been without a husband for 40 years. And they wake up and their backs are sore, and their knees are sore, and they've got cataracts, and they can't hear. And **they're the ones who are like let's treat this if it makes me feel better, but I don't want to be sick with chemo to get an extra 6 months or an extra year. Or can we just do supportive care**? They gave me a transfusion, and I felt so much better. Can't we just do that again? [Physician, Physician-Owned/Private Practice]*
*We also want the patients to be very, very involved in their care. The patients and the caregivers and their families. We want this to be a team approach, not just the physician and the staff telling the patients what we're going to do. Sometimes we can make an offering of several options and let the patients kind of decide what they want to do. Sometimes we learn things from them that we hadn't thought of **and the patients would say, look, I would rather live less time and have a happier, productive life rather than living longer and I'm totally dependent on someone**. We let that all be a part of that conversation that we are having with the team and the patients, as well as their caregivers. [Physician, Academic Setting]*
*I will tell you that for both acute myeloid leukemia and MDS, I will have patients who I feel are medically fit for potential induction chemotherapy or a transplant evaluation, or both, and **sometimes patients will just say I don't want to travel the 2 hours to go to Kansas City to have my treatment done, so do whatever you can locally, and that's all that I want done**. And some of those patients we'll give induction chemo to but knowing that might only buy them some extra time. But patients sometimes trump what we want to do for them. [Physician, Hospital/Health System]*

Table 2. Definitions and Approaches to Assessing Fitness

Gestalt Approach
Even from when you start to look at them, you can really get the impression, as well, whether these patients would require oxygen supplementation or not, and how much muscle mass they have. ***When you look at these patients you can get also a fair estimate on them****. [Physician, Academic Setting]*
Once you see the patient ***you get the gist****. [Physician, Hospital/Health System]*
Usually we define fitness as whether or not we think a patient is likely to be able to tolerate intensive chemotherapy. ***We have kind of a binary system for deciding whether a person is fit or is not fit.*** *[Physician, Academic Setting]*
There are scoring systems, but I think I have learned to rely on my clinical acumen to get a better and more comprehensive understanding of the patient's history than just the score. [Physician, Hospital/Health System]
Trust in Tacit Knowledge
After being in the business for 30 years, many times you don't necessarily need an official scale system. ***You can make up your mind just looking at a patient****. [Physician, Physician-Owned/Private Practice]*
*Most of the time****, this is physician judgement*** *whether this patient is fit or not according to the age. [Physician, Academic Setting]*
I know there are tools to do that, scoring systems, but we have not done that. We are looking at ECOG functional status. We work closely with pulmonary and cardiology and endocrinology, and these are the most common comorbidities that the patients have. Again, not a formal process. ***It becomes like a judgment call quite often****. You have to decide whether your patient is essentially, not in MDS but at least in leukemia, you have to make this call whether your patient is going to be handling intensive chemotherapy or not.* ***Oftentimes, it's to start off, an eyeball test****. I think we probably err on the side of caution. [Physician, Hospital/Health System]*
We all try to look for the ECOG performance status, and that's what we use at least for just assessing if the patient will be eligible for high chemotherapy like 7+3, even Vyxeos. So ***ECOG performance status but there's also a subjective level to it****. Even if someone has a good performance status but is the eyeball test like you sometimes see. [Physician, Hospital/Health System]*
Age and Its Gray Areas
So, a patient who is on the younger end of 65 – so maybe they're 50 and completely fit – or the patient who's 90 and is bedbound and debilitated, those are fairly easy to assess for most people. ***It's the people in the gray areas in between who are maybe 70 and have, you know, one or two comorbidities****. And you have to make a more informed decision based on how functional they are, how, you know, fit they are, what other medical conditions they have, and what their life expectancy is. And so, I think that's more of a Gestalt. [Physician, Academic Setting]*
Most MDS patients are older patients, so they will benefit from those assessments, even without MDS. It's always good to get a sense of how an older person is doing and not just their medical comorbidities, but also their geriatric vulnerabilities, which are factors that affect their tolerability to treatment, affect their quality of life, and also affect their independence to live in the community and live at home. There will also be patients who are vulnerable even before they were diagnosed with MDS or AML. Those are the patients then obviously you would consider whether there is a way you can optimize or improve their function or remedy their vulnerabilities. **It is this group of patients who are the most tricky when it comes to the medical decision-making by the physicians**. [Physician, Academic Setting]

Table 3. Factors Determining Eligibility for Intensive Therapy in High-Risk MDS

Age
I know age is a factor, also performance status. *So typically, if it's someone who is older, if they have a higher risk, if they have certain mutations that we can possibly target, then that might be something that we would treat here, start on a hypomethylating agent. If we can do some of the orals like Bcl-2 inhibitors, or again, they have those mutations and the IDH mutations, then we can target those. [Pharmacist, Academic]*
It's depending on the age. *They may be slotted in for the high risk, either like a hypomethylating agent and then adding like other…depending on what the mutations are, like venetoclax with it, or there's the other drug called…that's fairly new, though. So depending on what their age, if they are younger, of course, and then going into transplant from after that if they're high risk. [NP, Academic Setting]*
If they're over 70 – is kind of my cut-off point, 70 or 75 *– and they have a lot of other comorbidities going on, then you certainly can't be more intense than really a hypomethylating agent or maybe danazol. [Physician, Academic Setting]*
If a patient has higher-risk MDS, doesn't have very many comorbidities, ***we do have a little bit of an age cut-off there. It's roughly around age 75****. So, it's very similar to what we would think about if the other patients are fit for chemotherapy. [Physician, Academic Setting]*
The main factor at the end of the day, like I said, would be ***whether somebody's fit or not fit which in reality comes along with age. So that is the main factor****. Well, of course, there are other factors. Let's say we know that somebody's not fit, we decide whether somebody is going to be compliant or noncompliant. A patient might want to say I really want very little treatment-wise, I mean I agree for the treatment, but I don't want it to be too aggressive, I want you to be aware of it. So individual patient's wishes, and there is no specific format how they express it, would matter. [Physician, Hospital/Health System]*
Fitness
For ***high-risk patients who have mild alterations in their blood counts but high-risk genetics, I think that is more of a gray area****, in terms of whether they should be treated like a high-risk patient and put on the trajectory for stem cell transplant, if they're eligible, versus a high-risk patient who has an elevated blast count and/or, you know, substantial cytopenias – a hemoglobin less than 10, a neutrophil count that's reduced, or thrombocytopenia with a platelet count less than 100 – to the point where they're kind of getting into that danger zone that they're going to develop symptoms. For those patients, again, we kind of stratify them by their age, eligibility, down the road for an allogeneic stem cell transplant, which is really the only curative therapy. [Physician, Academic Setting]*
Age and the performance status – these are the two major factors*. You can add comorbidities like someone has maybe advanced, very complicated diabetes or someone has rheumatoid arthritis or very uncontrolled other or renal failure. So even if their performance status might be good, but that kind of push them to the unfit patients. [Physician, Academic Setting]*
ECOG 2 and above would be considered unfit *and those would not be offered usually a definitive treatment with a transplant. [Physician, Academic Setting]*
A lot of it is just clinical gestalt *and just looking at their comorbidities, and looking at their performance status, and looking at if they're willing to travel to as well, but I'm really using like can they walk, can they walk up a flight of stairs, can they walk more than a half a mile? Do they have any major heart disease, lung disease, liver disease that's going to exclude them from a transplant? Are they willing to travel? Those are the main ones. [Physician, Hospital/Health System]*

Right off the bat, you have to decide is this a good performance status, so we look at the ECOG immediately. That way you do intensive therapy or just hypomethylating agent, venetoclax. [Physician, Hospital/Health System]
*Using ECOG classification and a little bit of age, too, you know. We used to focus a lot on biological age more than just the chronological, but **we'll be very careful with somebody who was above 70**. [Physician, Hospital/Health System]*
***That is a more subjective measure.** And in part it has to do with their comorbidities, any other organ dysfunctions they might have. It has to do with their functional ability. I think patients who spend greater than 50% of their day in bed or in a chair and you have poor performance status, do worse, are patients that I would be concerned about being able to tolerate intensive chemotherapy. [Physician, Academic]*
Tolerance for Therapy
***There's an assessment of their tolerance of intensive therapy**. I look at hypomethylating agents as kind of intermediate between kind of low-dose therapy and intensive therapy. At the standard dose of decitabine and azacitidine, they clearly are acting as cytotoxic agents. [Physician, Academic]*
We are trying to look at the comorbidities the patients may already be experiencing because of the age group. It's usually diagnosed with 70 and up. We're looking at how they may tolerate these different regimens of medications. Also we're looking at their risk stratifications, as well as their quality versus quantity of life. [NP, Physician-Owned/Private Practice]
*Once the patient begins their treatment, then obviously depending on what kind of treatment and where the patient is, with MDS and AML, as you well know, we have options. We can admit the patient to the hospital and give them very intensive chemotherapy. If they're frail we can give them a less intense chemotherapy, still in the hospital. If they are healthy, we can treat them outpatient. A lot of those things are determined by several factors. One is frailty of the patient. **Are they going to be able to withstand the treatment**. That's the first, if you will, the decision point. What intensity can they tolerate.* [Pharmacist, Physician-Owned/Private Practice]
Age, comorbidities, performance status, **how much he or she can take**….If he is more on the elderly side and not really as excited to do an allotransplantation, then the next best thing is what's available to us. In this case, still HMA alone is the standard therapy with or without growth factor support if they are anemic or neutropenic. After assessing the disease, **then you look at the patient and see what he or she can take**. So in an MDS world where hypomethylating agents are the drug of choice, that's kind of our baseline.[*Physician, Physician-Owned/Private Practice]*
Patient Preference/Quality of Life
You look at the patient's comorbidities and whether the patient wants to be aggressive with the therapy, or whether they're, for whatever reason, that they're inclined not to. They're trying to avoid being in a hospital. They understand what their situation is. They accept it in some fashion, and therefore you don't have to necessarily try to be as aggressive. [Physician, Physician-Owned/Private Practice]
*We want this to be a team approach, not just the physician and the staff telling the patients what we're going to do. Sometimes we can make an offering of several options and **let the patients kind of decide what they want to do**. Sometimes we learn things from them that we hadn't thought of and **the patients would say, look, I would rather live less time and have a happier, productive life rather than living longer** and I'm totally dependent on someone. We let that all be a part of that conversation that we are having with the team and the patients, as well as their caregivers.* [Physician, Academic Setting]
Let's say we know that somebody's not fit, we decide whether somebody is going to be compliant or noncompliant. A patient might want to say I really want very little treatment-wise, I mean I agree for

the treatment, but I don't want it to be too aggressive, I want you to be aware of it. So individual patient's wishes, and there is no specific format how they express it, would matter. [Physician, Hospital/Health System]
Patients' wishes also come into play. There are people who are much more motivated if they have a good support system, then we know that things will fall through the cracks. These folks will require multiple trips to the clinic, multiple labs, infusions. Sometimes insurance can bet in the way also, particularly for targeted therapies. The copay costs can be excessive. One of the targeted drugs for IDH1 and IDH2, each drug is probably $1000 a pill. Even the copay cost, even if it is 10% to 20%, that becomes unaffordable. [Physician, Hospital/Health System]
We have a lot of patients that don't want to be admitted to the hospital for treatment. Anything you can do for me, as an outpatient, I'll do. I don't want to be admitted is a very common theme we hear, especially in the older patient population and especially with COVID. [NP, Academic Setting]
If we do MDS, say the treatment they planning to do that as outpatient, and they have limitations for transportation, that's not going to work. So before they start the treatment, I'm involved in there. So we talk about it, what's going to work for them or not, like they're going to need transfusion support and things like that, transportation and all that, so we can work out the best plan that's going to be workable and patient can be compliant with it. Insurance, also. So I look at the aspect of the insurance, as well, as anything that could be…before the decision is made to let's just treat with this, just kind of making sure that everything is going to be…and not like in the midst of treatment we're going have problems. [NP, Academic Setting]
I've got people that are in their seventies, and they're exercising, and they've got a trip planned to Europe, and they want whatever they can do as aggressive. They've got a daughter's wedding up, or they've got a grandbaby coming or even a great grandbaby coming that they want to make it to. They want to be aggressive. And ***you've got to talk to your patients, and you've got to get a feel****. [Physician, Physician-Owned/Private Practice]*

Table 4. Newly Diagnosed High-Risk MDS

Goals of Care
In general, those patients who don't get a transplant, they will be provided these supportive care measures. We also have drugs like what they call hypomethylating agents. Those are the azacitidine, the Vidaza, the Inqovi and Onureg. Those are the four commercially available drugs that you can give them to allow for the marrow to try to reconstitute and be as close to normal as possible with the goal of preventing or reducing the number of transfusions they will require. Sometimes our measure is how frequently are we having to transfuse this patient. That alone is considered a benefit of giving these drugs such as the ones I mentioned. [Physician, Physician-Owned/Private Practice]
If they're not a transplant candidate and they're high-risk MDS, then mostly the overall treatment approach is palliative. The standard treatment hasn't shown to really prolong survival while maintaining quality of life that much better. If they're not curative, then you also want to pay attention to their quality of life. You don't want to have a treatment approach which might extend their life expectancy by a few months but in the process basically making them hospital bound most of the time. That's what I think about it. [Physician, Academic Setting]
Evaluation for Transplant/Intensive Therapy
7 + 3, right. If we're talking about induction chemotherapy that's a fairly easy call on us. If we see somebody with bad kidneys, heart failure, bad neuropathy, in general a poor protoplasm, a patient with an ECOG 2. ***You would hesitate to pull the trigger****. You have to tread lightly.* ***Oftentimes it is just a gut feeling.*** *You see the patient, they are moving around, active. There are people who have been runners all their life, you know they're in good condition, it's just unfortunately they got diagnosed.* ***There you could be more aggressive. I don't have a good answer. It's a clinical judgment at that point of time.*** *There could be people that you might look at, 72,* ***anybody who is older than 70 we hesitate****. Then there are people who are older, and we have treated them aggressively. [Physician, Hospital/Health System]*
Some of those patients who are maybe very fit, we may also refer them for an allogeneic bone marrow transplant as well. I will probably say maybe ***9 out of 10 patients that I do see with high-grade MDS in my center are probably not fit for a bone marrow transplant*** *right away. [Pharmacist, Hospital/Health System]*
If we know they're high risk, the first thing is to evaluate whether they are a candidate for allogeneic transplantation*. That's obviously considered the only curative approach for patients with high-risk MDS. For transplant to work, you also have to consider social support system, psychiatric stability, and the availability of caregivers.* ***Those are not medical, but they are important for the success of a person to go through intensive treatment****. [Physician, Academic Setting]*
The group that I work with, who they are going to look at for a transplant based on, a lot of times, age. So, under age 75. And it's kind of been a moving target, but probably close to that. ***If you have a really healthy 75 or younger, you can still be transplant eligible, but for the most part, I have not had them think that someone above that age is going to be eligible.*** *So how frail they are, what their geriatric scores or comorbidity scores are, and then age does come into a factor of deciding transplant eligible and ineligible. [Physician, Hospital/Health System]*
Not everybody needs a transplant and ***not everybody qualifies for a transplant. Some of the barriers to receiving a transplant would be frailty****. Not necessarily age, but just physical performance status and so on. It's a rough course. If you have, say a 72-year-old that has diabetes and COPD, they are not good candidates for a transplant. Age alone is not a factor.* [Pharmacist, Academic]
Bridging Therapy

*The rare case where we might use something more intensive, is a patient that we want to take directly to transplant and **where we want to be able to cytoreduce them significantly before we do so**. In those cases we do consider more intensive therapy. [Physician, Academic Setting]*
*Because HMA alone has been challenged in its effectiveness. But I would say, certainly, there is modest improvement – so not everybody responds – and if they respond, their response can be short lived. So **you need to use it as a bridge to see what else you want to do**. [Physician, Physician-Owned/Private Practice]*
*If the patient is a candidate for it, then obviously you have to evaluate whether the patient can go straight to the transplant if they have an available donor, what the timeframe will be, and whether their disease can withstand this time period of securing a donor. **If not, then it's appropriate to give them some additional treatment before going to transplant**. [Physician, Academic Setting]*
*If they have a very high blast percentage, sometimes you begin intensive chemotherapy for especially those with very, very high, about 15%, 20% or so of blasts percentage. Others, **you would try to get them hypomethylating agents plus venetoclax, and then eventually think about transplant**. It all really depends on the performance status and age of the patient. [Physician, Academic Setting]*
*I have sent people straight to transplant also. More often than not, **the whole transplant process takes time. They would need some therapy**, usually azacitidine. [Physician, Hospital/Health System]*

Table 5. Response Assessment in MDS

Bone Marrow Timing
I usually will obviously look at their blood counts and see if they are getting better, or if they have any other symptoms like fatigue or night sweats or anything else which are pretty rare in MDS but can happen, I will use symptoms as an agent, mainly cytopenias. And then usually after about 2 to 3 cycles of whatever we're going to give if it's not an induction chemotherapy, I will assess with a repeat bone marrow biopsy to see what's going on. [Physician, Hospital/Health System]
After first month, second month, after 2 cycles or 3 cycles, I will do the bone marrow biopsy, and then we will reevaluate how the patient is doing [Physician, Academic Setting]
PROs/Transfusion Burden
At the end of the day the goal here would be to stabilize blood counts; that means if somebody receives transfusion-independence, whether this is for red cells or platelets, that is one of the parameters. Of course, you always ask a patient how he or she is doing. We also recognize that at the end of the day this is multifactorial, which means that other factors might play a role, and it is quite uncommon that you'll hear a direct answer. [Physician, Hospital/Health System]
The easiest way to do it is just like do their transfusion needs decline, are they able to come in like a little bit less often? Are their blood numbers starting to improve a little bit? Are they feeling a little bit better? Like if they were short of breath, tired, or fatigued, are those symptoms getting a little bit better? So I look at all of that. Like quality of life symptoms, transfusion needs, and whether the blood numbers are improving. Those are all factors that kind of play a role. Maybe somebody who needed a transfusion every week, maybe now they need it every 2 weeks. Maybe if you had to give 2 units of blood every week, now you are doing 1 unit of blood, and that makes a big difference. [Physician, Academic Setting]
The goals of treatment are going to be symptom relief, alleviation of any symptoms that are being caused from the disease itself. If a patient, for example, is anemic and needing transfusions, 1 assessment of response would be, are they now no longer anemic. Do they now no longer need blood transfusion? Are they able to maintain hemoglobin on their own? That's an example of what I would look for in a response.[Physician, Hospital/Health System]
If the patient's initially symptomatic, so if their counts are improved, their symptoms are improving, are they still needing transfusions, are some of the things that we look at. Patient-reported outcomes, how they're feeling. The counts is the biggest thing, so in terms of if they're needing transfusions, depending on what their main cytopenia was and how that's been responding.

Table 6. Newly Diagnosed Patients with AML—Eligible for Induction Chemotherapy

7+3 as Standard
Newly diagnosed AML, depending on their risk factors, they will be…and if they are young, tolerate it. Even if the elderly unable to tolerate, if the performance score is higher then they will be slotted in for like 7+3, the standard. And then they may add, depending on if they have FLT3 or any of the IDH mutations, then they may add another oral pill like venetoclax or ivosedinib and things like that. So, depending on what their mutations are. [NP, Academic Setting]
A person who is under 70 years of age, we would talk about doing induction chemotherapy with either idarubicin or daunorubicin, along with Ara-C, we do 7+3. And if the patient is FLT3 positive, then we obviously will talk about adding Rydapt into that regimen. [NP, Physician-Owned/Private Practice]
If you can do it with agents like that in APL, we've been looking for that, I think in AML. Right now, 7+3 is really the kind of chemotherapy that we use for AML. That is very effective; 70%, 80% of patients that are under the age of 60 can get in remission. Depending on their chromosome risk, they might be cured with intensive therapy alone and a little bit of maintenance at inv(16), or they've got bad chromosomes and you have to transplant right away. [Physician, Academic Setting]
Daunorubicin and Cytarabine
Most patients will get 7+3 induction, which has been the standard for decades. I think the improvements that have been made are adding a targeted agent to that induction. And so, the most notable one would be targeting FLT3 mutations in combination with 7+3 induction. Oh, right, I was thinking of Vyxeos, which is like 7+3, in a way, for treatment-related secondary AML. So, you know, that might be different for those patients. But most fit patients who are transplant-eligible will get 7+3 plus or minus, you know, a FLT3 inhibitor, if they have the mutation. [Physician, Academic Setting]
We would consider using a hypomethylating agent or low-dose cytarabine. And that's if the patient would be able to tolerate that. [Physician, Hospital/Health System]
Most patients are getting that combination [azacytidine and venetoclax]. There are some patients who have what looks like to be secondary disease or therapy-related disease. Those patients, if they are not totally unfit, might be able to receive something like Vyxeos, which is a liposomal chemotherapy formulation. [Physician, Academic Setting]
If they have suspected secondary AML, which about 10% of patients in the United States with AML have with Vyxeos [Physician, Academic]
If they have low risk, usually I do consultation and treatment with HiDAC (high-dose cytarabine), if they are intermediate or high risk it will be allogeneic bone marrow transplant. [Physician, Academic Setting]
If the patient is an elderly patient that had MDS that transformed into AML, if you do Vyxeos, which is the liposomal 7+3, followed by a transplant, they have a higher overall survival over patients that receive 7+3 and a transplant. So it's an overall survival benefit. It's very expensive. Hospitals don't like to do it inpatient. We do it outpatient now. [Physician, Hospital/Health System]
Consolidation
If they're going to transplant, we would have already typed them up. We would have their siblings set up to get typed, and the transplant process starts working. I may still need to give them 1 cycle of consolidation, and I just use cytarabine consolidation. If the patient does not need a transplant, then I would finish off four cycles of consolidation. If they need a transplant, then I send them to transplant right away. I still might have to admit them again for cytarabine, for which I will do. [Physician, Hospital/Health System]
If they are of good risk and have achieved remission, they don't need transplantation, the next option would then be to consolidate them with high-dose chemotherapy. Typically, there are many agents

you could use, but high-dose cytarabine is what we use for a good risk AML that does not need to get transplant as achieved with CR1. [Physician, Hospital/Health System]
For poor-risk patients, multiple factors go into consideration. First of all, is this MDS-related or treatment-related AML? Then I would put them on Vyxeos for induction and then take them to transplant. And if they have FLT3 mutation, I would add midostaurin upfront with induction and then take them to transplant. If they have none of these above, I might still use 7+3 and HiDAC co-consolidation and take them to transplant. [Physician, Hospital/Health System]

Table 7. Factors Influencing Therapy Selection in Newly Diagnosed AML

Fitness
It's relatively easy to identify the patients who are clearly not fit for any therapy: Someone who's, you know, bedbound, wheelchair bound, you know, advanced dementia, things that where their life expectancy before the leukemia diagnosis was probably less than a year. And so, treating them with induction is probably going to shorten their life expectancy anyway, and so those patients would probably benefit more from palliative and end-of-life care. Whereas patients who, let's say they're 80 but maybe have some diabetes, hypertension, but still fit enough, and they're fully functional – you know, they spend time with their family, their grandkids, you know – those patients probably are not fit enough for stem cell transplant, but still, you could treat them with, you know, a hypomethylating agent and maybe venetoclax, as well. [Physician, Academic Setting]
It really is not a decision between hypomethylating agent therapy versus hypomethylating agent therapy plus venetoclax – ***it's whether the patient is eligible for venetoclax plus azacitidine versus 7+3 or Vyxeos****. [Physician, Academic]*
Cytogenetics
Their risk, I think, plays into that. I think a patient, for example, that has favorable-risk cytogenetics with no other concerning factors, we maybe can't treat as intensively as you could, you're still shooting for cure, so you're going to treat, maybe perhaps with intermediate-level intensity or lower-intensity chemotherapy as opposed to doing something like a hypomethylating agent, which we think is unlikely to be curative.[Physician, Academic Setting]
Age
I think age is definitely important. As much as oncology is heading away from solely relying on age as a factor for deciding on therapy, I do think it's still important, because most patients, unless they have favorable, you know, cytogenetic risk, most patients will probably not be cured without an allogeneic stem cell transplant…and cytogenetics, because now we have targeted therapies that are being looked at in the first-line or are already approved in the first-line treatment. [Physician, Academic Setting]
The main thing, ***transplant eligibility versus ineligibility is really important****. So, we'll start with that. For transplant-eligible patients who are really usually younger than age 70, I often will start with more intensive regimens, and that often is 7+3****. If they're older than 70, if they're still transplant eligible but I think they're not going to be necessarily a good candidate for intensive induction****, I'll use a hypomethylator agent plus venetoclax.* [Physician, Hospital/Health Care Setting]
Patient Preference/Willingness/Social Support
What I look for is just the same factors – what does the patient want, what is their motivation, what's their social support, what is their comorbidities, what is their physical strength, and can they handle it? [Physician, Academic Setting]
Their willingness to take treatment or not*, and also because some patients might live far away and they feel like coming for these IV infusion might be troublesome. Or they have many other comorbidities also could be dictating their longevity which is not very common but it could happen. I've had patients who have severe pulmonary issues or cardiac issues and AML, given all these issues*

together patients opted out not to receive any treatment for AML. ***One other scenario would be patients, as I said, who don't have much social support.*** *In first line if they are not candidate for intensive treatment, my go-to for almost all patients if they are agreeable is a combination of HMA and venetoclax, but in second line I would do more of a targeted approach based on patient's molecular makeup. If they have FLT3 I do Xospata, if they have IDH1 or 2 I use Idhifa or Tibsovo. [Physician, Academic Setting]*

Table 8. Newly Diagnosed Patients with AML—Ineligible for Induction Chemotherapy

Standard of Care
The standard of care now has changed. I think in the past we had several different options we could have considered, but with the addition of venetoclax and fairly high response rates in that patient population, I think that would be the way to go. [Physician, Academic Setting]
Now we have really good data, and I forget the name of the trial, things like VIALE-A trial shows an overall survival benefit. So in those patients, I like to combine most likely the HMA, like decitabine or azacitidine with venetoclax is what's commonly done in patients that are not candidates for intensive therapy.
My one size fits all, I told you, is venetoclax plus aza. Right now this is one size fits all. But I talked about the future that if you know he has FLT3, or you know he has IDH mutation on top, you have room for improvement. But right now, the go back to regimen is the combination of 5-azacitadine plus venetoclax. [Physician, Physician-Owned/Private Practice]
If you determine the patient is ineligible for intensive induction therapy, then there are multiple other treatment options available. The most exciting and the most new of which has been the addition of venetoclax to a hypomethylating agent. This has sort of become the new standard for these patients. [Physician, Hospital/Health System]
I would say overarchingly our probably preferred treatment option is going to be azacytidine plus venetoclax, based on the results of the VIALE-A trial which show an overall response benefit.
Slower Adopters
We are looking at, I think, a little bit more supportive care, so we are also using some of our newer agents on formulary, such as the luspatercept, so one is just maintaining quality of life and trying to reduce transfusion need. So by working from that angle as well as, again, ***our normal hypomethylating agents or possible oral agents that are available for Bcl-2****, or the specific mutations that could be present. [Pharmacist, Academic]*
And if they cannot tolerate or don't accept intensive therapy, then there are a variety of approaches. ***We might offer them a hypomethylating agent plus venetoclax****, which again it's hard to know whether to call that intensive or not. But it tends to be very myelosuppressive; with dose adjustments, one can mitigate some of the myelosuppression of that therapy. And* ***that might be what's offered to patients who are older and unfit in lieu of intensive therapy****. [Physician, Academic Setting]*
7+3 or Vyxeos
I look a little bit at what the cytogenetics or FISH are, but I think you can do azacitidine plus venetoclax for everybody, so that's easy. ***The intense therapy you can do also for everybody, the 7+3****. [Physician, Academic Setting]*
The other group (nonfavorable AML), which fall into the intermediate or high risk, those are the ones we worry about because we know chemotherapy alone does not cure it. ***It works very well, but it's not going to cure them****. [Physician, Physician-Owned/Private Practice]*

Table 9. How HMA Agents are Being Used in MDS

Current Standard
For the vast majority of patients, ***even if they are fit, we don't consider intensive chemotherapy as the best option for these individuals****. While it can put people into remission, it is quite toxic, and those remissions are often very short lived. So, we typically go with hypomethylating agents even in those individuals.* [Physician, Academic Setting]
Like almost everyone else, *when deciding if they need some sort of chemotherapy and high risk,* ***hypomethylating agents are the first things that I start with****. [Physician, Hospital/Health System]*
For somebody with high-risk by a revised IPSS score MDS ***it's a pretty straightforward for our institution. It's going to be single agent azacytidine, as is per the NCCN guidelines****.*
Higher-risk MDS, we would do probably venetoclax and Dacoge*n, depending again on their performance status, and then we would try to keep everything as an outpatient so the patient can, obviously, be at home.* [NP, Physician-Owned/Private Practice]
For those who are high risk and not transplant eligible, ***the most common thing is hypomethylating agents. I almost never use intensive induction therapy for those people, because the goals really for them are mostly palliative****.* [Pharmacist, Academic Setting]
Then would be the azacitidine regimen*. The purpose of that is to delay progression or to extend life. It can be used at any age. It has a good performance status, and with the absence of any major comorbidities for the patient. Of course, we're always looking for a cure, but it's been known to have excellent performance status in patients who are 60 to 75 years old.* ***These are for patients where the stem cell transplant has not, at that time, yet been considered****.* [Physician, Academic Setting]
For those who are high risk and not transplant eligible, the most common thing is hypomethylating agents. ***I almost never use intensive induction therapy for those people, because the goals really for them are mostly palliative****, and clinical trial are kind of for both, but definitely more for – we have a non-transplant eligible patient who would like to go for a clinical trial, oftentimes, I'll try to get them on that. And if they don't, a hypomethylating agent.* [Pharmacist, Academic Setting]
Interchangeability of HMAs
If they have some cytopenias, either their neutropenic or they're needing blood products or platelets, we usually will start with one of the hypomethylating agents like Vidaza. We also use oral Dacogen. We use that quite a bit lately with our patients over 80 because they seem to tolerate that better. I've used venetoclax with patients that have gone from MDS to AML with Vidaza. That has worked very well too. [NP, Academic Setting]
Another one is called azacitidine or decitabine. Those are the most common that we use. These are in the National Cancer Registry. This regimen of medication is used throughout the AML/MDS system. Everyone, every cancer center probably in the United States is basically using this same regimen of medications, along with the same prognostic scoring system. [Physician, Academic Setting]
In general most people prefer azacitidine. I have looked at the literature to see if there is anything strongly supporting either one. The literature supports both drugs. It's a matter of personal preference. [Pharmacist, Physician-Owned/Private Practice]
When it comes to hypomethylating agents, the two most commonly used are decitabine and azacitidine. And ***for the most part, they're used interchangeably****…except there's data for patients who have higher-risk cytogenetics with a P53 mutation that they may do better with decitabine.* ***I tend to give more azacitidine because of the survival data*** *in a general cohort of patients and* ***because of its sort of synergy with other agents like venetoclax*** *in leukemia.* [Physician, Academic Setting]
Drug Availability/Institutional Preference and Pathways

*Azacitidine is most commonly used, that's the most commonly used drug we have. I think **it's just a matter of habit. Both drugs [decitabine] are good**. [Physician, Physician-Owned/Private Practice]*
*One was the drug availability. I think when we're using an HMA, Vidaza was the formulary drug locally…basically, **our go-to drug was Vidaza, and that was because of what we had available**. [Physician, Hospital/Health System]*
I will look to the NCCN guidelines and our internal pathways to help me guide what I should use therapy-wise, and really patient preference as well. [Physician, Hospital/Health System]
Preference for One HMA Over Another
[Azacytidine] is really only 5 days in a 28-day cycle, so that's something that is doable. Often in combination with venetoclax if they are agreeable. [Physician, Academic Setting]
Aza is easy because it's oral therapy. So you can take the oral therapy for about 3 weeks, and then you take the 7 days subcutaneous. You don't have to give IV; you can do subQ 5-azacitidine. [Physician, Physician-Owned/Private Practice]
You can do the decitabine subQ as well, but we traditionally use more of the decitabine, the five-day regimen. And in patients that don't have good IV access, we have utilized the subQ azacitidine in those patients. But one of the things we always have issues with is all these multiple injections that the patients get due to the volume of the azacitidine. [Pharmacist, Hospital/Health System]
Higher-risk MDS, we would do probably venetoclax and Dacogen, depending again on their performance status. [NP, Physician-Owned/Private Practice]
Combination
I would say overarchingly our probably preferred treatment option is going to be azacytidine plus venetoclax, based on the results of the VIALE-A trial which show an overall response benefit. [Physician, Hospital/Health System]
*Increasingly, if patients don't respond or respond ineffectively, we increasingly are using venetoclax, which we're using also for unfit elderly AML patients. But **there's fairly compelling data that the addition of oral venetoclax benefits patients with high-risk MDS/higher-risk MDS**. So we will then sometimes add that. In some cases, the decitabine is changed to azacitidine because the combination is generally…we **generally use venetoclax plus azacitidine**. Certainly, if the patient has very high risk or what looks like evolving AML, then the combination therapy is usually instituted.*[Physician, Academic]
I tend to add the venetoclax when they're kind of close to being the leukemia. If they're just purely MDS, you can do like…the difference is really just a hypomethylating agent. *[Physician, Academic Setting]*
If I feel like they have higher-risk MDS I will put them on a treatment; in today's world most of the time azacitidine and venetoclax. if the patient is requiring a lot of transfusions, is having a lot of infections or is neutropenic, then I will talk to them about initiating treatment usually with azacitidine and venetoclax. [Physician, Hospital/Health System]
Different Dosing Regimens
There are different regimens. We've done dose reductions. Or for like the azacitidine, we've done the seven-day treatment. We've done like a five-day treatment of the azacitidine instead of the seven and lower dose. [Pharmacist, Hospital/Health System]
I do the dose escalation those first 3 days. I'll dose reduce patients down to 70 mg once a day of venetoclax per the package insert. I know we've definitely had some discussion as to if we should be doing 70 or if we should be doing 50. The 50 is what they did in the VIALE-A trial. I remember the old package insert said you could do 100, which is a little bit easier to kind of manipulate those tablets. It's always a little bit of a discussion. I will say probably the past 10 patients I've done I've just strictly followed the package insert for that dosing. [Pharmacist, Hospital/Health System]

You could always still use the hypomethylating agent but lower doses of it. [Physician, Physician-Owned/Private Practice]

Table 10. Administration and Dosing Schedules for Venetoclax

Dose Reduction
The thing with the venetoclax is you can dose reduce it, you can go all the way up to 400, but maybe you just drop it to 100. Like I had somebody who couldn't tolerate 200, so I went down to 100, and they were fine. [Physician, Academic Setting]
These treatments are not meant to be discontinued, but they can be modified. You can stretch the intervals. You can dose-adjust. [Physician, Physician Owned/Private Practice]
Stopping Venetoclax or Both Agents
If I had to stop one, I'd probably stop the venetoclax. Or actually the HMA, too. It depends on what the side effects were. But most of the side effects for both are really overlapping, in terms of, you know, the effects on their hematological, you know, adverse events. So, it may be hard to tease that out. [Physician, Academic Setting]
We do stop venetoclax often, holding it because of blood count issues. It's pretty clear, I think, from the data that venetoclax does very little on its own to AML. It's really not a very good drug. Its benefit is only when it is added. The key is to continue on with the HMA. [Physician, Academic Setting]
This is a tough group to figure out whether the cytopenias are from the hypomethylating agent, from the disease itself, or from the venetoclax. If they're having nausea, vomiting, feeling super fatigued, I will interrupt their venetoclax to see if their symptoms get better off the therapy, and if they do then we will either talk about dose reductions or we will talk about stopping that part of the therapy completely. [Physician, Hospital/Health System]
Usually with any toxicity I would stop both in general. [Physician, Academic Setting]
I have typically stopped both, because I think it's almost impossible to ascertain what is causing what, unless it's a very specific side effect. [Physician, Hospital/Health System]
I would first stop venetoclax and keep the azacitidine going. I think that's probably because we are much more comfortable with azacitidine. I don't have a good answer for that. I am not sure what is the right thing to do? [Physician, Hospital/Health System]
I know in the label they say give it continuously, but most of the time we are giving 2 to 3 weeks and stopping based on cytopenias. If there's significant cytopenias with a white count less than 1 and persistent, usually we will stop at around day 20 and repeat the marrow and see where we are. Even experts I've talked to they would stop some at day 15, some at day 21. [Physician, Physician-Owned/Private Practice]
We do opt for 28 days consecutively, unless they experience really febrile neutropenia with complications, which I feel like I often see some around the day 21 or so mark. Then we might kind of hold off and then proceed forward with our bone marrow biopsy to assess any sort of response. We'll do Vidaza for days 1 through 7, the venetoclax 1 through 28. I try my hardest to finish that 28 days. I depends on the hypomethylating agent they had as well. I know with Dacogen there is some data that says maybe you could do at day 21. [Pharmacist, Hospital/Health System]

Table 11. Assessing Treatment Response with Venetoclax

After 1 Cycle
AML disease is pretty aggressive and much faster growing. You're ready to perform a bone marrow biopsy after induction or after 1 cycle of treatment just to see where the response is. The quality of life is important. Untreated AML will give you very poor quality of life in a very short period of time. It is not just related to the anemia and the thrombocytopenia. It's mostly also related to the infections and other things. [Physician, Academic Setting]
You are doing your bone marrow at day 28 usually to see what percentage of blasts is the usual AML assessment after cycle 1 of intensive chemo. You're looking at their blast percentage, and you can do your flow cytometry to be accurate, and then cytogenetics, did we clear the clone, you know? How much did we do with one cycle? [Physician, Physician-Owned/Private Practice]
I've almost had to do four to six-weekly marrows on the one patient I had because I didn't know if the cytopenias were coming from venetoclax or because they were not responding to the treatment and the AML was progressing. So it's a case-by-case basis. I don't know if there's a protocol for that. [Physician, Academic Setting*]*
it's a lot different than just giving a single agent hypomethylating agent, where you could easily just treat through the counts and repeat the bone marrow biopsy in 6 months and assess response at that point. We know that with this new combination it's a way different thing that needs to be treated much differently. We would really try to treat it like it's induction with a cycle 1 bone marrow biopsy. I think that once the VIALE-A trial came out and we got more experience with it, we were really trying to follow exactly what the trial did as far as response. If they don't have response how we retreat into cycle 2 as well. [Pharmacist, Hospital/Health System]
After 2-3 Cycles
They do get CBCs very frequency initially, twice a week. Then we space it out to once a week. So I would expect response in about two to three months. You should expect to see start improvement in about one or two months. And then, once they are sustained ANC over 1,000 and platelet over 100, and you've seen what looks like a complete morphologic response, you're going to follow it up with a bone marrow biopsy.[Physician, Academic Setting]
But most of the time, what our practice is that we should not do the bone marrow before 2 cycles. most of the time what we do is just the peripheral blood counts. We just follow them, we are getting the peripheral blood count, we are supporting them, and then we do it. After first cycle, no. [Physician, Academic Setting]
No Rush to do Bone Marrow Biopsy
I'd be more likely to, at some point in the first year, to repeat a bone marrow biopsy to really determine whether a patient is in a complete remission. [Physician, Academic Setting]
We typically don't do the bone marrow. Basically, if hematologically they are doing better. That's how it goes. [Physician, Physician-Owned/Private Practice]

Table 12. TP53-Mutations in MDS

High-Intensity/Aggressive Therapy or Clinical Trial
I don't quite understand fully what I'm going to do in the non-transplant setting for a TP53 mutation that's different. I know that clinical trial is preferred in this setting, but again it's very hard for our patients to travel for these clinical trials, and we don't offer that many MDS clinical trials at our institution. [Physician, Hospital/Health System]
TP53 is the adverse prognostic marker. We all know that. I would just be more alert and watchful and perhaps treat them or see them more closely. No, my treatment would not change. [Physician, Hospital/Health System]
Courtney DiNardo has published that the patients that have p53 and receive HMA plus venetoclax they're actually very good, even better than the historical controls of the regular just hypomethylating agent by themself. So that's what I try to do. [Physician, Hospital/Health System]
Decitabine Preferred
There's data for patients who have higher-risk cytogenetics with a P53 mutation that they may do better with decitabine. There was a New England Journal paper that showed that patients had a better prognosis. Patients did better when they were treated with decitabine, but it wasn't necessarily a head-to-head comparison to azacitidine. [Physician, Academic Setting]
I know there's some literature suggestive that Dacogen might be better in these cases as compared to azacitidine. I would try my best to get them to a transplant, but those are the only few things that I can think of. [Physician, Hospital/Health System]
Investigational Therapies
We have had clinical trials open with, to me, a very important drug, APR-246, which had had some good results with p53-mutant MDS. I'm persuaded by the results in MDS that APR-246 has benefits. So those patients are generally referred for that trial. If they don't have p53 mutation but they are in the higher-risk category, they're generally started with a hypomethylating agent. [Physician, Academic]
We have this proteosome and the CD47 and some targeted agents that are now looking at p53 and may be able to improve on that specifically. I can't remember the name of the agent because it's not approved yet, kind of a proteasome inhibitor. [Physician, Academic Setting]
That drug [magrolimab] has shown interesting results in TP53 mutations with MDS and with really high response rates, including CR rates. [Physician, Academic Setting]
There are a couple of things with p53 that are very interesting. It's called the APR-246, I believe, it unfolds the p53. I think they have it on Moffitt. We haven't been able to get those clinical trial, but if I have a patient that is p53, sometimes I ask for to send a couple other places. And we are going to start getting magrolimab, a clinical trial of magrolimab. It's an antibody that makes the macrophages eat the blasts, the cancer cells. And those respond very well to p53. I have a couple of patients lined up for the clinical trial. [Physician, Hospital/Health System]
These patients don't do as well. There are trials using the specific anti-p53 agent. So if there is something around a trial of that nature, you may consider sending that patient on that trial. But otherwise, we just try to treat them aggressively because we know they have usually bad disease. [Physician, Physician-Owned/Private Practice]

Table 13. Reported Therapeutic Approaches for Patients with TP53-Mutated AML

Transplant
I mentioned there is so-called intermediate and so-called poor risk. Among the poor risk are the TP53, chromosome 5 deletion, 7 deletion, complex karyotype – all of these are under the bad group. 11q minus is sort of intermediate to poor, but it's more in the intermediate, and they don't do well you need a transplant for this as well. [Physician, Physician-Owned/Private Practice]
If they have a TP53 mutation, that is a high-risk thing, and usually until that time we have involved the transplant team because there's a very high risk of relapse. We have not added yet to any of our patient venetoclax during the induction or consolidation, intensive induction or consolidation of venetoclax we will send them for the transplant. And if they are transplant eligible, they will go straight away for transplant. [Physician, Academic Setting]
Chemotherapy is not terribly effective in that population, so they may be better off with a less-intensive regimen approach, and consider definitely transplant if that's a possibility. [Physician, Physician-Owned/Private Practice]
If we can do something like, for example, that gets them to a very low TP53 mutant allele burden state, then taking them to transplant is still probably our best bet, even though it doesn't have great outcomes. I think for most patients, maintenance HMA is the bare minimum of what we can do. Most patients will tolerate that. [Physician, Academic Setting]
If they're eligible or they're able to, he's going to elect to do a transplant. I'm talking older. Younger, full dose chemotherapy, Rydapt in between, transplant as soon as we can. [NP, Academic Setting]
Clinical Trial
But there are emerging data, that was presented at ASH, of a P53 inhibitor, but I think the latest update is not necessarily positive, in terms of the findings. So, you know, I think you try to get them on a clinical trial. And if not, I think we don't necessarily have any particular targeted agents for that subgroup to treat them any differently. They just would mandate that they proceed to stem cell transplant, if possible. [Physician, Academic Setting]
First of all, there's distinction that needs to be made whether somebody is a candidate for aggressive treatment or not. If somebody is a candidate for aggressive treatment, in all likelihood this patient will not be with me, but my desire and my recommendation to the patient and the family would be that they seriously consider a clinical trial. Now, if it is a patient who is not a candidate for aggressive treatment, then it's going to be something along the lines of hypomethylating agents and venetoclax. Well, of course, I will take patients' individual considerations as well. [Physician, Hospital/Health System]
Well, that's again, a problem. I would say they're good for a study. So find a study is their best possibility. Chemotherapy is not terribly effective in that population, so they may be better off with a less-intensive regimen approach, and consider definitely transplant if that's a possibility. Because they're not, again, going to do well. But the right answer probably is a study somewhere. [Physician, Physician-Owned/Private Practice]
That's pretty much the same as MDS patients, maybe even worse. Even with transplantation, those are very poor outcomes. Our general approach for those patients we don't even provide them with 7 + 3 or intensive induction chemotherapy. We really go to HMA plus venetoclax, because those patients are relatively resistant to traditional chemotherapy. Then, obviously, a clinical trial will be the first consideration. [Physician, Academic Setting]
That's terrible. Those patients don't do well, and we have nothing good that works. So I would push them to a clinical trial if they're willing to go somewhere for a clinical trial. If they're not, I really will talk to them about palliative care options and hospice. If they really want to try something I will try a

hypomethylating agent and venetoclax to see if it will do something for them, knowing that more than likely nothing is going to work. [Physician, Hospital/Health System]
HMA with Venetoclax
There is a regimen called CLAG, which is a regimen that was initially published in Poland. We have seen some good benefits, especially in this MDS AML population using that regimen. The other option is to use something like a hypomethylating agent which they have not seen before, add the venetoclax to it and give them that option. Even maintenance with one of the oral agents to see if that can help. [Pharmacist, Physician-Owned/Private Practice]
I think right now our typical approach for an older patient with TP53-mutated AML is probably still going to be HMA venetoclax. I think we do let them know probably up front that this is a very poor prognostic feature. There are not really any really strong, good treatment options that can be much more directed towards that. I know there is some data that maybe says decitabine might be a little bit better for p53 mutated AML or we may ought to try that along with venetoclax. It's one of those really difficult situations I think in AML for older patients right now. [Pharmacist, Hospital/Health System]
p53 itself makes itself high-risk AML. And if they're not candidates for intensive chemotherapy, then the decitabine I mentioned, along with venetoclax, is an excellent regimen for these patients. The decitabine has high response rates in this setting. If you're not doing intensive chemotherapy, decitabine would be our drug of choice. [Physician, Academic Setting]
the one group I'd consider more using hypomethylator plus venetoclax in these transplant-eligible patients would be the p53 patients because of how poorly they do. And for those, the hypomethylator that I prefer to use is decitabine for 10 days. [Physician, Hospital/Health System]
Induction Chemotherapy
My preference would be to give intensive chemotherapy. That's a very high-risk patient, and those patients it's more difficult to get them into remission and also keep them in remission. In looking at the data with venetoclax plus hypomethylating agent, there was a fair bit of activity in p53-mutant AML and also in secondary AML. But I think the best results are obtained with intensive chemotherapy. I would also try to get that patient to transplant, although I think there's some data that suggests that TP53 mutations even affect the outcome after transplant. But I would try to treat that patient as intensively as I could. [Physician, Academic]
*That's challenging. I do the 7+3. **If it is young patient, I do 7+3. If it's elderly, I think about HMA**. Adam Goldberg at MSK did a retrospective analysis on patients that received Vyxeos but had a p53 mutation. And they did terrible, like terrible, terrible, terrible. So on those patients, sometimes I'm inclined to put them on a hypomethylating agent plus venetoclax. [Physician, Hospital/Health System]*
The induction part would all be the same. They would get induced. We are hoping they will achieve remission, patient continues to have adverse risk factor, that automatically puts patients in the poor risk category. These are the patients that will need evaluation for bone marrow transplant so I would send them that way. [Physician, Hospital/Health System]
We've used typical induction therapy. We've used Dacogen for 10 days. We've used the midostaurin, Rydapt. We've used that typically for those patients. [NP, Academic Setting]
Those patients they will be on high risk depending on the type of whether they're able to tolerate, then they'll go for the 7+3 and an oral agent and then also go into, once they in remission, transplant. [NP, Academic Setting]
I probably would use more intensive treatments such as 7+3. For those who were not transplant eligible, I may use something like cytarabine and venetoclax, which is another option. But for the people who are transplant eligible, I would want something such as 7+3. [Physician, Hospital/Health System]

It's not going to be any different in terms of the, 7+3 is going to be still the standard for us in terms of that treatment. So I think if a patient's not fit to get it, it's just their prognosis is not going to be as good. But I think there's near targets, where we may be able to utilize something else. But I think at this point it's still going to be if the patient has a FLT3 mutation, we're going to add on the midostaurin in those patients. But otherwise, 7+3 is kind of still the standard. [Pharmacist, Hospital/Health System]

Table 14. Access to Clinical Trials for Patients with Newly Diagnosed MDS/AML

At Diagnosis and Beyond
We will discuss right at the beginning and kind of…you know, being on a community center, we're always having a discussion and offer for patients to go immediately after induction, right, if the patient…as soon as the patient would be discharged from the hospital, that's when we will tell, look, this is your chance to go to the academic centers if there's any additional, you know, therapy or clinical trials that would be open. And we would encourage patients to do that. [Physician, Hospital/Health System]
At the beginning, when they make that initial visit to us, we have a clinical research coordinator who is going to come in and just let them know of the availability of the clinical trials. [Physician, Academic Setting]
We discuss it at diagnosis when we have all the information. You wait until the bone marrow comes back and until the results come back. You discuss the treatment plan with them. You give them the option of a clinical trial, and if we feel that clinical trial is the best option then obviously, we're going to promote that. [NP, Academic Setting]
At Relapse
Relapsed/refractory, there are more options. Not only that, those who cannot go through intense chemotherapy as you asked me. There may be more likelihood of having a clinical trial. Relapsed/refractory, not fit for intense chemotherapy up front. That's where it is. [Physician, Physician-Owned/Private Practice]
For the acute myeloid leukemia, usually we induce with the 7+3 and then at the time of relapse or if the patient relapses later on and down the road then we usually use the trials. [Physician, Academic Setting]
In order to be a clinical trial candidate, they have to have good labs, good social support. The trials aren't going to take somebody who's supportive care, so you've got to be cognisant of that. So step one is you have to assess and make sure they're a candidate. So if they're a candidate based on all of those factors, that's step one. Step two is, I think, after they've failed one line of therapy. You give it one shot, and you can mention hey, there's a clinical trial. [Physician, Academic Setting]

FIGURES

Figure 1. Bone Marrow Biopsy in Evaluation of Patients with Suspected MDS or AML

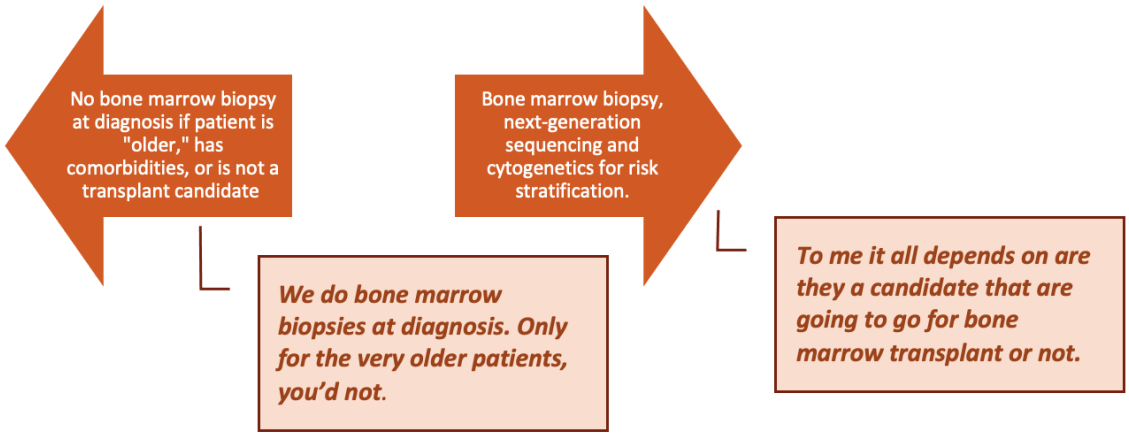


Figure 2. Clinician Reasoning on Fitness Determination

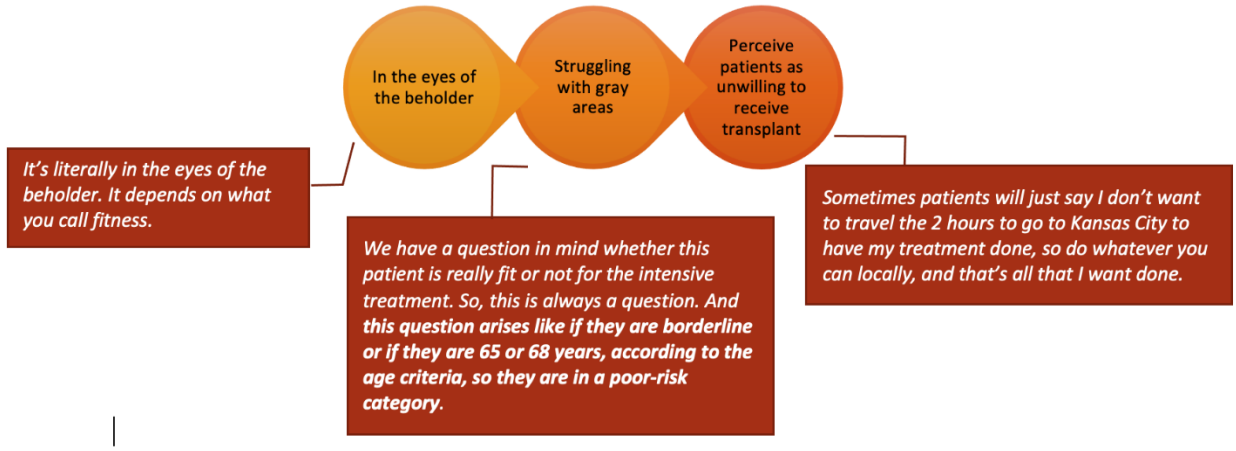


Figure 3. Primary Preferred Standard Treatment for Clinical Scenarios in MDS, US

US-based Clinicians Case Scenario, n, (%)	Azacitidine	Azacitidine + venetoclax (off label)	Decitabine	Oral decitabine (decitabine + cedazuridine)	Induction chemotherapy (3+7 or similar)	HMA followed by allo-HSCT	Unsure	Other	N
Newly diagnosed, higher-risk MDS	35 (21.88)	31 (19.38)	7 (4.38)	11 (6.88)	22 (13.75)	29 (18.13)	23 (14.37)	2 (1.25)	160
Newly diagnosed, higher-risk MDS with TP53 mutation	15 (9.43)	31 (19.50)	10 (6.29)	16 (10.06)	14 (8.81)	32 (20.13)	37 (23.27)	4 (2.52)	159
High-risk MDS previously treated with HMA; ineligible for transplant	4 (2.52)	56 (35.22)	7 (4.40)	22 (13.84)	11 (6.92)	9 (5.66)	39 (24.53)	11 (6.92)	159

Figure 4. Primary Preferred Standard Treatment for Clinical Scenarios in MDS, ex-US

Ex-US Clinicians Case Scenario, n, (%)	Azacitidine	Azacitidine + venetoclax (off label)	Decitabine	Oral decitabine (decitabine + cedazuridine)	Induction chemotherapy (3+7 or similar)	HMA followed by allo-HSCT	Unsure	Other	N
Newly diagnosed, higher-risk MDS	13 (38.24)	5 (14.71)	0 (0)	2 (5.88)	2 (5.88)	10 (29.41)	2 (5.88)	0 (0)	34
Newly diagnosed, higher-risk MDS with TP53 mutation	4 (11.76)	9 (26.47)	2 (5.88)	2 (5.88)	5 (14.71)	9 (26.47)	2 (5.88)	1 (2.94)	34
High-risk MDS previously treated with HMA; ineligible for transplant	4 (11.76)	12 (35.29)	2 (5.88)	5 (14.71)	6 (17.65)	2 (5.88)	3 (8.82)	0 (0)	34

Figure 5. Agents Matched from Memory to their Target or Mechanism of Action, US (n=163)

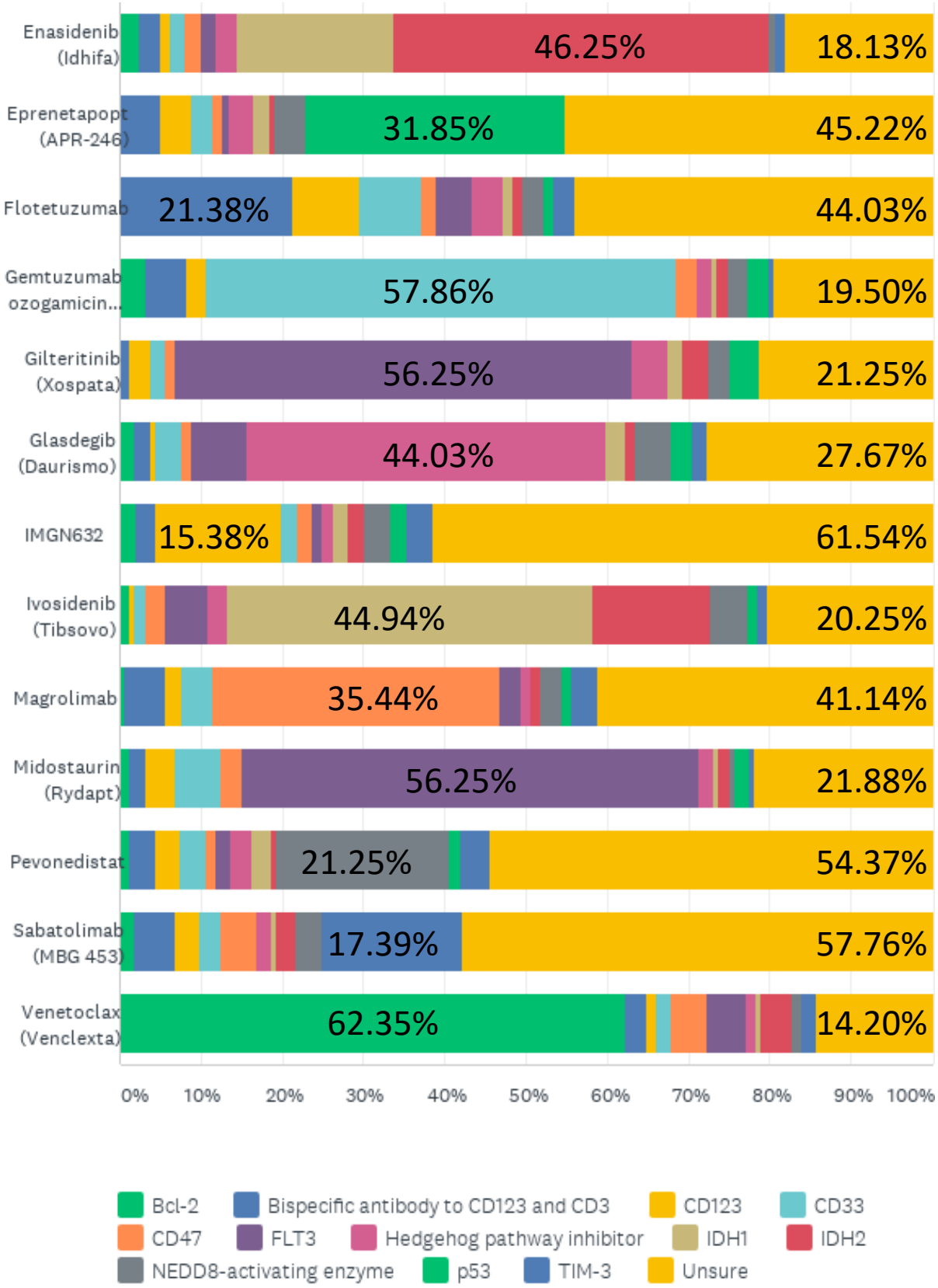
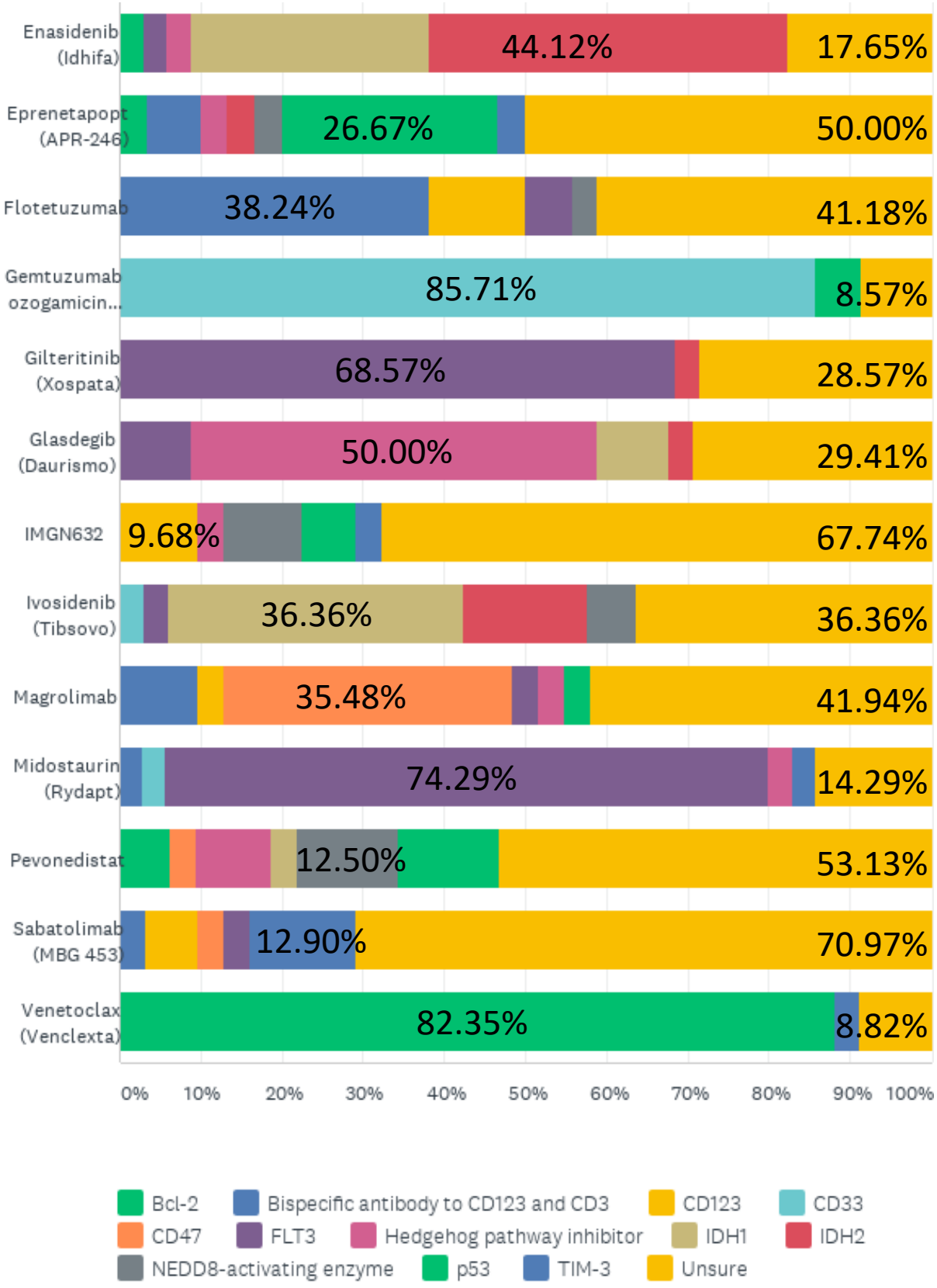


Figure 6. Agents Matched from Memory to their Target or Mechanism of Action, ex-US (n=35)



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Provider Gaps in Key Areas of Contemporary Viral Hepatitis Management and the Value of Targeted Education

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Background

Best practices in the management of viral hepatitis have undergone significant changes in recent years, challenging healthcare providers (HCPs) to keep up with an evolving standard of care. Evidence suggests that many HCPs do not rapidly incorporate new data and recommendations into their management approaches for viral hepatitis.

This study evaluated data from a series of educational activities to determine knowledge and competence gaps for HCPs in key areas of contemporary viral hepatitis management. In addition, the value of timely, expert-led educational interventions in closing these gaps was evaluated.

Methods

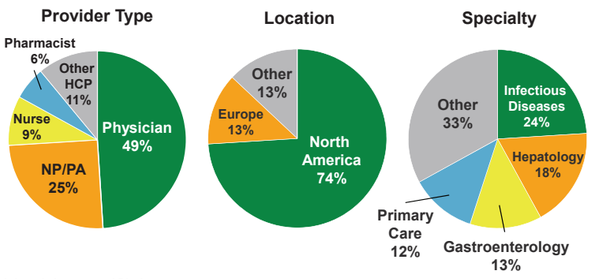
In this study, we analyzed baseline knowledge and subsequent learning in HCPs who participated in a series of live, expert-led educational webinars that occurred between October 2017 and January 2018 on topics relevant to contemporary management of viral hepatitis, including first-line HCV therapy, retreatment following DAA failure, post-SVR surveillance and management, and HBV therapy.

For each webinar, participants were asked a case-based, multiple-choice competence question based on the learning objective for the program at the following stages: immediately prior to the live meeting (baseline), immediately following the informing content during the live meeting (post content), and via email following educational reinforcements (a summary email and link to an expert-authored, case-based commentary), which concluded approximately 2 months after the live meeting (follow-up). We analyzed responses of participating HCPs at each stage to determine knowledge gaps and the impact of educational interventions.

Results

Participant Demographics

- 1495 learners attended a live webinar



Acknowledgments and Disclosures

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Ryan P. Topping, PhD; Jenny Schulz, PhD; Edward King, MA; Jennifer Blanchette, PhD; and Danielle Plachy have no real or apparent conflicts of interest to report. Jordan J. Feld, MD, MPH, has disclosed that he has received funds for research support from Abbott, AbbVie, Gilead Sciences, Janssen, and Merck, and consulting fees from AbbVie, ContraVir, Gilead Sciences, Janssen, and Merck. Nancy Reau, MD, FAASLD, AGAF, has disclosed that she has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, and Merck. Norah Terrault, MD, MPH, has disclosed that she has received consulting fees from Dynavax, Echosens, Gilead Sciences, Merck, and Novartis, and funds for research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck. Stefan Zeuzem, MD, has disclosed that he has served as a consultant or on advisory boards for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, and Merck/MSD, and has served on speaker bureaus for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck/MSD.

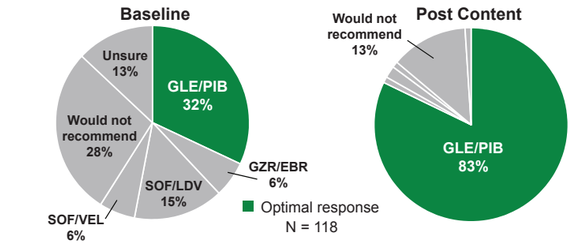
Results

Gaps in Provider Knowledge and Impact of Live Education

Topic 1: First-line HCV Therapy

Case: 53-year-old white man **newly diagnosed with GT1a HCV** infection, **F3 fibrosis, HCV RNA 7,640,000 IU/mL**

Question: Based on the current AASLD/IDSA recommendations, which regimen would you recommend for 8 weeks?



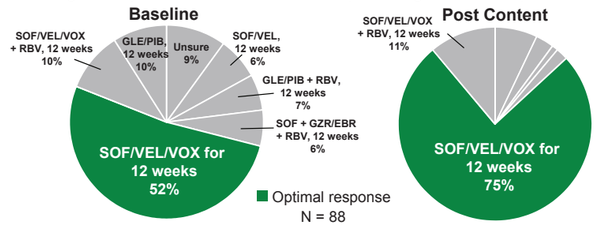
Date of webinars: 10/2017. Additional postcontent responses: GZR/EBR, 1%; SOF/LDV, 2%; SOF/VEL, 1%; unsure, 1%.

Stage	Notable Findings
Baseline	▪ Only **32%** selected the optimal 8-week therapy for this patient ▪ **27%** would use an 8-week course of regimens not recommended at that duration for this type of patient ▪ **28%** would not recommend an 8-week regimen for this patient despite eligibility and guideline recommendations
Post Content	▪ **Significant improvement in optimal answer** from baseline ($P < .0001$) ▪ **13%** still would not recommend 8-week therapy, suggesting possible ingrained preference or need for further education

Topic 2: Retreating After NS5A Inhibitor Failure

Case: 65-year-old white man with **GT1a HCV, compensated cirrhosis**, **failure of 12-week SOF/LDV** as initial treatment (posttreatment Week 4 relapse)

Question: Based on the current AASLD/IDSA recommendations, which of the following would you choose as the best therapeutic regimen for this patient?



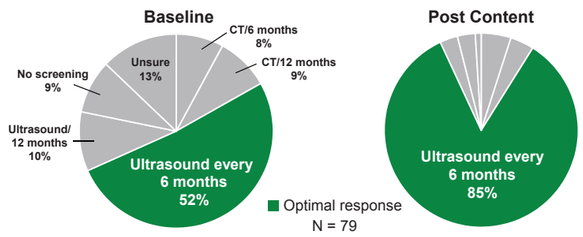
Date of webinars: 10/2017. Additional postcontent responses: GLE/PIB for 12 weeks, 7%; GLE/PIB + RBV for 12 weeks, 3%; SOF + GZR/EBR + RBV for 12 weeks, 1%; SOF/VEL for 12 weeks, 2%; unsure, 0%.

Stage	Notable Findings
Baseline	▪ Almost **one half** of respondents were unable to select the guideline-recommended treatment regimen for the case patient ▪ **17%** selected a GLE/PIB-based regimen, although GLE/PIB is considered an alternative recommendation of the AASLD/IDSA ▪ **23%** selected a regimen that included RBV
Post Content	▪ **Significant improvement** in optimal answer from baseline ($P = .0005$) ▪ **11%** would continue to recommend the addition of RBV to SOF/VEL/VOX

Topic 3: HCC Screening After SVR

Case: 59-year-old white man with GT1a HCV; **achieved SVR12 with 12-week SOF/VEL; F3 fibrosis**

Question: Based on the current AASLD/IDSA and EASL recommendations, how would you screen this patient for HCC?



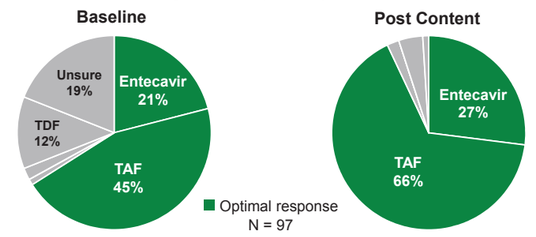
Date of webinars: 1/2018. Additional postcontent responses: CT scan every 6 months, 5%; CT scan every 12 months, 4%; ultrasound every 12 months, 3%; no further HCC screening, 3%; unsure, 1%.

Stage	Notable Findings
Baseline	▪ Almost **one half** of respondents were unable to identify the guideline-recommended screening interval/modality for the case patient ▪ **9%** would not offer further screening for this patient
Post Content	▪ **Significant improvement** in optimal answer from baseline ($P < .0001$) ▪ **9%** would recommend CT scans instead of ultrasound

Topic 4: First-line HBV Therapy

Case: 62-year-old woman from Vietnam with **previously untreated HBeAg-negative chronic HBV;** HBV DNA: 2100 IU/mL; ALT/AST: 35/49 U/L; **CrCl: 42 mL/min; TE: 12.7 kPa;** US: slightly nodular liver, mild splenomegaly

Question: Which of the following HBV therapies do you choose for this patient?

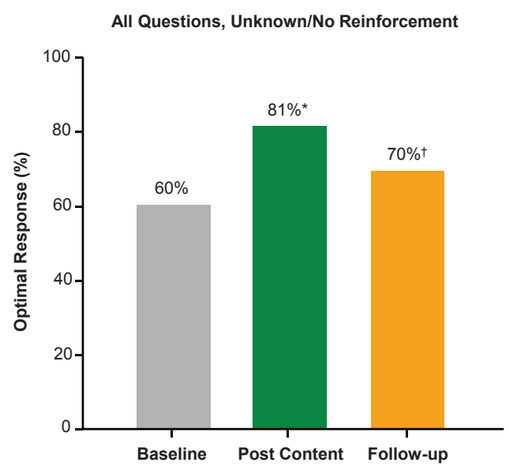


Date of webinars: 4/2018. Additional baseline responses: adefovir, 0%; lamivudine, 2%; peginterferon, 1%. Additional postcontent responses: adefovir, 0%; lamivudine, 0%; peginterferon, 2%; TDF, 4%; unsure, 1%.

Stage	Notable Findings
Baseline	▪ **34%** did not select optimal therapy for this patient ▪ **12%** would select TDF for a patient with decreased renal function ▪ Twice as many chose **TAF vs entecavir**
Post Content	▪ **Significant improvement in optimal answer** from baseline ($P < .0001$) ▪ The predominant shift was away from a choice of Unsure or TDF toward the **selection of TAF** (+21%)

Engagement and Impact of Educational Reinforcement

- In an analysis of participants who answered a question at baseline, post content, and follow-up, **lack of reinforcement was associated with knowledge regression** (Figure)
  - In a very small subset of participants who engaged in reinforcement education, reinforcement appeared to improve retention



Matched individual responses (N = 43).
*$P = .0325$ vs baseline.
†$P = .3652$ vs baseline.

Conclusions

- Clear practice gaps were observed in numerous key areas of contemporary viral hepatitis management; these included the use of recently approved HCV treatment regimens and HCC screening in patients with HCV who achieved SVR
- Live education was effective in improving learners' treatment intentions assessed through case vignettes

Scan me

Uncovering Clinicians' Gaps and Attitudes Toward Biosimilars: Impact of a 2-Phase Educational Program

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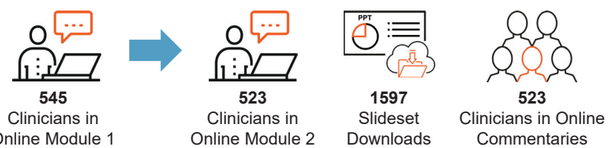
Background

- Biosimilars are biological products designed to be equivalent to an already-approved biologic. Eleven biosimilars have been approved by the FDA since 2015
- We sought to measure clinicians' understanding of biosimilars to identify and address educational gaps related to their clinical application and acceptance

Methods

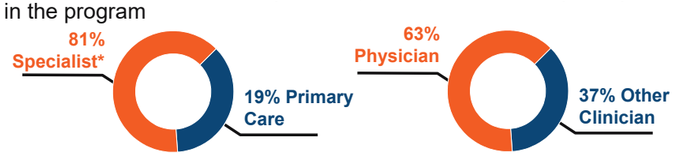
- We designed a 2-phase online educational program on biosimilars
  - Questions measuring clinicians' knowledge and competence were asked before and then repeated after the education was delivered
  - Clinicians also submitted their own questions about biosimilars
- To uncover key educational gaps, we identified questions with high incorrect responses at baseline, persistence of incorrect responses, and queries submitted by clinicians during Phase 1 of the education
  - These gaps were used to refine Phase 2 of the education
- Results of oncology participants have been presented elsewhere[1]
  - Current study analyzes results of non-oncology participants

Educational Phase 1 **Educational Phase 2**



Participant Demographics

- Between March 2017 and April 2018, N = 1585 clinicians participated in the program



*20% gastroenterology; 9% rheumatology; 6% dermatology, allergy, immunology; 9% infectious diseases, HIV/AIDS; 5% hepatology, 2% surgery, 31% other.

Results: Competence in Using Biosimilars

Gaps in Competence

- Among the subset of n = 336 clinicians who answered at least 1 baseline or posteducation question in Phase 1 or Phase 2, we identified persistent pre-education misunderstandings about biosimilars

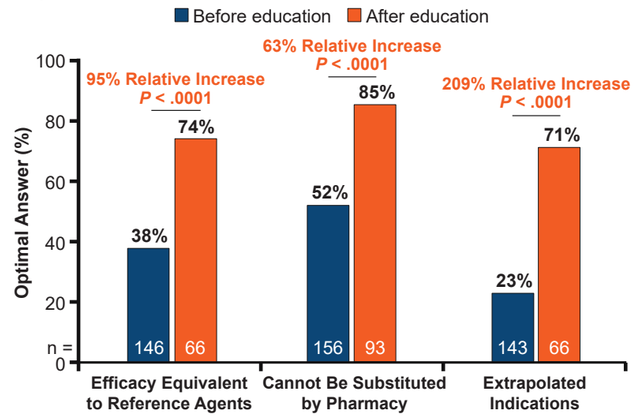
Clinicians' Pre-education Gaps About Biosimilars

- **61%** Mistakenly believed **efficacy** could differ from reference agent (n = 164)
- **62%** Did not understand **substitution** rules in the US (n = 157)
- **77%** Did not understand **extrapolation of indications** (n = 143)

Switching, substitution, and **extrapolation of indications** were also common concerns identified from clinician-submitted questions in Phase 1

Improvement in Competence

- After Phase 2 of the education, clinicians significantly improved their competence in all 3 domains



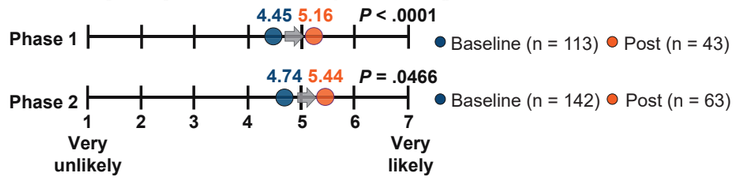
Results: Clinician Attitudes

Likelihood of Prescribing Biosimilars

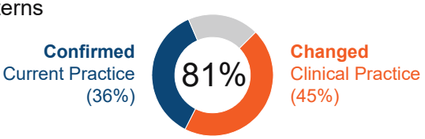
- Clinicians noted that patient education is a key factor required for acceptance of biosimilars

- **84%** Believed patients will accept biosimilars with appropriate explanation (n = 80)
  - The education increased clinicians' likelihood of prescribing a biosimilar

How likely are you to consider prescribing a biosimilar?



- As a result of the education, participants planned to change their practice patterns



Conclusions

- Clinicians' gaps in understanding of the **efficacy, substitution,** and **indications of biosimilars** may explain why some are reluctant to consider this new treatment option
  - Similar baseline gaps were observed in a separate CCO video program available at a similar time (Nov 2017 to April 2018)[2]
- This educational program increased clinicians' competence with biosimilars, potentially removing barriers to their use
  - Similar education may further **increase clinicians' willingness to consider biosimilars** as a treatment option for their patients

Contact: zschwartz@clinicaloptions.com. **Acknowledgements:** This research is based on activities supported by an independent educational grant from Pfizer Inc.
References: 1. Schwartz Z, et al. J Clin Oncol. 2018;36(suppl 30). Abstract 91. 2. Clinical Care Options. Expert Perspectives on Biosimilar Agents. August, 2018.
Disclosures: Z. Schwartz, J. Schulz, A. Vinther, A. Kuklinski, None; K. G. Saag, Abbott, Amgen, Bayer, Bristol-Myers Squibb, Ironwood/AstraZeneca, Merck, Pfizer, Roche/Genentech.

Targeting GI Nurses' Competence With Inflammatory Bowel Disease (IBD): Uncovering Regional Differences

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Background

- The shift to personalized therapy has created a gap in the appropriate risk stratification and monitoring of patients undergoing treatment for IBD
- Our research shows that nurses are challenged to keep current with the risk/benefit profiles and clinical applications of newer IBD treatments[1]
- Evidence suggests that poor adherence to IBD therapies arises from gaps in communication and shared decision making between healthcare providers—including nurses—and IBD patients[2,3]

Methods

- We developed a series of 12 live meetings for nurses—plus online worksheets, slidesets, and a CE-certified video for IBD clinicians—to provide tools for GI nurses involved in IBD care
- This case-based education focused on:
  - Assessing and risk stratifying patients with IBD to optimize routine health screenings and preventive care
  - Evaluating risk/benefit profiles and monitoring requirements for current IBD therapies
  - Applying principles of shared decision making and strategies to promote adherence in the care of patients with IBD

Live Education

CE-Certified Local Live Meetings

256 Live Meeting Attendees

Web-Based Education

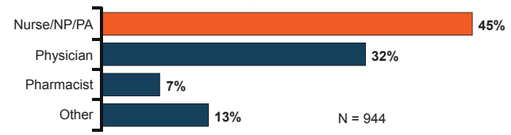
1007 Slideset Downloads

2159 Worksheet Downloads

688 Participants in CE-Certified Video

Participant Demographics

- Program predominantly reached nurse and physician target audiences



Targeting GI Nurses' Competence With Inflammatory Bowel Disease (IBD): Uncovering Regional Differences

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zschwartz@clinicaloptions.com

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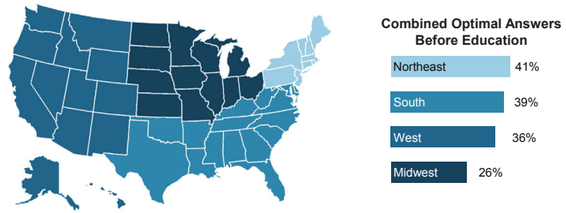
Results

US Regional Variation in Baseline Competence

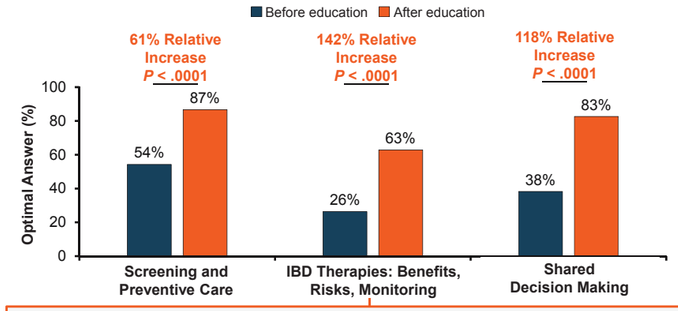
- Clinicians in the Midwest had the largest gap in baseline competence



- After the education, competence was not significantly different across US regions

Improvements in Competence

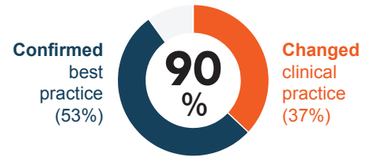
- After the education, clinicians significantly improved their competence in all 3 learning objectives for the program
  - 348 clinicians answered questions assessing level 4 outcomes
  - Cohen's *d* effect size was +0.82 (large)

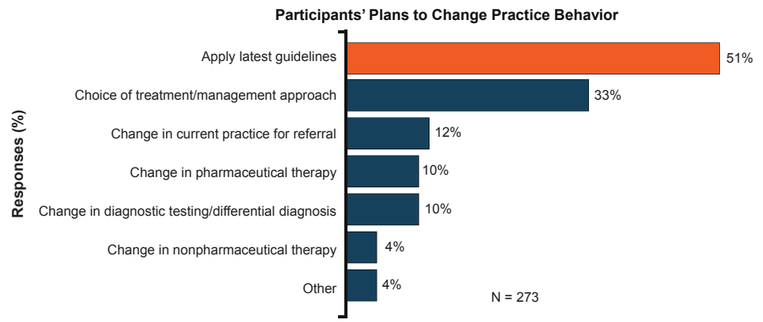


- Clinicians' lowest competence—and highest improvement after education—was in **risk/benefit profiles and monitoring requirements for IBD therapies**

Impact on Practice

- As a result of the education, clinicians planned to apply the latest guidelines and change their treatment choice/ management approach for IBD





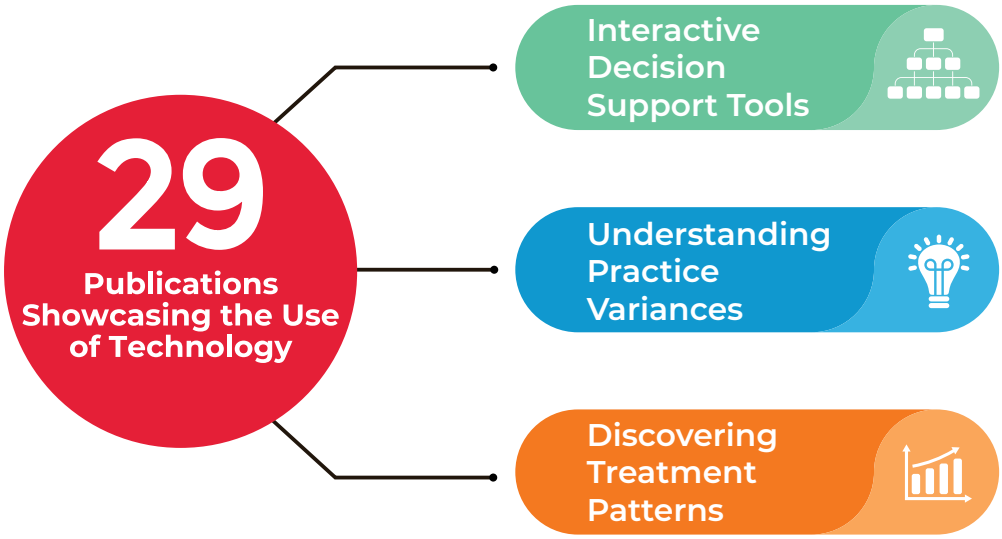
Impact on Patients

15,519
Patients likely to benefit from clinicians' participation in the live and Web-based education

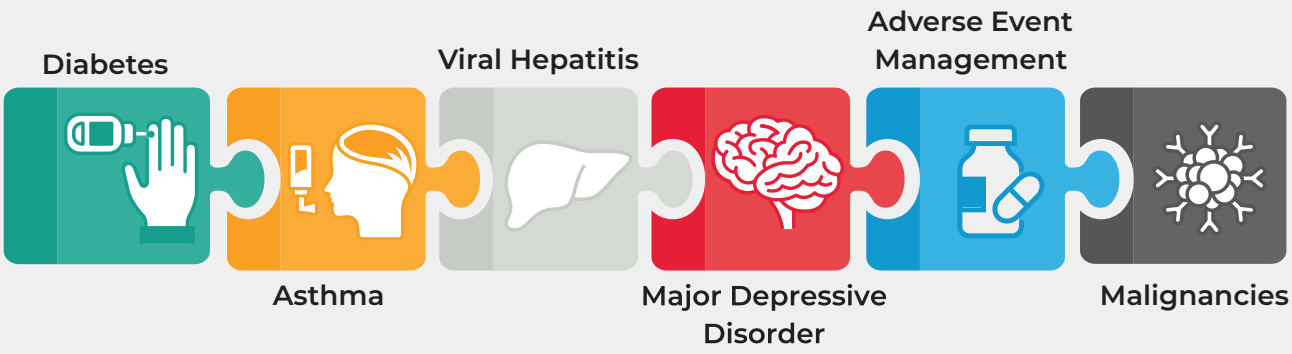
Program Summary

- This education **improved learners' competence** in screening and preventive care, monitoring/treatment considerations, and shared decision making in IBD
  - By topic, **risk/benefit profiles and monitoring requirements for IBD therapies** had the greatest pre-education and posteducation learning gaps—and the greatest improvement—suggesting that future education should continue to focus on this need
  - By region, greatest need for education was in the **Midwest**
- Many learners planned to **change their clinical practice** as a result of this education, mostly by applying latest guidelines and by changing their treatment approach

TECHNOLOGY TO ENHANCE LEARNING AND UNDERSTAND PRACTICE GAPS



Treatment guidelines reinforced for:



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Real-World Impact of Interactive Decision Support Tools in Changing Clinical Practice at the Point of Care

January 2018

Decision Making Challenges in Oncology

In the last decade, clinical advances in treating solid tumors and hematologic malignancies have surged toward tsunami proportions. In 2017 alone, the FDA added 16 new agents to its current list of more than 200 approved anticancer drugs, as well as additional indications for 28 existing drugs, and several new cancer diagnostic tests.[1] These advances in treatment are welcome and have substantially improved patient outcomes. Yet the rapid introduction of multiple new therapeutic options adds significant complexity to oncology treatment decision making.

Clinical practice guideline recommendations are reliable and familiar resources that help oncologists make evidence-based decisions and translate cutting-edge advances into practice. Clinical practice guidelines have evolved as standard tools to support evidence-based medicine, reduce variability in clinical practice, and improve the quality of oncology care.[2,3]

However, the standardized structure of oncology clinical practice guideline recommendations seldom maps adequately to the complex comorbidities and chronic degenerative diseases that oncology patients experience in the real world, nor do they provide specific treatment recommendations to optimize the care of specific patients.[7,8] Thus, clinicians are forced to choose from among multiple "reasonable" therapeutic options that, in practice, may be insufficiently adaptive to unique patient and disease characteristics.

> Although guidelines can be helpful in steering clinicians toward evidence-based decision making, they have a **poor record in changing clinical practice**, and their **implementation is associated with well-documented barriers**.[2,4-6]

Interactive Decision Support Tools

Interactive decision support tools (IDST) offer a means to narrow the gap between clinical practice guideline recommendations and individualized treatment decision making. To be effective in generating significant improvements in clinical decision making, IDSTs must ***involve experts*** in the translation of research into practice and actively offer evidence-justified, patient-specific advice ***at the point of decision making*** that encourages learners to ***modify behaviors*** or reinforces effective practice.[8-10]

Accordingly, Clinical Care Options (CCO) recognized the need for an innovative approach and developed entirely new software for an extensive series of tumor-specific IDSTs, each authored by a panel of multiple experts, to address changing treatment paradigms in oncology and address gaps in guideline specificity across a range of tumor types.

For information on how IDSTs work, refer to the Appendix.

Our hypothesis was that individualized and/or consensus recommendations (≥ 3 experts recommending the same treatment) for specific cases from known and trusted experts will change clinician behavior. To optimize learning, our IDSTs were designed according to the following principles of clinical education[11-13]:

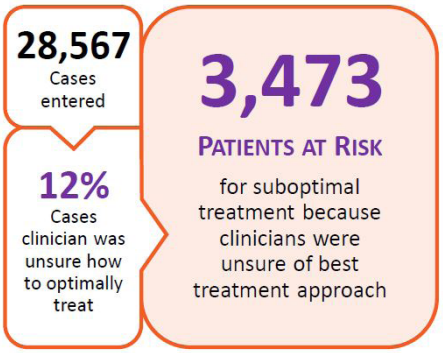
- Expert guidance is distilled in an accessible, readily usable format
- Users can access the tool when they are ready to learn (ie, when they have a challenging case)
- Baseline assessment captures current practice
- Expert recommendations provide feedback for learners on their practice
- Assessment following tool use captures and reinforces the impact of expert recommendations on learner intentions to change their practice
- Ongoing educational needs are pinpointed via the accrual of outcomes data over time

Optimizing Learning, Improving Clinical Practice

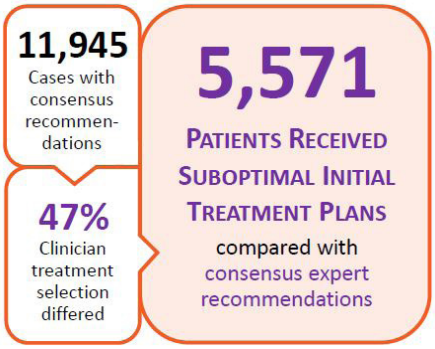
To further explore the utility of IDSTs as an educational resource, CCO conducted a meta-analysis of 21 IDSTs developed since 2013, each with treatment recommendations for thousands of case scenarios across multiple disease treatment settings. These 21 distinct IDSTs covered 10 different cancer diagnoses and issues and also included 21 individual outcome studies designed to measure their effectiveness and impact.

Users entered 28,567 specific patient cases into the IDSTs. These cases span 7124 unique scenarios across multiple tumor types and issues (Table).

Overall, when analyzing clinician confidence in their intended treatment, 12% reported uncertainty with how to optimally treat their patient. Across all disease treatment settings, 3473 patients were at risk for suboptimal treatment as a result.



We further examined 11,945 patient cases for which there was an expert consensus treatment recommendation (≥ 3 experts recommended the same treatment). Clinicians' intended treatment for 47% of these cases differed from the expert consensus recommendation, again indicating that these patients (n = 5571) were at risk for suboptimal treatment.



An important question is whether the use of IDSTs have an impact on actual clinical practice. As part of the IDST design, we captured tool impact and changes in learners' treatment planning intentions by offering an optional survey following each tool interaction. In almost one half of the cases (41%) across tools, clinicians reported that they changed their treatment plan for a specific case in response to the customized expert recommendations they received via the IDSTs.

In addition, tool survey data indicate that approximately 38% of clinicians have used the tools to get treatment advice on an actual patient in their practice vs 62% who used the IDSTs as an educational resource and entered a hypothetical patient. This finding underscores the power of IDSTs to support clinical decision making in real-world patient care.

In total, as many as 9044 patients (32%) were at risk for suboptimal treatment due to either clinician uncertainty or selection of suboptimal treatment.

Table. Details of Tools Included in Meta-analysis

Tumor Type/Topic	No. of Tool Versions	No. of Patient Scenarios Addressed	No. of Patient Cases Entered
Lung cancer	3	532	3981
Kidney cancer	2	972	1992
Multiple myeloma	4	1794	4317
Chronic lymphocytic leukemia	3	2134	3101
Immune-related adverse events	1	29	3572
Chronic myeloid leukemia	1	78	722
Malignant melanoma	1	90	1446
Myeloproliferative neoplasms	1	26	443
Breast cancer	3	1040	7082
Non-Hodgkin lymphoma	2	429	1911

Benefits of IDSTs

Clinical decision making in oncology is a multifaceted process that demands attention to the specificities of both disease and patient characteristics. As oncology shifts toward value-based care, rapid learning systems based on systems biology (eg, genomics, proteomics), and healthcare systems data (eg, patient-reported outcomes),[14] clinical decision making will become increasingly complex. Guidelines can be difficult to apply to individual patients, particularly when there are 2 or more treatment options with similar levels of evidence. Therefore, clinicians will need access to tools and resources beyond guideline recommendations that enable them to navigate around gray clinical practice areas.[15-17]

Continuing medical education (CME) is uniquely poised to provide such navigation and reinforce evidence-based frontline decision making via IDSTs. Such tools are able to capture real-world clinical practice at ***baseline*** as a resource for identifying ongoing educational needs. Through IDSTs, known and trusted experts can provide customized, patient-specific clinical expertise on either real or hypothetical cases, at the point when clinicians are ***ready to learn***. In turn, exposure to expert recommendations serves as ***feedback*** for learners, which, when delivered in a usable format, can strengthen the capacity of clinicians to select real-time, individualized treatment that is based on the optimal course of action at a specific point in a patient's disease trajectory.[15] Such tools can also ***reinforce*** expert recommendations by assessing learner intentions to change their practice following interaction with the tool.

> Analysis of CCO's IDSTs shows that although the intended practice of clinicians at baseline often varies from expert recommendations, interaction with the tool prompts the adoption of expert-recommended treatment strategies. Since 2013, ***almost one third of learners have changed their planned treatment*** for a specific patient for whom they sought expert advice.

Call to Action:

CCO's scalable IDSTs have broad applicability across multiple disease states and global impact. They provide customized, patient-specific expert advice that support learning, influence real-time clinical decision making, and increase the number of clinicians who make optimal treatment decisions for patients. The CME community can use clinically relevant innovations—such as IDSTs—to improve educational programming in ways that change practice and affect patients.

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APPENDIX

How IDSTs Work: CCO Decision Support Tools in Practice

For each tumor-specific IDST, learners enter a myriad of information about their planned treatment for one patient via a drop-down menu (Figure 1) and specify whether the case they have entered is hypothetical (ie, as a foundation for learning) or an actual patient in their practice.

A group of experts—we recommend 5 in each IDST group to promote consensus—supplies data points that map to all possible patient permutations for that tumor type (eg, age, performance status, prior treatment). For each specific tumor area or topic, experts also provide a single treatment recommendation for each case entered into the tool, rather than multiple "reasonable" options as presented in guideline recommendations (Figure 1).

After learners have entered the details of their patient case, they receive a custom report showing exactly how experts would treat that patient. Subsequently, learners can opt to complete a survey that asks if the expert recommendations changed their planned treatment for that patient. Structured query language is used to extract participation and outcomes data, and standard data analysis techniques are used to evaluate individual program metrics, such as number of cases entered, whether cases represent real or hypothetical patients, and learner-reported impact on practice.

Capturing Practice Discrepancies at Baseline

Across IDSTs, 12% of users indicate uncertainty about their treatment planning approach at baseline, and wide gaps are also evident between the intended treatment of healthcare providers (HCPs) and expert recommendations. A 2017 analysis of 2 annually updated multiple myeloma IDSTs illustrates the extent of these gaps in the context of induction therapy for patients with specific comorbidities.[18] For instance, experts recommended bortezomib/lenalidomede/dexamethasone (VRd) for 87% of patient cases with cardiac dysfunction compared with 41% of HCPs, whereas in cases involving peripheral neuropathy, experts recommended carfilzomib/lenalidomide/dexamethasone (KRd) in 60% of cases vs 10% of HCPs (Figure 2).

Figure 1. Patient case drop-down menu and expert insights in multiple myeloma.

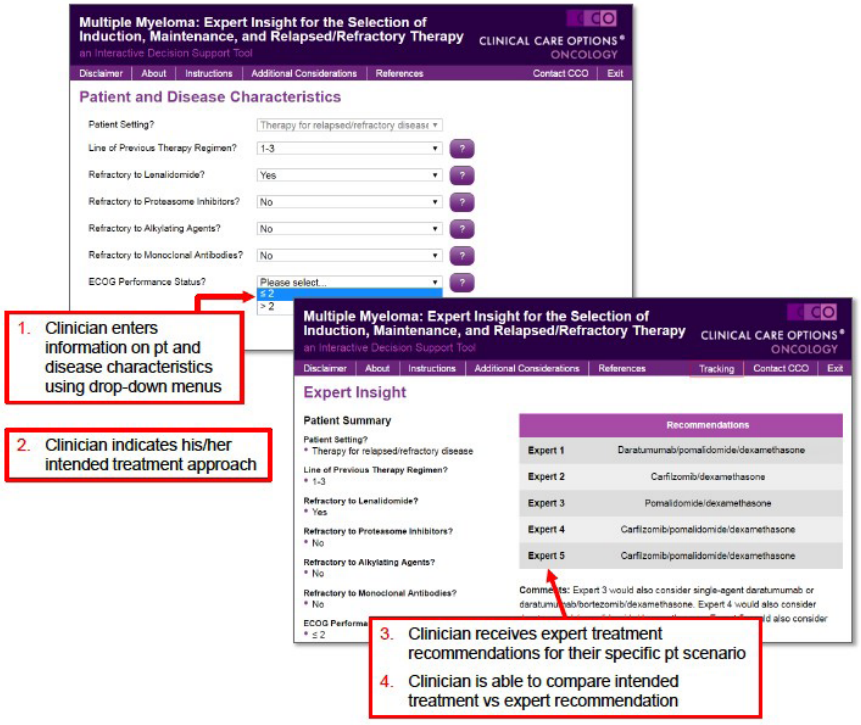
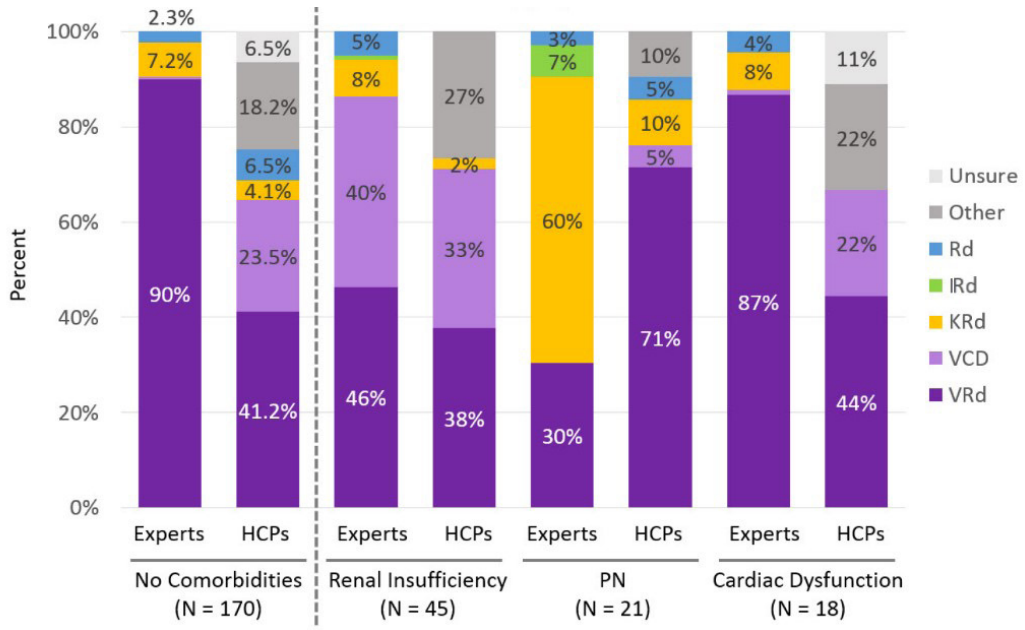


Figure 2. Gaps between learners and experts in multiple myeloma induction therapy.



Assessing the Impact of Expert Recommendations on Planned Treatment

We captured tool impact and changes in learners' treatment planning intentions by fielding an optional survey following tool interaction. In almost one half of the cases (41%) across programs, learners report that they changed their treatment plan for a specific case in response to the customized expert recommendations they received via interaction with the tools.

In this tool, experts compiled recommendations for 235 different patient case scenarios based on the following variations: neoadjuvant or adjuvant therapy, subtype, nodal status, tumor size, menopausal status, recurrence score, and BRCA1/2 status.[19] Between April and November 2015, 796 HCPs sought guidance on 1476 patient case scenarios from (53% real, 47% hypothetical), including scenarios in neoadjuvant treatment for hormone receptor–positive (HR+) early breast cancer (EBC). Comparison of expert and HCP choices showed distinct lack of concordance at baseline between expert recommendations and learners for use of neoadjuvant therapy. Although none of the experts recommended hormonal neoadjuvant therapy for HR+ EBC, 71% of tool users intended to use this approach. ***In 86% of cases, learner interaction with the tool either changed the user's intended clinical approach or confirmed their approach in line with expert recommendations.***

About Clinical Care Options

CCO, a leader in the development of innovative, interactive, online, and live CME/CE-certified programs and proprietary medical education technologies, creates and publishes original CME/CE and information resources that are designed specifically for healthcare professionals. CCO's educational programs are developed not only to provide the latest scientific information, but also to support the understanding, confidence, application, and competence of healthcare professional learners. In addition to the latest point-of-care resource—*in*Practice®—CCO provides a spectrum of live and online educational programs and formats.

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Clinical Impact of Internet-Based Decision Aids to Provide Expert Guidance on Clinical Management of Cancer

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Clinical Care Options, LLC, Reston, Va.

CLINICAL CARE OPTIONS®

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

Learning Objectives

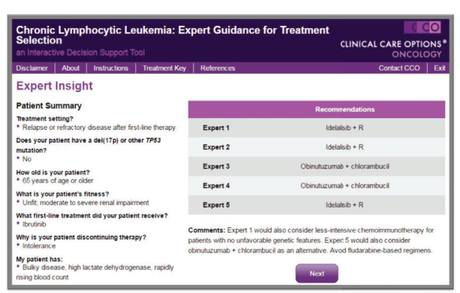
- Contrast the differences between treatment guidelines that provide general options for patient populations, and online decision aids that provide specific recommendations for individual patients
- Discuss the impact of expert guidance in the learner's selection of evidence-based therapy for a patient with cancer
- Describe how online tools can be used to reinforce or change clinician behavior to conform with evidence-based medicine

Background

- In oncology practice, clinicians are increasingly challenged by the growing number of treatment options, making it more difficult to select a therapy for a specific patient at hand
- Treatment guidelines may suggest numerous suitable treatments, but offer little guidance on what to choose for an individual patient scenario
- Online tools that provide expert clinical guidance have been proposed as an adjunctive approach to help clinicians make more informed treatment decisions
- To evaluate this hypothesis, we have evaluated data from a series of online Interactive Decision Support Tools designed to provide expert guidance to help community practitioners make therapeutic decisions for specific patients.

Decision Support Tools

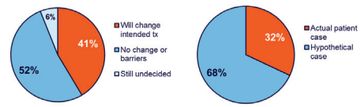
- More than 25 different oncology tools have been developed as part of CME-certified educational programs to provide expert treatment selection for specific patient cases
- In each tool, 3-6 clinical experts provide specific treatment recommendations for a large number of potential patient scenarios (as many as 1,862 scenarios per tool)
- Variables include patient characteristics (eg, age and preexisting comorbidities) and disease characteristics (eg, tumor stage, histology, and molecular profile)
- Participants receive expert recommendations customized to the patient and/or disease characteristics they entered



Practice Impact: CLL Tool

- Across multiple tools, results consistently show that a substantial proportion of users are positively impacted by the expert recommendations
- **Example: Decision Support Tool for Chronic Lymphocytic Leukemia (CLL)**
  - 41% intended to change treatment based on the expert feedback they received
  - 32% used the tool to help guide care of an actual patient

Impact of Tool on Intended Treatment (N = 173)



Practice Impact: Aggregate

- To measure impact on clinical decision making in aggregate, we analyzed cases that learners entered in tools for
  - Chronic myeloid leukemia (CML)
  - Non-small-cell lung cancer (NSCLC)
  - Breast cancer
- For these 3 tools, impact questions were answered for 1613 of 2760 cases entered (58%)
- In a majority of cases, the expert recomendations either confirmed or changed the user's clinical approach

Impact (n = 1613)	Cases, n (%)
Yes, changed or confirmed clinical approach	1055 (65%)
No, did not impact clinical approach	558 (35%)

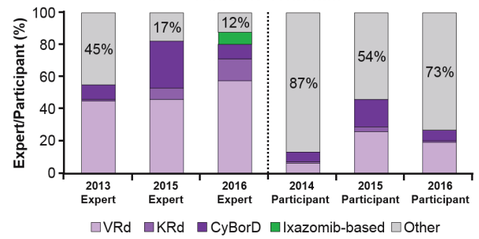
Myeloma Tool: Evolution Over Time

- We studied practice patterns and expert responses from 2013-2016 across 3 very similar myeloma tools we developed
- Changes in expert recommendations and practice patterns were observed over time for induction, maintenance, and relapsed/refractory treatment settings
- 532 different patient cases were entered by healthcare practitioners in 2016. Examples follow:

Induction, Transplant Eligible

- Expert choice of induction therapy migrated toward Bort/Cyclo/Dex and Carfil/Len/Dex away from the Len/Dex combination; support emerged for ixazomib-based therapy (recently approved in the relapsed setting)
  - Participant treatment choices* overall differed substantially from the experts, identifying areas of educational need
    - Bort/len/dex, which was the most recommended regimen by the experts was only selected as the intended treatment of 18% of the cases entered in 2016

Induction Therapy for Transplant Eligible Patients With MM

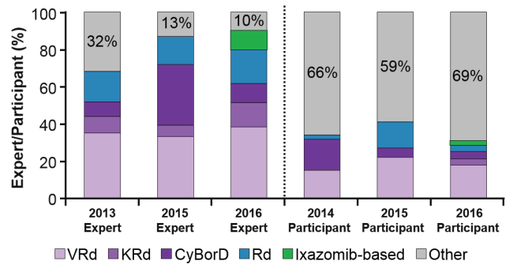


***Note:** Users were prompted to select treatment before viewing the expert recommendations (ie, the expert recommendations did not influence their self-reported treatment choice)*

Induction, Transplant Ineligible

- Dramatic drop-off in expert recommendation for melphalan tx, from more than a third of the case scenarios in 2013 to zero in 2015 and 2016; however, some users selected melphalan*, suggesting an ongoing educational need
- Consistently across the tools, the intended treatment of clinical users differed substantially from those recommended by the experts

Induction Therapy for Transplant Ineligible Patients With MM

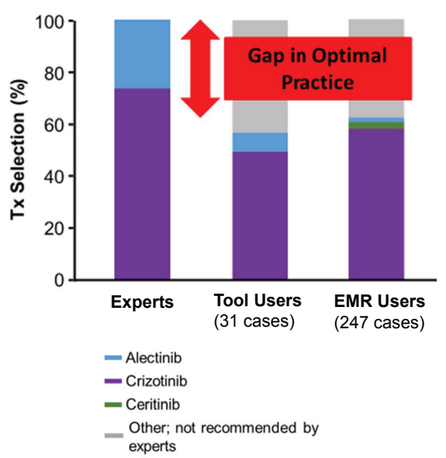


- Experts integrate new agents and consider the latest clinical data when making treatment decisions; whereas clinicians using the decision support tools tend to lag behind in the integration of newly approved agents and data
- Sequential analysis of cases and intended treatment entered into the tools has provide a snapshot showing enduring and emerging educational needs

Tool Data vs Actual Clinical Practice: EMR Analysis

- We compared data our users entered in one tool (854 patient cases) to actual EMR data obtained from community practices (18,174 patient entries)
- Tool provided expert recommendations on optimal care for pts with non-small cell lung cancer (NSCLC)
- **Example: Choice of first-line therapy for patients with non-squamous, ALK-positive NSCLC**
  - Data reveal close parallel between data sets, revealing similar gaps in optimal practice (see graphic)
  - Likewise, similar proportion of users appropriately chose an ALK TKI in the tool (58%) and EMR (64%)

ALK TKI, %		
Experts	**Tool**	**EMR**
100%	58%	64%



Conclusions and Implications

- Expert recommendations delivered via online, interactive decision support tools changed or confirmed the practitioners' clinical approach in the majority of cases
- Impact on practice is observable in both individual tools and in aggregate data across tools
- Data from tools provides unique window into expert recommendations and real-world practice patterns, both as a snapshot, and over time (as shown in the Myeloma tool analysis)
- EMR Analysis: gaps in care observed in Decision Support Tool were verified in EMR data
  - This suggests that our tool data and identified gaps and educational needs are reflective of actual community practice
- Providing customized, patient-specific expert advice may increase the number of optimal treatment decisions
- Decision aids can be a "bridge" between treatment guidelines (which provide general options for a broad group of patients) and clinical practice (where clinicians must make specific decisions for specific patients)

References

For a complete list of recent publications related to CCO Decision Support Tools, please see the Publications Page on the CCO Web site.

Acknowledgments: This research is based on activities supported by educational grants from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Genentech BioOncology, Janssen Biotech, Lilly, Merck & Co., Inc., Novartis, Pfizer, Sanofi-Aventis, Takeda Oncology, and Veridex.

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Evolving Immunotherapy Practice Patterns in Advanced NSCLC: Analysis of an Online Treatment Decision Tool

David R. Gandara, Timothy A. Quill, Martin J. Edelman, Suresh S. Ramalingam, Heather A. Wakelee, H. Jack West, Kevin L. Obholz

Disclosures for David R. Gandara, MD

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Online Treatment Decision Support Tool for Advanced NSCLC

- **Rationale:** The therapeutic landscape in advanced NSCLC is rapidly changing and growing in complexity. As previously published, this interactive online tool is designed to educate clinicians on recent advances and to provide expert guidance.[1]

- **Methods:** A lung cancer expert panel (DRG, MJE, SSR, HAW, HJW) identified key patient/tumor characteristics and made treatment recommendations for 280 possible patient scenarios. Participating oncologists entered individual characteristics for their patient and their preferred treatment approach using drop down menus online before seeing expert recommendations.

- **Goal:** Here we present results from this online tool for the impact of immunotherapy on treatment decision-making (to April 2018).

Results: Participating Oncologist Demographics

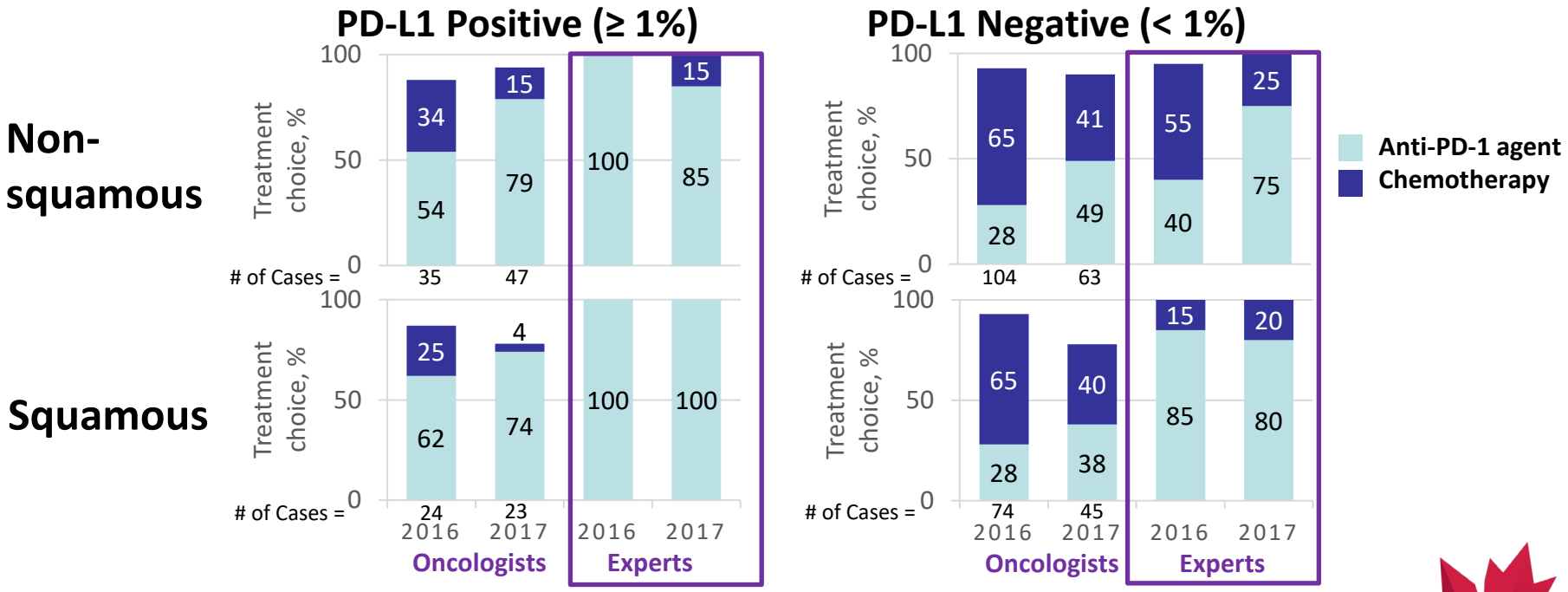
Region	Oncologist Participants, %	
	2016 Tool (N = 388)	2017 Tool (N = 474)
• US	20	19
• Europe	34	31
• East Asia	6	7
• RoW	39	43
Cases entered, n	708 (June 2016 – Feb 2017)	773 (Feb 2017 – Apr 2018)

Selected Biomarker Driven 1st -Line Practice Patterns

Treatment choices (per scenario), %	EGFR mutation (n = 75 cases)	ALK rearrangement (n = 21 cases)	ROS1 rearrangement (n = 14 cases)	High PD-L1 (≥ 50%) (n = 34 cases)
Experts	EGFR TKI, 100	ALK TKI, 100 [Alectinib, 80]	Crizotinib, 90	Pembrolizumab, 95
Oncologists (Overall)	EGFR TKI, 81	ALK TKI, 81	Crizotinib, 57	Pembrolizumab, 65
US	• Afatinib, 66 • Erlotinib, 33 • Gefitinib, 0	• Alectinib, 33 • Ceritinib, 33 • Crizotinib, 33	----	Pembrolizumab, 60
EUR	• Afatinib, 72 • Erlotinib, 17 • Gefitinib, 11	• Alectinib, 0 • Ceritinib, 0 • Crizotinib, 100	Crizotinib, 60	Pembrolizumab, 50
RoW	• Afatinib, 59 • Erlotinib, 33 • Gefitinib, 12	• Alectinib, 36 • Ceritinib, 0 • Crizotinib, 36	Crizotinib, 56	Pembrolizumab, 75

- For High PD-L1: 66% indicated they would change their recommendation based on expert opinion

Selected 2nd -Line Practice Patterns After Platinum-based Chemotherapy



- 57% of participants initially agreed with expert recommendations
- 21% indicated they would change their recommendation based on expert opinion

Conclusions

- In 2017, most participating oncologists selected targeted therapy for cancers with driver mutations (EGFR – 81%, ALK – 81%, ROS1 – 57%)
  - Most commonly afatinib (EGFR), crizotinib (ALK/ROS1)
- Immunotherapy recommended less often by participating oncologists versus lung cancer experts in the following settings:
  - 1st-line treatment of PD-L1 ≥ 50%
  - 2nd-line treatment after platinum-based CT (e.g. PD-L1 < 1%)
- This interactive online tool is updated frequently and available at: www.clinicaloptions.com/Lungtool
  - A tool update is in progress incorporating new data & approvals through August 2018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Variance From Evidence-Based Management of Immune-Related Adverse Events Among Healthcare Providers: Analysis of an Online Management Decision Tool

Krista Marcello, BA; Kevin L. Obholz, PhD; Timothy A. Quill, PhD; Jeffrey S. Weber, MD, PhD

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Presenter Disclosure Information

Krista Marcello, BA
Managing Editor, Clinical Care Options, LLC

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No relationships to disclose

The development of the resource in this presentation was made possible through unrestricted independent medical education grants supported by Merck & Co., Inc.; Merck KGaA; and Pfizer Inc.

There will not be discussions about the use of products for non-FDA approved indications in this presentation.

Background

- Immune checkpoint inhibitors are being integrated into the care of a rapidly increasing number of patients with many different tumor types
  - Profiles of toxicities, some of which are better tolerated than chemotherapy, are unique and require a specific knowledge base for optimal identification and management
  - Effective immune-related adverse event (irAE) management allows for optimal treatment and mitigates potentially serious treatment-related complications
- Many healthcare providers (HCPs) remain unfamiliar and inexperienced with managing the unique spectrum of irAEs

Methods

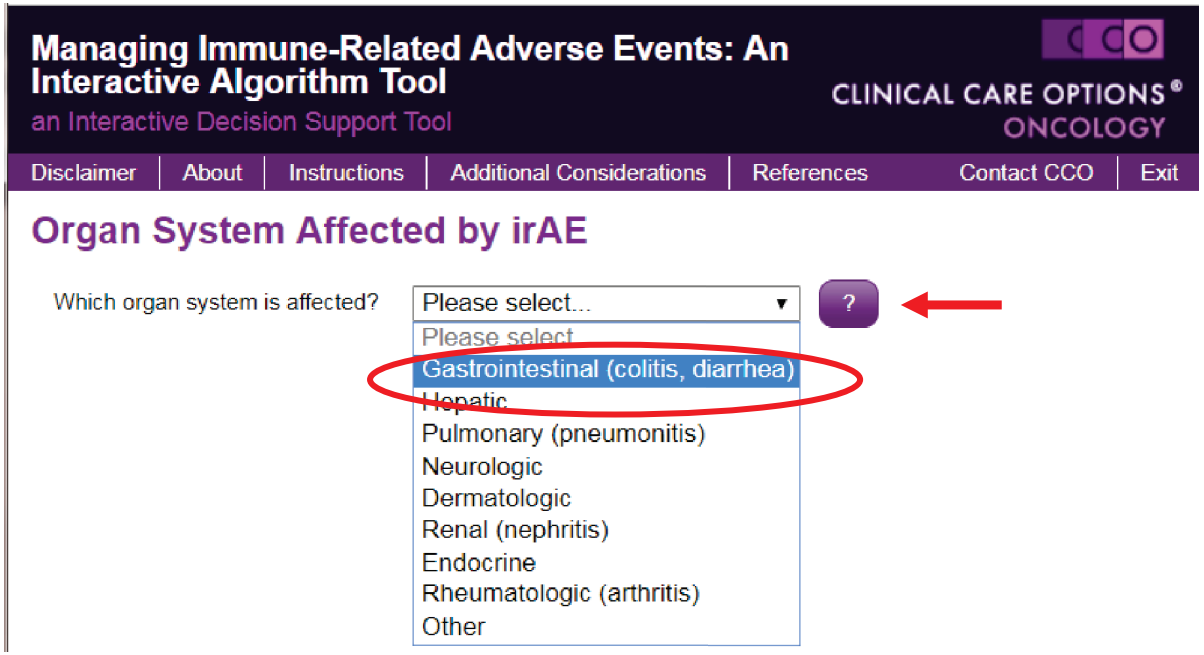
- CCO developed an online management support tool designed to give clinicians easy access to balanced, evidence-based management recommendations, based on
  - Organ system affected
  - Grade/severity of irAE (CTCAE)
- Recommendations from evidence-based guidance, peer-reviewed published literature, and Dr. Weber's personal clinical experience
- 2 versions of the tool
  - Initial version: data collected from 11/9/2016 through 7/21/2017
  - Updated version: data collected from 5/10/2017 through 9/27/2017
    - Recommendations updated based on available data and guidelines
    - Added categories "rheumatologic" and "other"

Methods

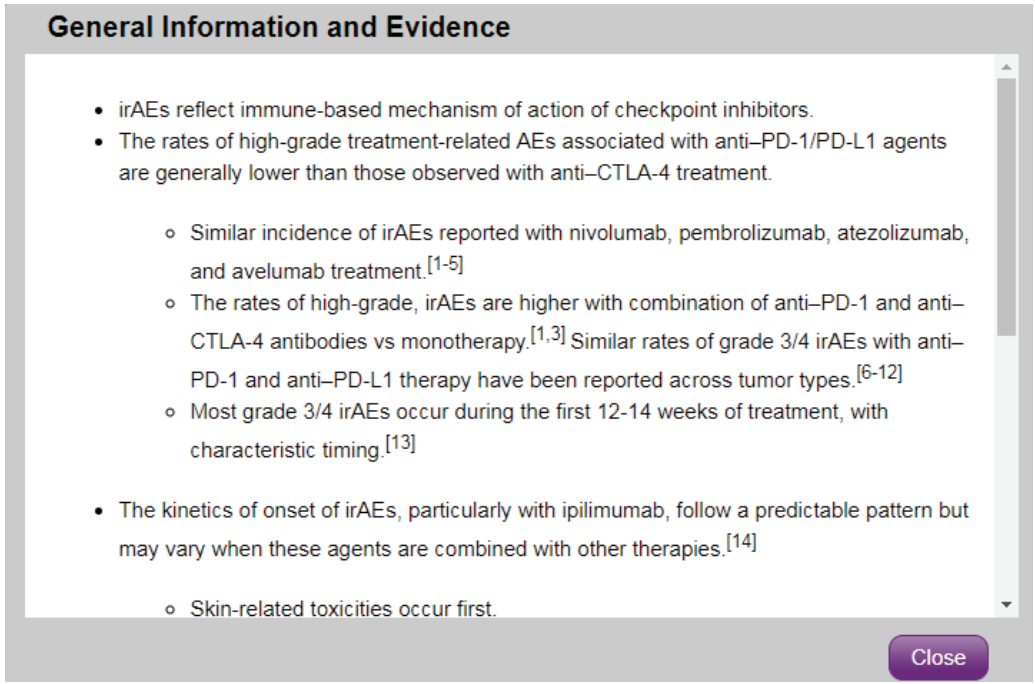
- Tool users were asked about their intended management plan before evidence-based recommendations were provided
- The current study includes an analysis of cases entered into the tool and comparison of the intended management of HCPs with the evidence-based recommendations in the tool
- Chi-square analysis was performed on the data collected from the tool for statistical significance of the variance of intended management vs evidence-based recommendations

How to Use the Tool: clinicaloptions.com/immuneAEtool

How to Use the Tool: clinicaloptions.com/immuneAEtool



How to Use the Tool: clinicaloptions.com/immuneAEtool



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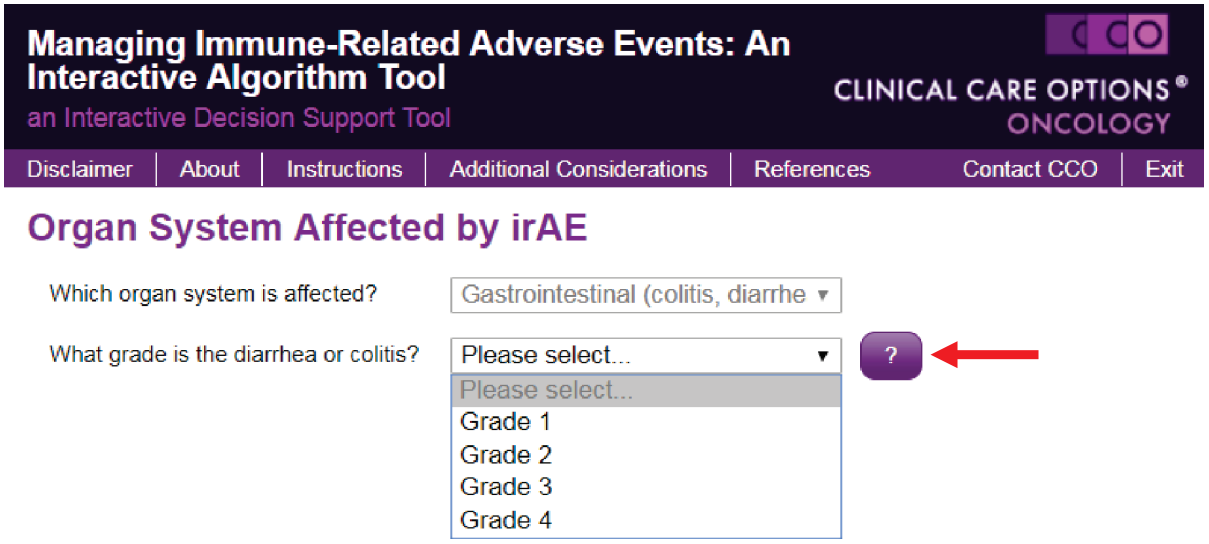

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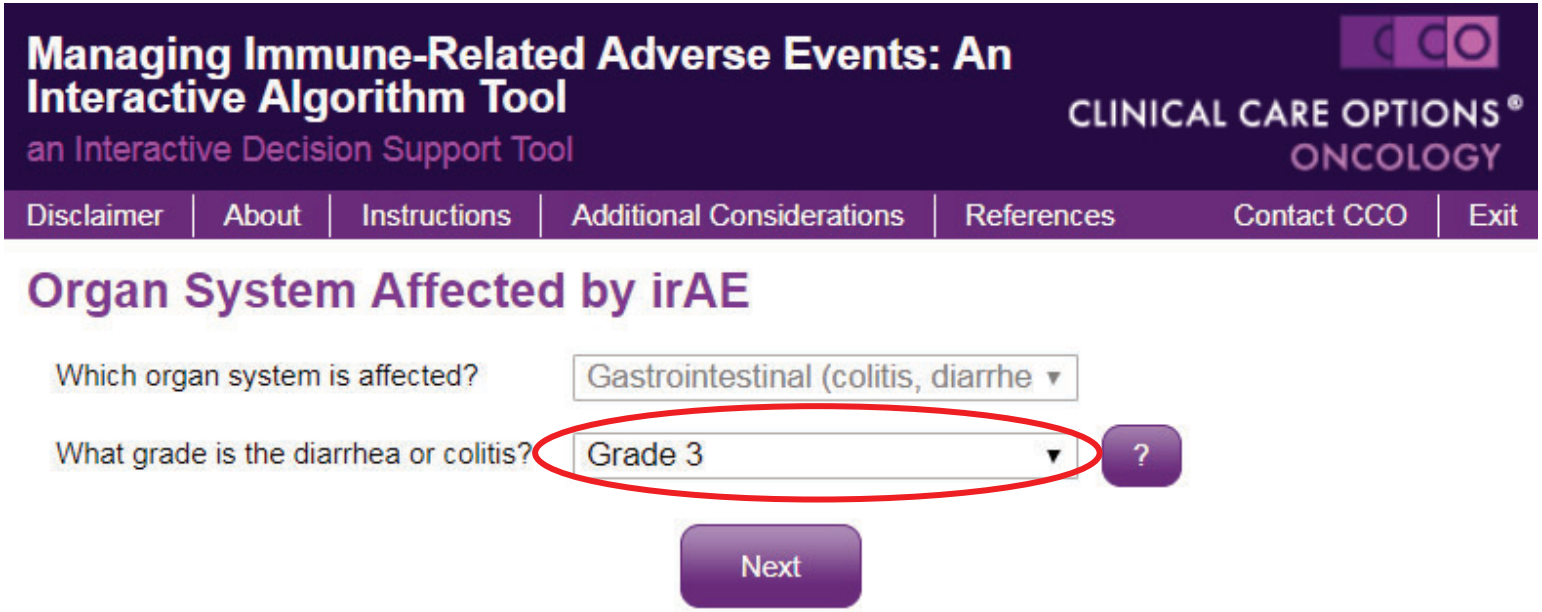


How to Use the Tool: clinicaloptions.com/immuneAEtool

Recommendations

-Consider permanent discontinuation of therapy (or eliminate ipilimumab from the combination regimen, if the patient was receiving combination immune checkpoint blockade)

-Consider hospital admission
-1.0-2.0 mg/kg/day IV methylprednisolone or equivalent
-Add prophylactic antibiotics for opportunistic infections if steroids are used for > 30 days
-Consider endoscopy; check C. difficile titres and cultures

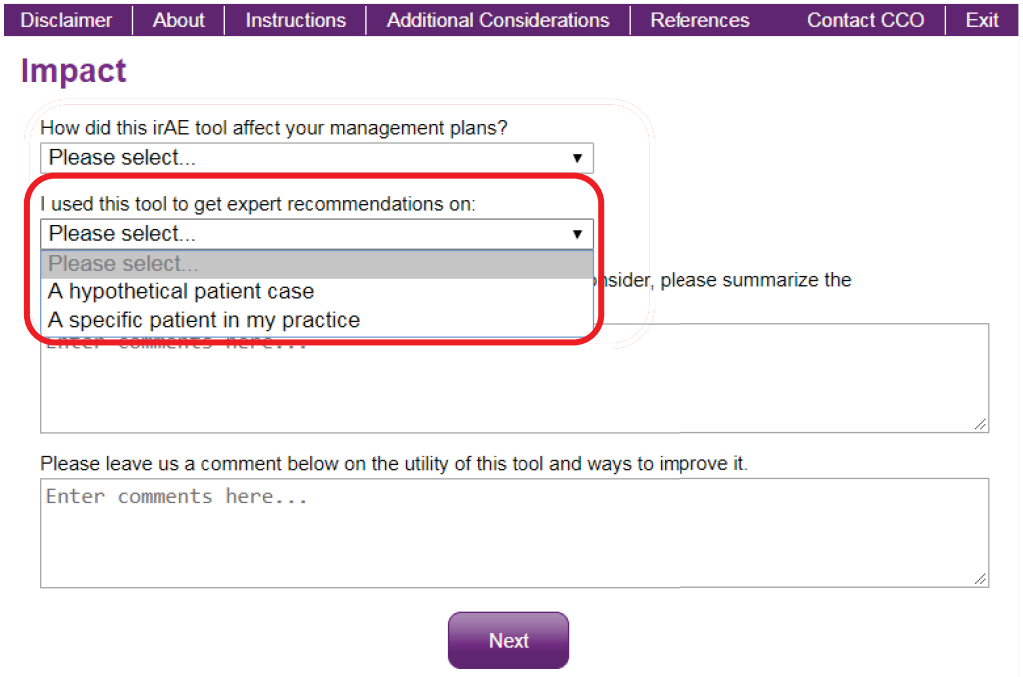
Follow-up: If symptoms improve, continue steroids until grade ≤ 1, then taper over at least 1 month

If symptoms persist > 3 days or recur after improvement: Add infliximab 5 mg/kg/day (if no contraindication, and should not be used in cases of perforation or sepsis)

Comments: Patients receiving > 4-6 wks of steroids require Pneumocystis carinii prophylaxis. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is established. Lower bioavailability of oral corticosteroids should be considered when switching.

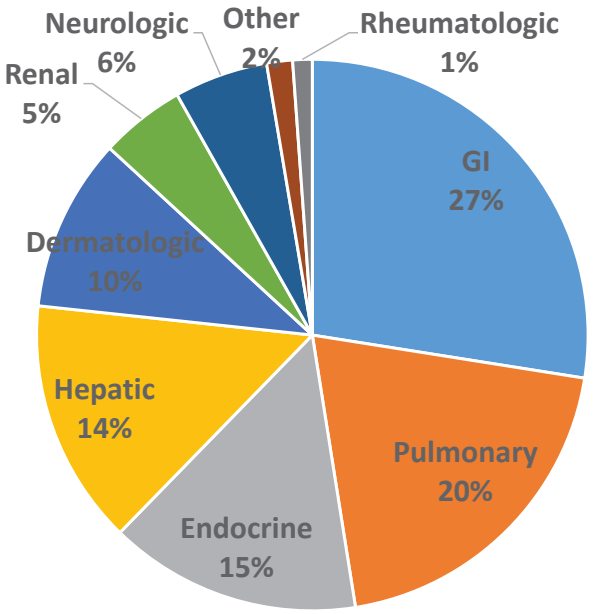
Next

How to Use the Tool: clinicaloptions.com/immuneAEtool

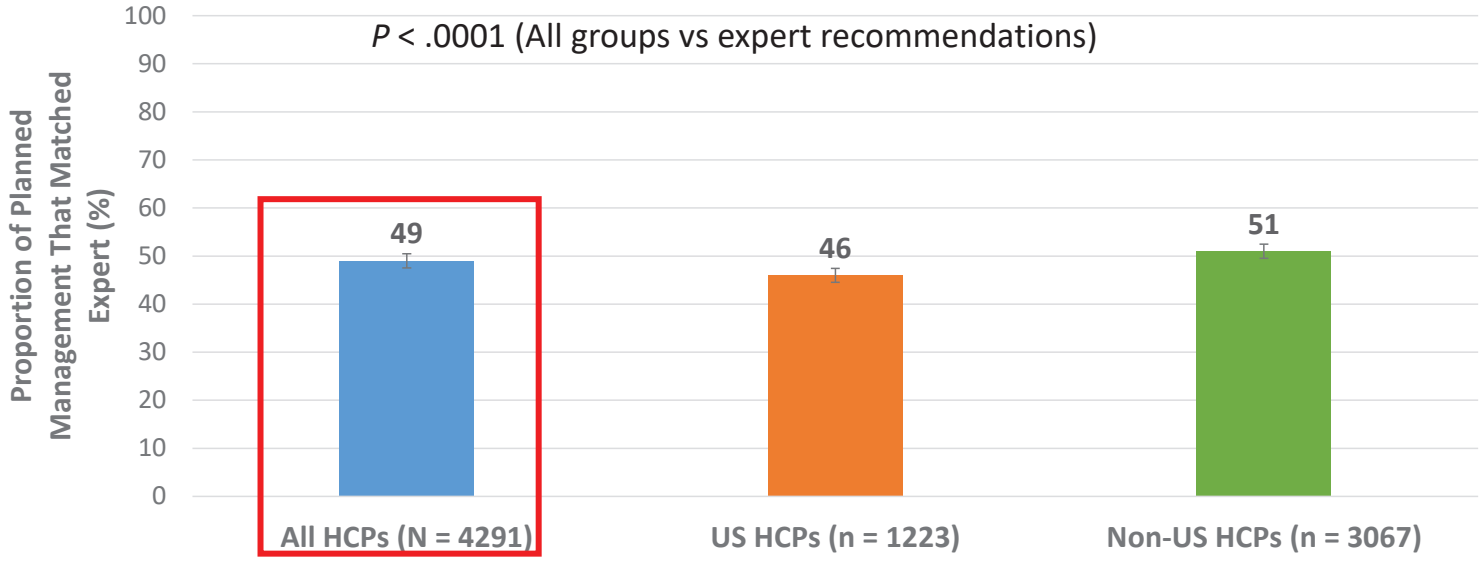


Cases Entered Into Tool by Organ System

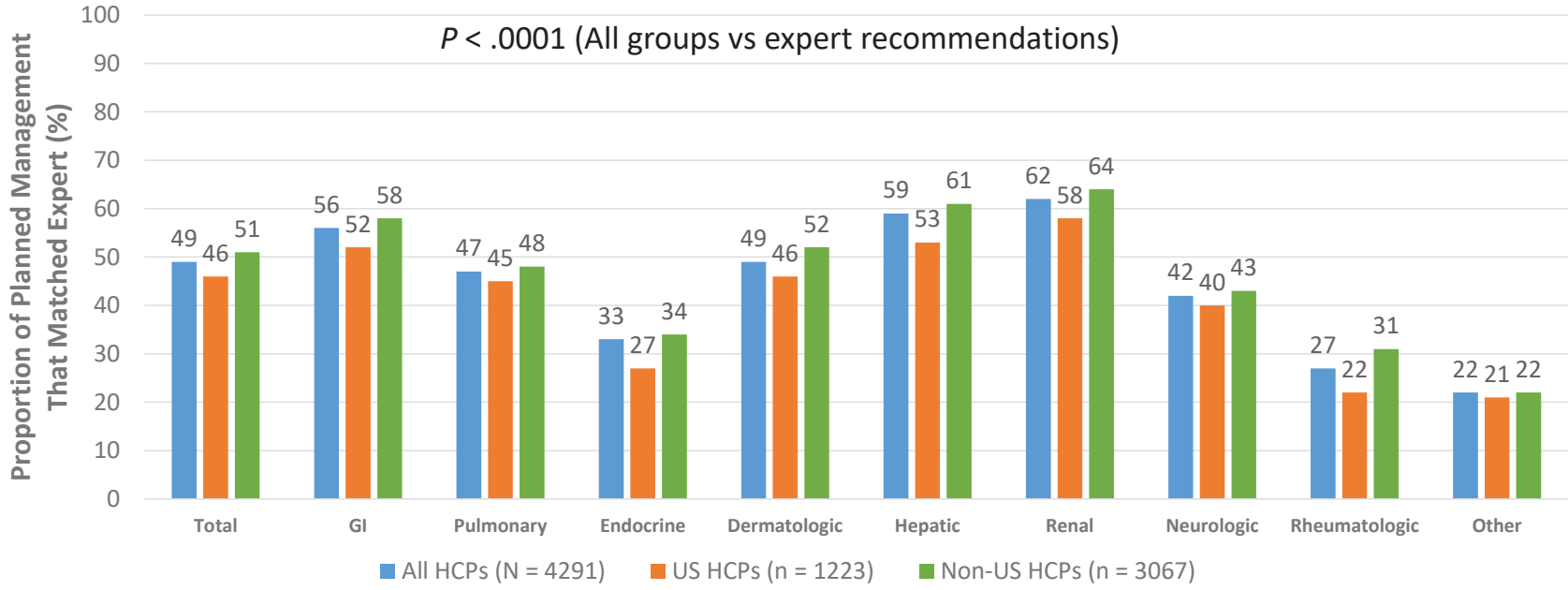
- In total, 4291 cases were entered into the tool by HCPs
- The most frequently entered cases were of GI origin (27%), followed by pulmonary (20%)
- "Rheumatologic" and "other" were added to the most recently updated tool and thus had the fewest cases



Planned Management of HCPs Compared With Evidence-Based Recommendations: Overall Cases Entered (N = 4291)

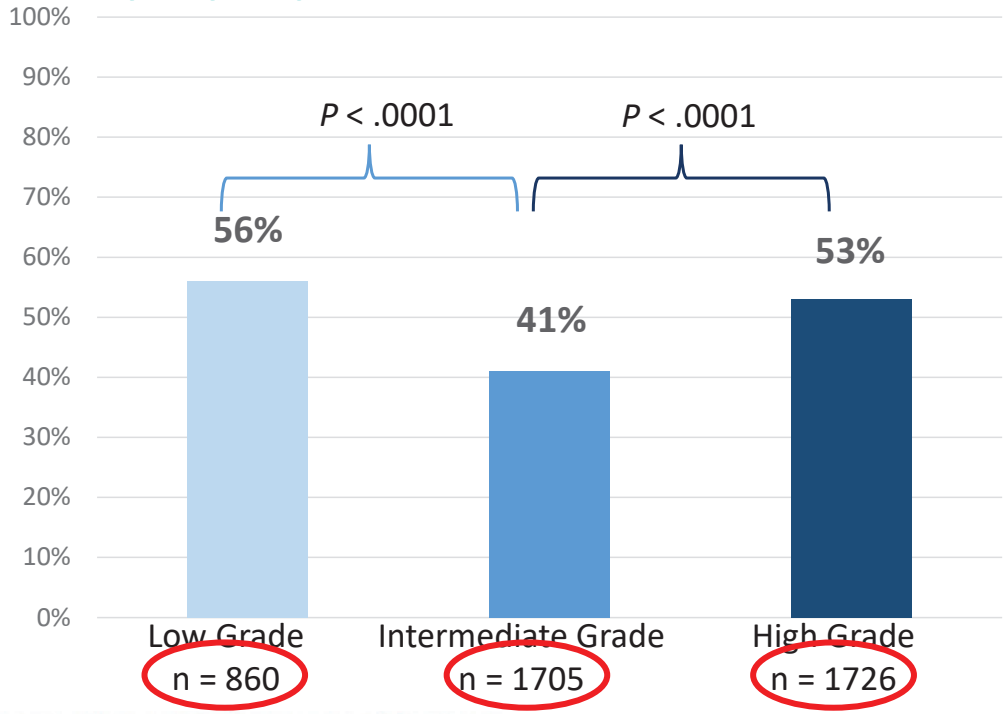


Planned Management of HCPs Compared With Evidence-Based Recommendations: Overall Cases Entered (N = 4291)



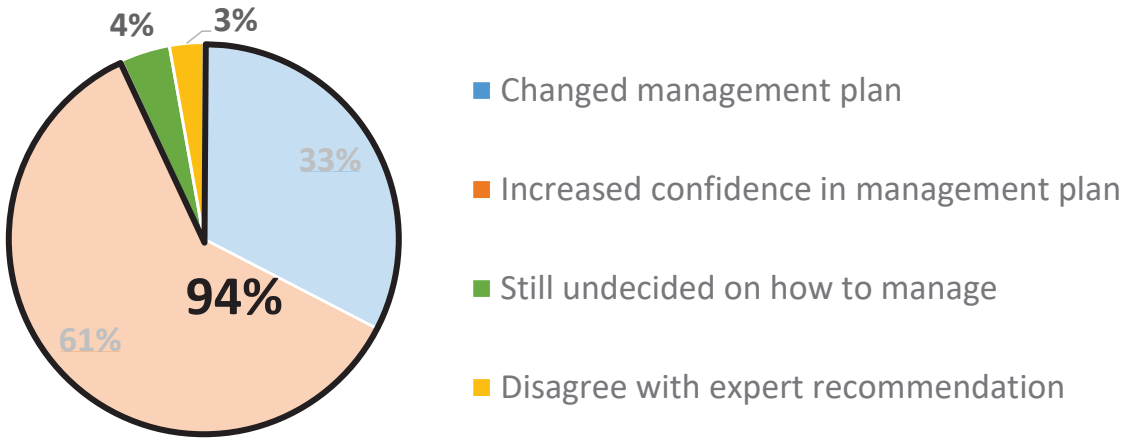
Planned Management of HCPs Compared With Evidence-Based Recommendations by Symptom Grade (N = 4291)

- Greatest variance between initial HCP management plan and evidence-based recommendation occurred with intermediate-grade events
- HCPs used the tool to research management of intermediate- and high-grade events twice as often as low-grade events



Impact of the Tool on Practice

- Of participants who answered the impact survey (n = 957):
  - **94%** indicated that the tool recommendations either confirmed or changed their management plan
  - **30%** were using the tool to manage a specific patient in their clinic



Lessons and Take-home Messages

- Despite available data, product inserts, and guidance on manufacturer Web sites, our analysis suggests many clinicians are not optimally managing irAEs associated with immune checkpoint inhibitor use
  - Overall, 49% of HCPs using the tool selected an initial management plan that matched evidence-based recommendations (46% US HCPs, 51% non-US HCPs; $P < .0001$)
  - Variance between HCP intended management and evidence-based recommendations was significant in each organ system
  - Lower concordance observed with intermediate vs low- or high-grade events
- A fair, balanced, evidence-based online irAE management tool is an important clinical resource that might improve patient care and safety
- The irAE tool will be updated regularly: **clinicaloptions.com/immuneAEtool**

Acknowledgments

- Jeffrey S. Weber, MD, PhD
- Colleagues and coauthors at Clinical Care Options
- Our clinician members
- Merck & Co., Inc.; Merck KGaA; and Pfizer Inc. for their support of our tool development

Analysis of an Online Tool to Explore Evolving Practice Patterns in Renal Cell Carcinoma

CLINICAL CARE OPTIONS® ONCOLOGY

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University of California, San Francisco, San Francisco, CA; Clinical Care Options, Reston, VA; Baylor Sammons Cancer Center-Texas Oncology, Dallas, TX; Memorial Sloan Kettering Cancer Center, New York, NY; Fox Chase Cancer Center, Philadelphia, PA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background

The complex and rapidly evolving treatment landscape for advanced renal cell carcinoma (RCC) poses significant challenges for treatment decision making. What is the best first-line therapy today? What is the best second-line therapy in a patient with TKI-refractory RCC? Given the multitude of options for first-line and subsequent-line therapies available today, these are important questions for healthcare providers (HCPs) who are making these decisions that can have an impact on patient outcomes.

In 2016, 5 RCC experts developed an interactive, online RCC decision support tool, in which HCPs entered RCC cases along with their treatment decisions. The tool reported treatment recommendations of the 5 RCC experts based on the key clinical factors. Nearly 500 cases entered by more than 300 HCPs were analyzed to explore practice patterns in RCC and to determine areas of agreement and difference in the first-line and second-line treatment recommendations compared with the 5 RCC experts. HCPs and the RCC experts generally agreed on sunitinib or pazopanib for first-line therapy for metastatic RCC, but there was substantial variation for all subsequent lines of therapy.

Since the tool was developed, multiple new agents, including nivolumab, cabozantinib, and lenvatinib/everolimus, have received regulatory approval for the treatment of advanced RCC, and multiple phase III clinical trials of novel therapies are ongoing, with promising results from phase I/II clinical trials. Given that the changes in the treatment landscape are leading to greater complexity than ever, we recreated the RCC decision support tool in 2017 to explore changes in practice patterns compared with 2016.

CCO Decision Support Tool for RCC

- Interactive, online decision support tool was developed by RCC experts:
  - 2017 tool: Thomas Hutson, Won Kim, Robert Motzer, Elizabeth Plimack, Brian Rini
  - 2016 tool: Toni Choueri, Thomas Hutson, Robert Motzer, Brian Rini, Charles Ryan
- Key clinical factors used in the support tool included histology, risk status, performance status, and prior therapies
- Using the tool:
  - HCPs enter cases, selecting the key clinical factors via pull-down menus
  - Users then submit their planned treatment approach
  - The tool displays the treatment recommendations of each of the 5 experts based on the key clinical factors; recommendations were based on clinical guidelines, available evidence, and experts' opinions at the time
  - Users are asked whether the expert recommendations confirmed or changed their intended clinical approach (clinical impact)
- 680 cases were entered by 420 HCPs between March 2017 and Sept 2017 (see Tables 1A and 1B); 470 cases entered in 2017 (data not shown)
- Tool online at: http://clinicaloptions.com/RCCTool

Results

User (HCPs) Demographics

- Approximately 81% of users were medical oncologists
- Approximately 25% of users were US based
  - Top 5 highest: US, India, Italy, United Kingdom, Spain

Case Demographics, 2017

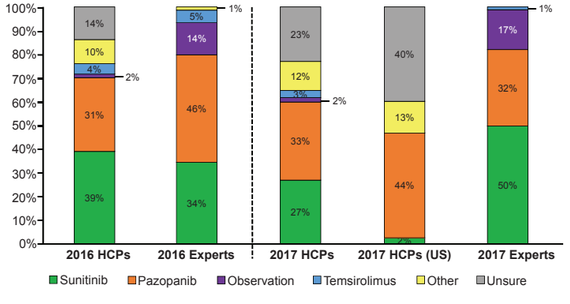
Table 1A. Cases Entered Into 2017 Tool, by Line of Therapy

Line of therapy	n (%; N = 680)
Treatment naive (first line)	304 (45)
After first-line TKI (second line)	271 (40)
Third line	105 (15)

Table 1B. Treatment-Naive Cases Entered Into 2017 Tool, by MSKCC Risk

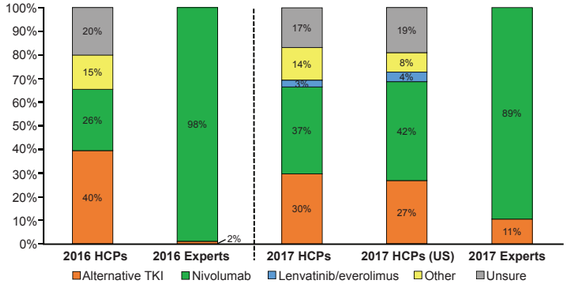
MSKCC Risk Status	n (%; N = 304)
Favorable	112 (37)
Intermediate	142 (48)
Poor	50 (16)

FIRST-LINE THERAPY



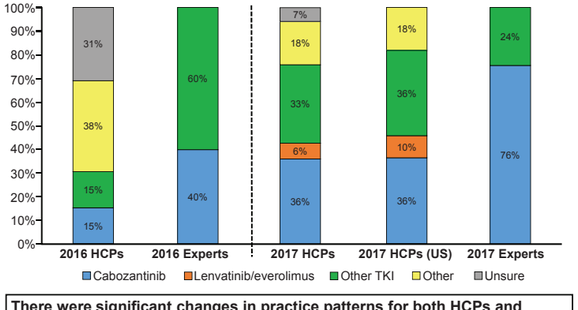
In 2016 and 2017, 65% of HCPs, compared with 81% of the experts, selected sunitinib or pazopanib as first-line therapy ($P = .0014$)

SECOND-LINE THERAPY (After 1st-Line TKI)



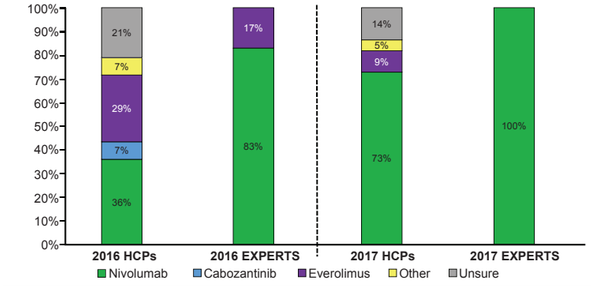
After first-line TKI therapy, experts more often selected nivolumab as second-line therapy compared with HCPs (2016: 98% vs 26%, $P < .0001$; 2017: 89% vs 37%, $P < .0001$). There was a slight increase in HCPs using nivolumab in the second-line setting in 2017 compared with 2016.

THIRD-LINE THERAPY (1st TKI, 2nd Nivolumab)



There were significant changes in practice patterns for both HCPs and experts for third-line therapy following a first-line TKI and second-line nivolumab between 2016 and 2017. In 2017, experts selected cabozantinib in 76% of cases compared with 40% in 2016. In 2017, 69% of HCPs selected a TKI as third-line therapy compared with only 30% in 2016.

THIRD-LINE THERAPY (1st TKI, 2nd Axitinib)

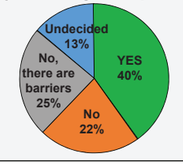


Nearly all experts in 2016 and 2017 selected nivolumab as third-line therapy following a first-line TKI and second-line axitinib. The proportion of HCPs selecting nivolumab as third-line therapy increased from 36% in 2016 vs 73% in 2017.

CLINICAL IMPACT

- 220 users answered the clinical impact questions in 2017
  - Overall, 46% of HCP users who differed in their treatment selection from expert recommendations indicated that the tool changed their intended treatment

HCPs who differed from experts in their treatment selection for second-line therapy after first-line TKI: "Did the expert recommendations change your management plan?"



Conclusions

- Practice patterns are changing rapidly in response to the evolving treatment landscape in advanced RCC
- Practice patterns between HCPs and RCC experts differed substantially in patients following first-line TKI therapy
- This online decision tool reveals significant and clinically relevant gaps between expert consensus and treatment decisions made by HCPs treating patients with RCC
- Given that the expert recommendations often changed an HCP's treatment plan, the potential of an online tool to improve clinical outcomes in advanced RCC warrants further investigation

For correspondences regarding this poster, please contact Won Kim, MD (won.kim@ucsf.edu)

Consensus and Disagreement Among Experts in Treatment of Patients With HER2+ Early-Stage Breast Cancer Suggests an Unmet Need for an Online Decision Support Tool

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[1]Texas Oncology, US Oncology. [2]Clinical Care Options, LLC. [3]David Geffen School of Medicine at UCLA. [4]Stanford Cancer Institute, Stanford University School of Medicine.
[5]Sarah Cannon Research Institute, Tennessee Oncology. [6]Baylor University Medical Center, Texas Oncology, US Oncology.

CLINICAL CARE OPTIONS® ONCOLOGY

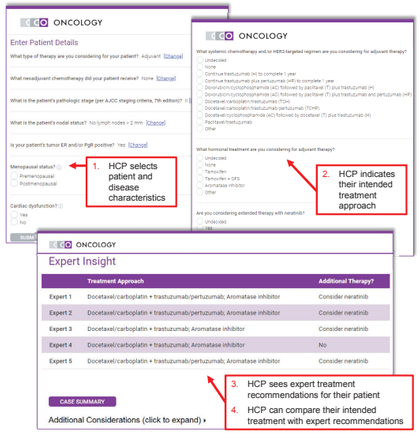
Background

Tx options for HER2+ EBC are continuing to evolve, increasing the complexity of Tx decision making. As Tx options expand, so does the need for online decision aids. The aim of this analysis was to assess real-world global practice patterns for HER2+ EBC and compare them with recommendations from US experts based on patient cases entered by healthcare providers (HCPs) into an online decision support tool designed to provide specific, patient-individualized expert recommendations.

Methods

- 5 experts provided Tx recommendations for 270 unique case scenarios for patients with HER2+ EBC (compiled in August 2018)
- Individual tool scenarios were defined by key patient and disease characteristics, including treatment setting, tumor size/nodal status, hormonal receptor status and menopausal status, relevant treatment history, comorbidities, or Tx-related AEs
- To use the tool, HCPs entered their patient's information and their intended Tx plan. Expert Tx recommendations for that specific patient are then provided to the HCP
- Tool online at **clinicaloptions.com/HER2_EBC_Tool**

Tool Screenshots (Examples)



Results

Tool Participant (HCPs) Demographics

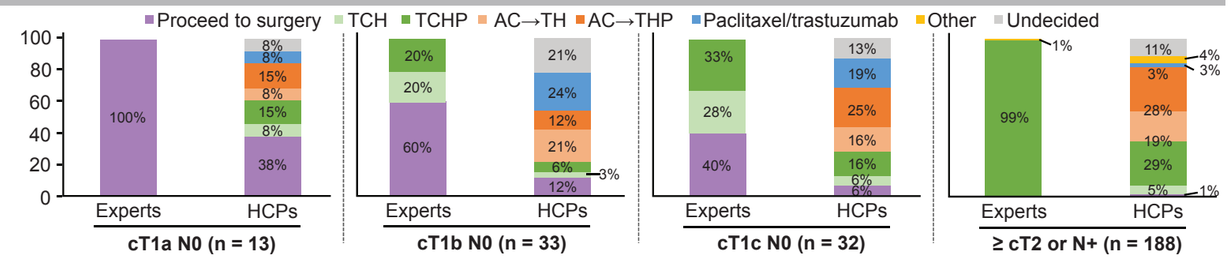
- Analyzed 571 patient cases entered by 338 HCPs between September 12, 2018, and November 12, 2018
- Approximately 80% of users were medical oncologists
- Approximately 25% of users were US based and 75% were outside the US
  - US (n = 89), Asia (n = 85), Europe (n = 73), Other (n = 91)

Case Demographics

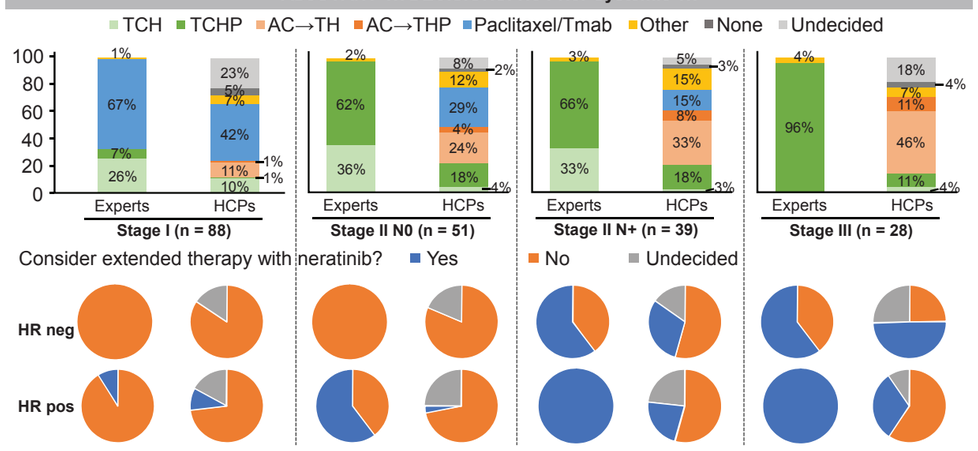
Table 1. Cases Entered Into Tool, by Tx Setting

Setting	n (%) (N = 571)
Neoadjuvant	267 (47)
Adjuvant	304 (53)

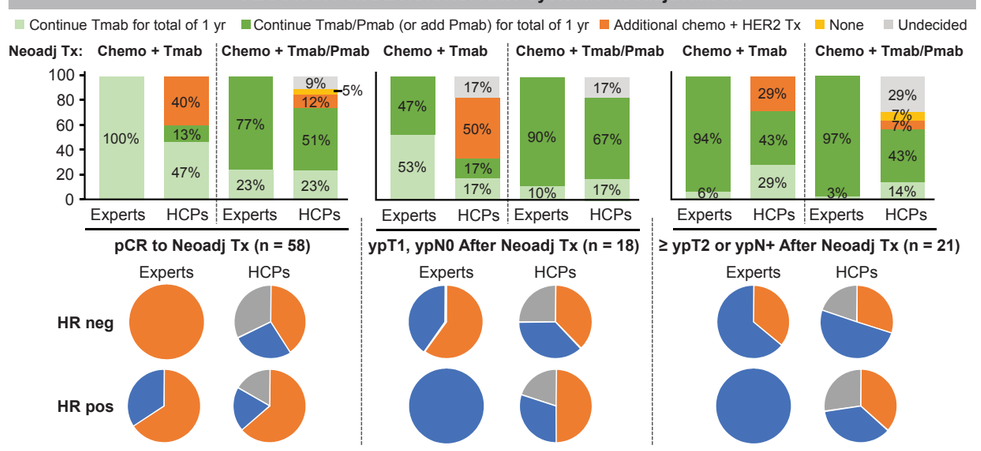
NEOADJUVANT Tx DECISIONS



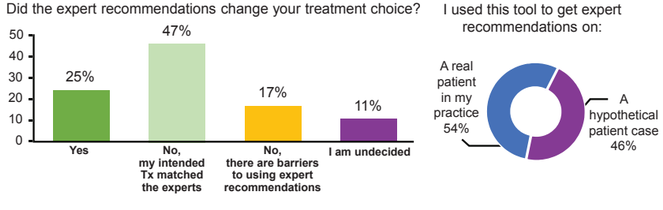
ADJUVANT Tx DECISIONS: No Prior Systemic Tx



ADJUVANT Tx DECISIONS: After Systemic Neoadjuvant Tx



CLINICAL IMPACT



Conclusions

- There were large differences between experts and HCPs regarding sequencing of chemotherapy and surgery for smaller tumors in the neoadjuvant setting, and there was marked variations between experts' and HCPs' choice of therapy for those receiving neoadjuvant Tx
  - Many HCPs chose anthracycline-based therapy, whereas experts generally recommend non-anthracycline–based chemotherapy in this setting
- Similarly, there was a wide variation in the choice of adjuvant therapy among HCPs vs expert recommendations for all patient subgroups
  - For those without prior neoadj chemotherapy, HCPs chose anthracycline-based Tx and many used paclitaxel/trastuzumab for patients not included in the APT clinical trial
  - For those with previous neoadj chemotherapy, up to 50% of HCPs would use additional chemotherapy despite lack of evidence
- Extended adjuvant therapy with neratinib was beneficial based on the ExteNET study that enrolled stage II-IIIc patients; however, HCPs considered neratinib less often than experts for eligible patients, with up to 25% indicating uncertainty regarding appropriate use of neratinib
- This online tool reveals significant and clinically relevant gaps between expert consensus and Tx decisions made by HCPs. Expert recommendations often reinforced or changed HCP's treatment plan, highlighting the need for ongoing education and the potential of an online tool to improve clinical outcomes for patients with HER2+ EBC

Title: Evolving Practice Patterns in Advanced NSCLC: Analysis of An Online Treatment Decision Tool

Authors: T.A. Quill, M. Edelman, S. Ramalingam, H. Wakelee, H. West, K. Obholz, D.R. Gandara

Background

The treatment (Tx) landscape for advanced NSCLC is rapidly changing and increasingly complex. To assess evolving NSCLC Tx patterns, we analyzed the planned Tx approaches for patient (pt) cases entered by healthcare providers (HCPs) into an online treatment decision support tool developed by NSCLC experts.

Methods

From June 2016 to July 2017, the tool was updated 3 times with new treatment recommendations from 5 experts for hundreds of different case scenarios. To use the tool, HCPs entered pt information and their intended Tx for that pt case. Tx recommendations from the experts were provided for the specific pt case and HCPs were then asked to complete an optional survey to determine if these recommendations changed their intended Tx plan. This analysis compared intended Tx recommendations of HCPs and experts for 1265 cases entered into the tool.

Results

Tx patterns evolved from 2016 to 2017 for both experts and HCPs. In the second-line EGFR T790M-positive setting, 100% of experts selected osimertinib in 2016 and 2017 vs an increase from 21% to 71% for HCPs. For ALK-positive pts, expert selection of first-line alectinib increased from 14% to 100% vs an increase of 20% to 40% by HCPs. In 2017, first-line pembrolizumab was recommended by experts for pts with high PD-L1 expression and no driver mutations more often than HCPs (95% vs 71%). In the second-line setting after chemotherapy, both tumor histology and PD-L1 expression level impacted treatment recommendations. For PD-L1 ≥ 1%, most experts and HCPs recommended a PD-1/PD-L1 inhibitor (Sq: 100% vs 80%; Nonsq: 85% vs 78%). For PD-L1 < 1%, there was more variance in PD-1/PD-L1 inhibitor recommendations between experts and HCPs (Sq: 80% vs 37%; Nonsq: 75% vs 53%). Over 60% of HCPs with a planned Tx that differed from expert consensus indicated that using the tool changed their Tx plan for that case.

Conclusions

Practice patterns of both experts and HCPs are evolving in advanced NSCLC care; however, substantial variance in Tx exists for many NSCLC subtypes. Given that expert consensus recommendations often changed the Tx plan of HCPs, the potential of online treatment decision tools to improve clinical outcomes in pts with advanced NSCLC warrants further investigation.

Evolving Treatment Patterns of Healthcare Providers (HCPs) and Multiple Myeloma (MM) Experts From 2013-2017: Analysis of an Annually Updated Online Treatment Decision Tool

Kristen M. Rosenthal, PhD; Carol Ann Huff, MD; Shaji Kumar, MD; Suzanne Lentzsch, MD, PhD; Sagar Lonial, MD; Kevin L. Obholz, PhD; Terrence Fagan; Timothy A. Quill, PhD; and Kenneth Anderson, MD

Background

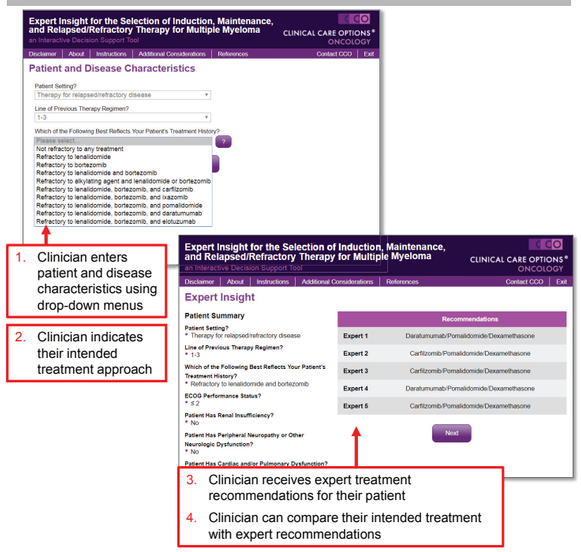
Availability of novel agents for treating MM has transformed management strategies, particularly for relapsed/refractory (R/R) disease. Since 2013, experienced MM physicians from leading academic institutions and cancer centers (experts) have annually updated an online tool designed to provide HCPs with treatment recommendations for specific patient cases. Previous reports from our tool analyses have shown yearly changes in treatment patterns among experts but a multiyear delay among HCPs in the adoption of many expert-recommended treatment strategies into their practice.

Methods

- For 2015, expert recommendations compiled in March 2015
- For 2016, expert recommendations compiled in June 2016
- For 2017, expert recommendations compiled in March 2017
- Tool scenarios based on variables including: eligibility for ASCT, ECOG PS, cytogenetic risk, presence of renal insufficiency, peripheral neuropathy, or cardiopulmonary dysfunction, as well as responsiveness to previous treatment for those with R/R MM

- Tool online at **clinicaloptions.com/MyelomaTool**

MM Tool Screenshots (Examples)

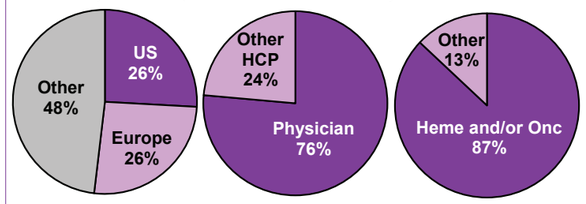


1. Clinician enters patient and disease characteristics using drop-down menus
2. Clinician indicates their intended treatment approach
3. Clinician receives expert treatment recommendations for their patient
4. Clinician can compare their intended treatment with expert recommendations

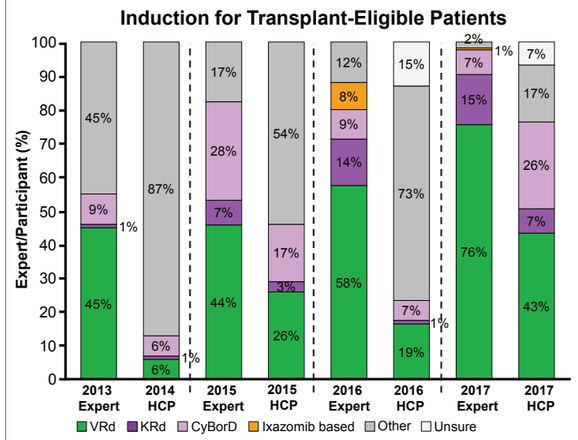
Results

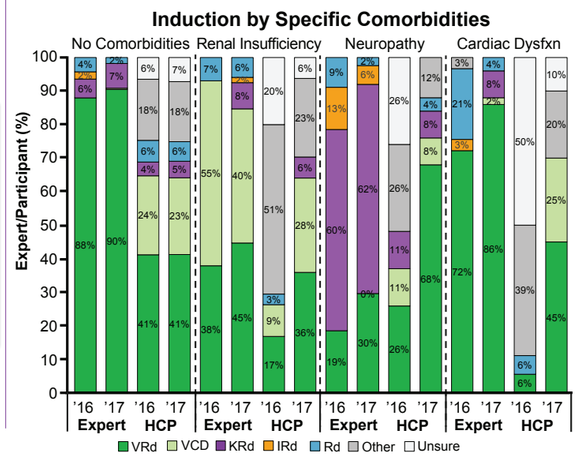
2017 Tool Participant Demographics

- Analyzed 746 patient cases entered by 413 HCPs

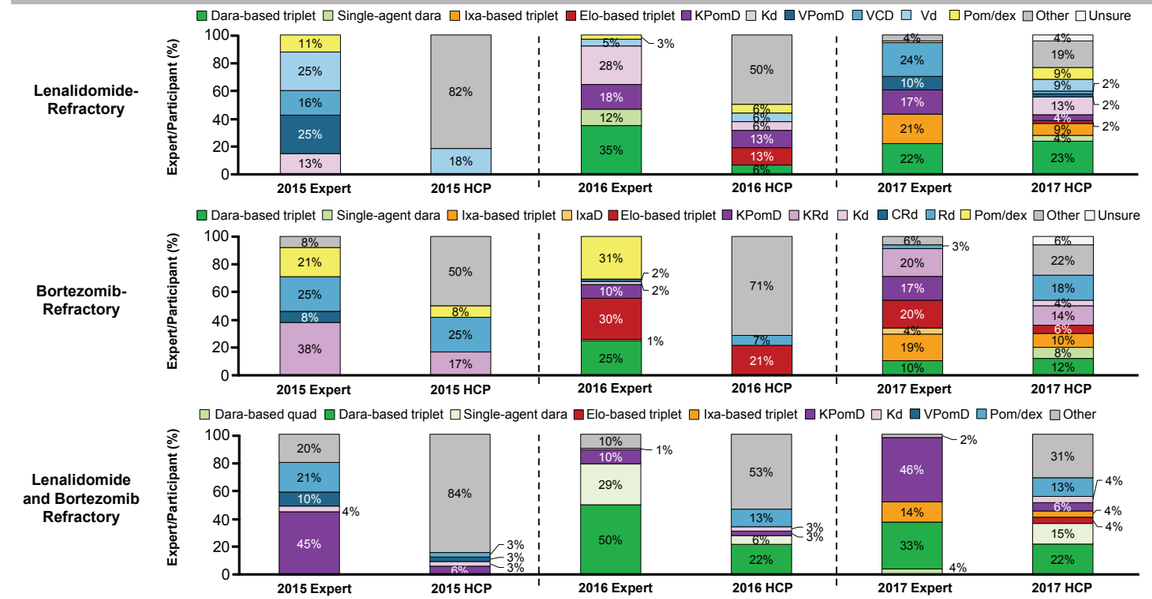


Induction Therapy (N = 401)





Treatment Options for Relapsed/Refractory Disease (N = 280)



- Optional survey on intended use and tool impact shown after experts' recommendations answered for 186 of 746 cases (25%)

Intended Use of Tool (n = 186)	Cases, %
Hypothetical patient case (educational resource)	47
Actual patient case (virtual consultation)	53

Self-Identified Clinical Impact Among Those Differing From Expert Consensus (n = 100)	Cases, %
Changed treatment plan to match experts	38
Confirmed treatment plan	17
There are barriers for implementing expert recommendations	37

Conclusions

- The majority of HCPs using this tool indicated that the expert recommendations confirmed or changed their treatment choice in the absence of barriers (eg, access to new therapies)
- For induction treatment, overall intended treatment choice of online HCPs differed from experts for the majority of entered cases although the use of VRd is increasing for both experts and HCP
  - Consensus among experts has increased incrementally from 2013 to 2017, with triplet VRd being recommended for 76% of cases overall in 2017 vs 45% in 2013; however, varying comorbidities altered expert recommendation
  - By comparison, HCPs intended to use VRd for 43% of ASCT-eligible patient cases overall in 2017 vs 6% in 2013 but did not select expert recommended treatment for the majority of patient cases with comorbidities
- For R/R MM, use of recently approved therapies dramatically changed treatment recommendations of the experts in 2016/2017 but the broad range of available regimens are reflected in lack of a consensus in treatment choice by both experts and HCPs
  - Use of novel triplet therapy including either carfilzomib, ixazomib, daratumumab, or elotuzumab increased from 2015 to 2017, with experts recommending triplet therapy for > 90% of cases in 2017 vs ~40% in 2015, while HCPs selected triplet therapy in ~40% of cases in 2017 vs ~10% in 2015

Acknowledgments and Disclosures
This tool was included in a CME-certified program supported by educational grants from Amgen; Celgene; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Takeda Oncology. **Terrence Fagan; Carol Ann Huff, MD; Kevin L. Obholz, PhD; Timothy A. Quill, PhD;** and **Kristen M. Rosenthal, PhD,** have no real or apparent conflicts of interest to report. **Kenneth Anderson, MD,** has disclosed that he has received funds for research support from MedImmune, has served on the board of directors or as an advisor for Bristol-Myers Squibb, Gilead Sciences, and Millennium; and is the scientific founder of OncoPep and C4 Therapeutics. **Shaji Kumar, MD,** has disclosed that he has received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck, Millennium, Noxxon, Onyx, Oncopeptides, Skyline Diagnostics, and Takeda and funds for research support from AbbVie, Amgen, Celgene, Genentech, Janssen, Merck, Millennium/Takeda, Novartis, Oncopeptides, Onyx, Roche, sanofi-aventis, and Skyline Diagnostics. Suzanne **Lentzsch, MD, PhD,** has disclosed that she has received consulting fees from Amgen and Bristol-Myers Squibb and holds stock in Caelum Biosciences. **Sagar Lonial, MD,** has disclosed that he has received consulting fees and funds for research support from Bristol-Myers Squibb, Celgene, Janssen, Millennium, Novartis, and Onyx.

Variability of Current Global Practice Patterns in the Management of Metastatic Colorectal Cancer

Tanios Bekaii-Saab, MD[1], FACP; Krista Marcello[2]; George A. Fisher, MD, PhD[3]; Scott Kopetz, MD, PhD, FACP[4]; John H. Strickler, MD[5]; Alan P. Venook, MD[6]; and Kevin L. Obholz, PhD[2]

1. Mayo Clinic Arizona; 2. Clinical Care Options, LLC; 3. Stanford University School of Medicine; 4. University of Texas M. D. Anderson Cancer Center; 5. Duke University; 6. University of California, San Francisco

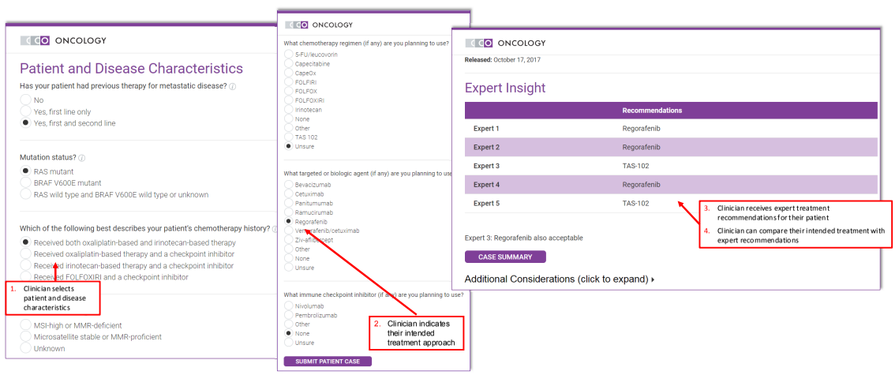
Background

Therapeutic options for metastatic colorectal cancer (mCRC) have changed dramatically in recent years, greatly increasing the complexity of therapeutic decision making. Treatment guidelines may limit flexibility to individualize patient care. The aim of this analysis was to assess "real-world" global practice patterns for mCRC and then compare them with recommendations from US experts based on patient cases entered by healthcare providers (HCPs) into an online decision support tool designed to provide specific, patient-individualized expert recommendations.

Methods

- A panel of 5 experts provided treatment recommendations for unique case scenarios across first-, second-, and third-line settings for mCRC
  - Expert recommendations were compiled in August 2017
- Individual tool scenarios were defined by key patient and disease characteristics including
  - RAS and BRAF V600E mutation status
  - Microsatellite instability (MSI)
  - Location of primary tumor (left, right/transverse)
  - Previous chemotherapy and biologic or targeted therapy exposure
  - To use the tool, clinicians entered their patient and disease factors and were surveyed about their intended treatment plan for that case. The expert treatment recommendations for that specific case were then provided to the clinician
- Tool online at **clinicaloptions.com/CRCTool**

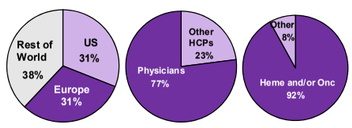
CRC Tool Screenshots (Examples)



Results

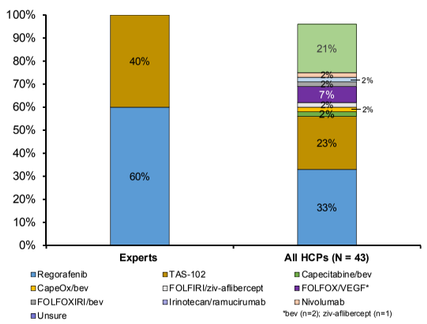
Tool Participant Demographics

- Analyzed 870 patient cases entered by 553 HCPs between October 17, 2017, and June 9, 2018.



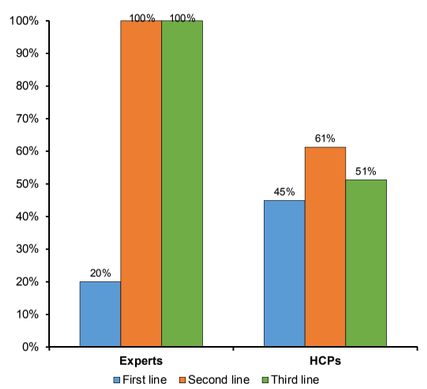
Impact of RAS Mutation on Third-line Therapy Selections

Third-line Therapy Selections in RAS MT mCRC, MSS, Previously Treated With Irinotecan, Oxaliplatin, and VEGF inhibitor, no EGFR



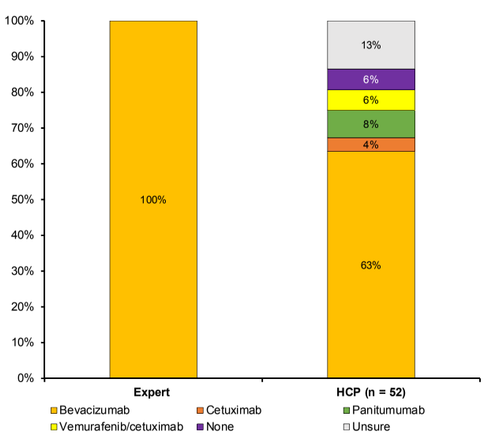
Impact of MSI-H status on Therapy Selections

Proportion of Clinicians Using Immune Checkpoint Inhibitors for MSI-H mCRC by Line of Therapy

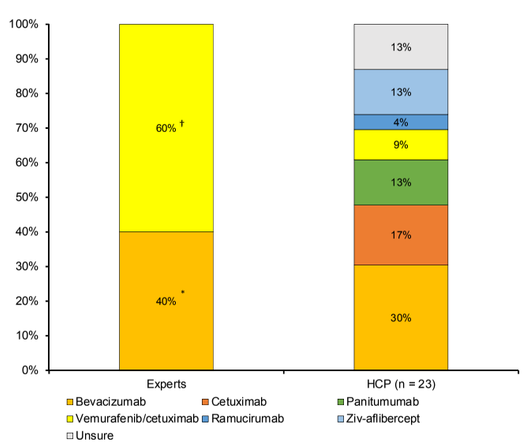


Impact of BRAF V600E Mutation on Therapy Selections

First-line Biologic Agent Selections in BRAF V600E–Mutant mCRC



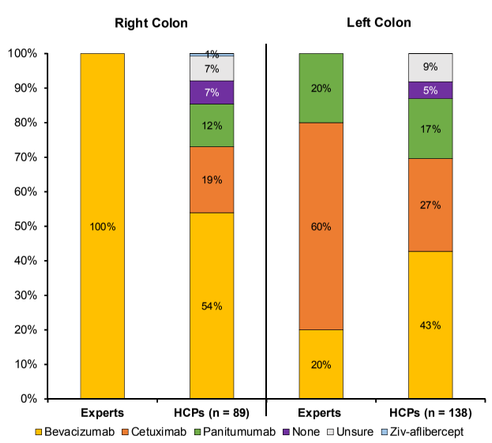
Second-line Biologic Agent Selections in BRAF V600E-Mutant mCRC



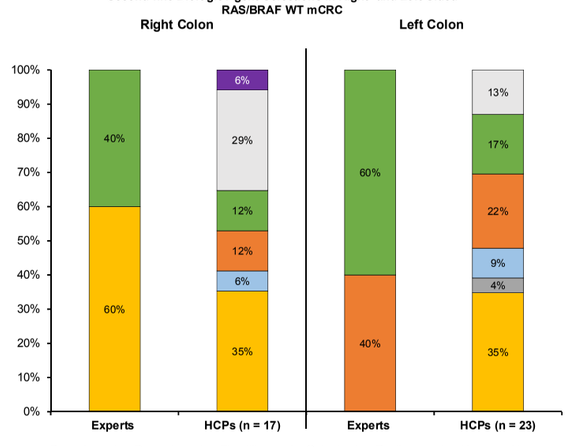
*Expert 1 would use regorafenib if patient received FOLFOXIRI in first line.
†Expert 5 would use CAPEOX + bevacizumab if patient had not yet been exposed to oxaliplatin in first line.

Impact of Sidedness on Therapy Selections

First-line Biologic Agent Selections in Right- and Left-Sided RAS/BRAF WT



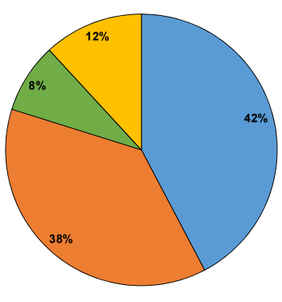
Second-line Biologic Agent Selections in Right- and Left-Sided RAS/BRAF WT mCRC



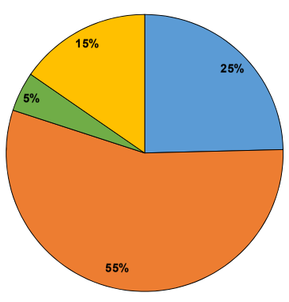
Impact of Decision Tool on Practice

- Optional survey on intended use and tool impact shown after experts' recommendations answered for 253 of 870 cases (29%)

Impact of Tool for Cases With Planned Treatment Differing From Expert Consensus, All Cases (n = 253)



Impact of Tool for Cases With Planned Treatment Differing From Expert Consensus, MSI-H Cases Only (n = 65)



Intended Use of Tool (n = 253)	Cases, %
Hypothetical patient case (educational resource)	64
Actual patient case (virtual consultation)	36

Conclusions

- Practice patterns were heterogeneous in several CRC subtypes and settings, including the impact of sidedness, BRAF V600E mutation, and MSI-H status
- Planned treatment of HCPs differed from the expert treatment consensus for several defined CRC subtypes*
  - VEGF inhibitor in the first line for right-sided RAS/BRAF WT mCRC (55% vs 100%)
  - EGFR inhibitor in left-sided RAS/BRAF WT mCRC in a patient who received VEGF in the first line (39% vs 100%)
  - VEGF inhibitor in the first line for patients with BRAF V600E–mutant mCRC (63% vs 100%)
  - Regorafenib or TAS-102 in the third-line setting for RAS-mutant MSS CRC previously treated with irinotecan, oxaliplatin, and a VEGF inhibitor (56% vs 100%)
  - Immune checkpoint inhibitors for MSI-H mCRC in second or third lines of therapy
- The majority of HCPs using this tool indicated that the expert recommendations confirmed or changed their treatment choice in the absence of barriers
  - In an even greater proportion of MSI-H cases, the expert recommendations in the tool changed HCP treatment choice (55% vs 38%, respectively)
- Practicing clinicians can benefit from an online tool with expert guidance to help navigate the rapidly changing therapeutic landscape of mCRC

*It should be noted that the expert recommendations were their most common treatment choices for each scenario, and that other factors may alter that choice and reflect a distribution similar to that of the HCPs polled in the tool.

Acknowledgments and Disclosures
This tool was included in a CME-certified program supported by educational grants from Bayer Oncology, Genentech, Lilly, and Taiho Oncology Inc. **Krista Marcello** and **Kevin L. Obholz, PhD,** have no real or apparent conflicts of interest to report. **Tanios Bekaii-Saab, MD, FACP,** has disclosed that he has received consulting fees from Amgen, Coherus, and Glenmark. **George A. Fisher, MD, PhD,** has disclosed that he has received consulting fees from Genentech, Ipsen, and Merck; funds for research support from Epicentrix, Ipsen, Merck, and XBiotech; and has ownership interest in Seattle Genetics. **Scott Kopetz, MD, PhD, FACP,** has disclosed that he has received consulting fees from Amgen, Array, Bayer, Genentech, MolecularMatch, and Taiho. **John Strickler, MD,** has disclosed that he has received consulting fees from Amgen, Celgene, and Genentech/Roche and funds for research support from OncoMed. **Alan P. Venook, MD,** has disclosed that he has received consulting fees from Genentech/Roche and funds for research support from Bristol-Myers Squibb, Genentech/Roche, and Lilly.

Variance Between Experts and Oncology Healthcare Providers in Managing Polycythemia Vera and Myelofibrosis: Analysis of an Online Treatment Decision Support Tool

Ryan P. Topping, PhD[1]; Michael W. Deininger, MD, PhD[2]; John Mascarenhas, MD[3]; Ruben A. Mesa, MD[4]; Brady L. Stein, MD, MHS[5]; Kevin L. Obholz, PhD[1]; Jason J. Everly, PharmD[1]; Srdan Verstovsek, MD, PhD[6]

1. Clinical Care Options, Reston, Virginia. 2 University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah. 3. Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York. 4. Mayo Clinic, Phoenix, Arizona.
5. Northwestern University Feinberg School of Medicine, Chicago, Illinois. 6. The University of Texas MD Anderson Cancer Center, Houston, Texas.

Background

The management of patients with Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs) polycythemia vera (PV) and myelofibrosis (MF) is evolving. US treatment guidelines for PV and MF were only recently published, and many clinicians still face substantial challenges in selecting therapy for patients with these MPNs. To assist with patient care and to help healthcare providers (HCPs) make informed decisions, an online treatment decision support tool for PV and MF was developed.

In this study, cases entered into the tool by HCPs were analyzed to determine:

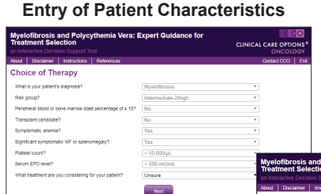
- Variance between the planned treatment of HCPs using the tool and recommendations from MPN experts
- Impact of the tool on the subsequent treatment decisions of those who used it

Tool Design and Planned Analysis

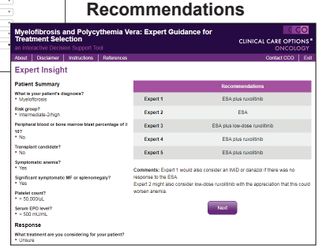
- The online decision support tool was developed by 5 MPN experts and included unique case variations based on factors experts considered important for treatment selection for patients with PV or MF, including the presence of disease symptoms, hematologic laboratory findings, and treatment history
  - Experts: Michael W. Deininger, MD, PhD; John Mascarenhas, MD; Ruben A. Mesa, MD; Brady L. Stein, MD, MHS; Srdan Verstovsek, MD, PhD
- Expert recommendations were compiled in February 2017
- In using the tool, HCPs were prompted to enter patient/disease information from pull-down menus and then indicate their intended clinical approach; recommendations from the 5 experts were then displayed
- HCPs were asked whether the expert recommendations confirmed or changed their intended clinical approach
- **Tool available online at: clinicaloptions.com/MPNTool**

Tool Screenshot Examples

Entry of Patient Characteristics



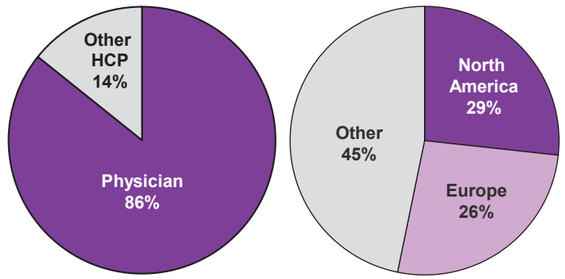
Expert Recommendations



Results

Tool Participant Demographics

- Analyzed 421 patient cases entered by 301 HCPs



Characteristics of Cases Entered by HCPs

Case Characteristic	Cases, n/N (%)
Diagnosis	
▪ PV	200/421 (48)
▪ MF	221/421 (52)
PV cases	
▪ Intolerance or inadequate response to HU	98/184 (53)
▪ No intolerance or inadequate response to HU	86/184 (47)
• Low risk (< 60 years of age, no prior thrombotic event)	41/81 (51)
• High risk (≥ 60 years of age and/or prior thrombotic event)	40/81 (49)
MF cases	
▪ Low/intermediate-1 risk	95/207 (46)
▪ Intermediate-2/high risk	112/207 (54)

Evaluable responses for each characteristic shown.

Use of the Tool and Impact on Treatment Plan

Intended Use of Tool (n = 85)	Cases, %
Specific patient in my clinical practice	**44**
Hypothetical patient case	56

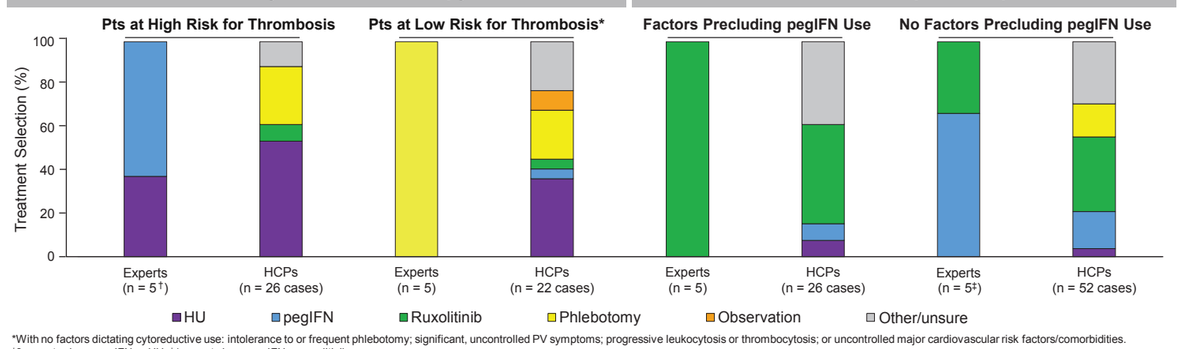
Impact of Tool on Practice (n = 85)	Cases, %
Changed management plans	**41**
Confirmed management plans	**41**
Barriers to implementing recommendations	9
Undecided	8

Intended use and tool impact questions were optional and available after users received expert recommendations.

Polycythemia Vera

First-line Cytoreductive Therapy

Prior Intolerance/Inadequate Response to HU

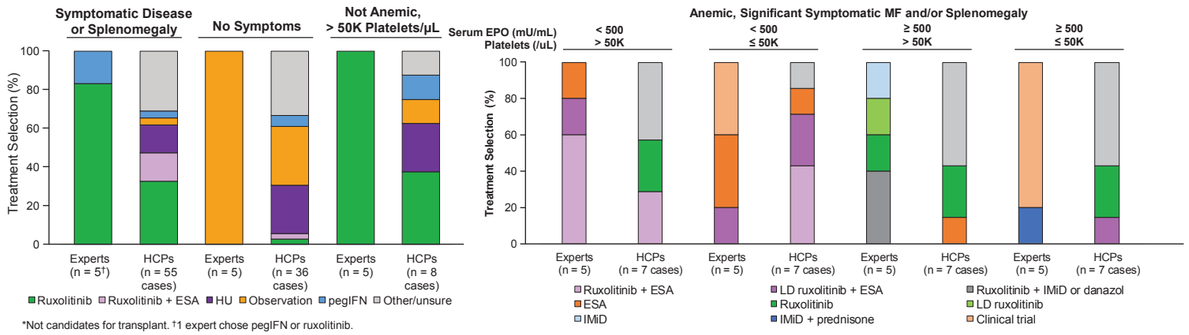


*With no factors dictating cytoreductive use: intolerance to or frequent phlebotomy; significant, uncontrolled PV symptoms; progressive leukocytosis or thrombocytosis; or uncontrolled major cardiovascular risk factors/comorbidities.
†3 experts chose pegIFN or HU. ‡1 expert chose pegIFN or ruxolitinib.

Myelofibrosis

Low/Intermediate-1 Risk

Intermediate-2/High Risk*



*Not candidates for transplant. †1 expert chose pegIFN or ruxolitinib.

Conclusions

- Analysis of an online treatment decision support tool for PV and MF revealed significant variance between expert recommendations and intended treatment of HCPs
- For patients with PV:
  - Experts are more likely to consider pegIFN for first-line treatment of patients at high risk for thrombosis
  - Compared with expert recommendations, many HCPs would overtreat patients at low risk for thrombosis and underuse ruxolitinib and pegIFN for patients with prior intolerance/inadequate response to HU
- For patients with MF:
  - Compared with expert recommendations, many HCPs would overtreat asymptomatic low/intermediate-1–risk patients
  - Experts are more likely to recommend ruxolitinib for many higher-risk patients vs HCPs
- Use of the tool had a positive impact on practice
  - Expert recommendations changed the original management plans or confirmed the planned treatment approach for 82% of HCPs
- Online tools that provide customized, patient-specific expert advice can increase the number of clinicians who make optimal treatment decisions for patients with PV and MF

Acknowledgments and Disclosures

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Analysis of Healthcare Provider Management of Immune-Related Adverse Events and Concordance With NCCN Guidelines®

Megan Cartwright, PhD[1]; Krista Marcello[1]; Jillian L. Scavone, PhD[2]; Kevin Obholz, PhD[1]; Timothy Quill, PhD[1]; **John A. Thompson, MD[3]**

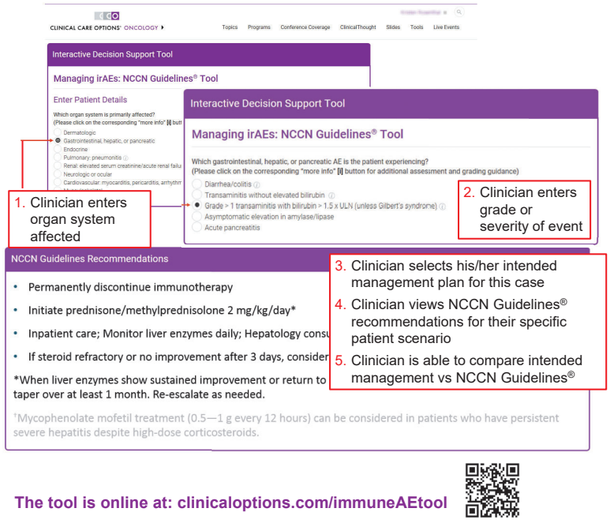
1. Clinical Care Options, LLC; 2. National Comprehensive Cancer Network® (NCCN®), Plymouth Meeting, USA; 3. Department of Medicine, University of Washington, Seattle, WA, USA.

SITC 2019 Gaylord National Hotel & Convention Center Nov. 6-10 NATIONAL HARBOR, MARYLAND

Background

- Immune checkpoint inhibitors (ICIs) have dramatically altered the therapeutic landscape across oncology. However, they are associated with a unique safety profile involving immune-related adverse events (irAEs) that require prompt recognition and management to ensure optimal patient safety.
- In 2017, we developed an online Interactive Decision Support Tool to provide healthcare providers (HCPs) case-specific, evidence-based guidance on management of irAEs. We reported substantial variances in HCP practice vs expert recommendations.[1]
- The National Comprehensive Cancer Network® (NCCN) publishes guidelines for managing irAEs in patients treated with ICIs across all organ systems.[2] In partnership with the NCCN, a new online tool was developed in 2019 providing case-specific recommendations from NCCN Guidelines® on irAE management.
- Here, we report a comparison of HCP-reported planned irAE management strategies of HCPs vs the corresponding management recommendations from the NCCN Guidelines®.

Methods



The tool is online at: clinicaloptions.com/immuneAEtool

Results

Demographics and Cases Entered by Organ System

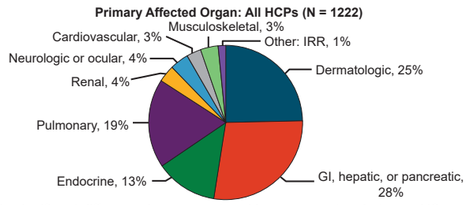
- 794 HCPs entered 1222 different patient cases between February 2019 and September 2019

Type of HCP: All HCPs (N = 794)

Annual No. of Patients Treated With ICIs: All HCPs (N = 152)

Intended Use of Tool (n = 235 cases)	Cases, %
Hypothetical patient case (educational resource)	54
Actual patient case (virtual consultation)	46

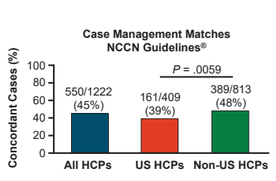
Primary Affected Organ: All HCPs (N = 1222)

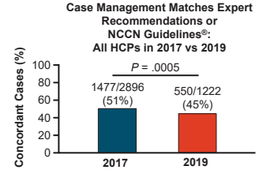


- No significant difference in cases entered by organ system between US vs non-US HCPs (P = .332)

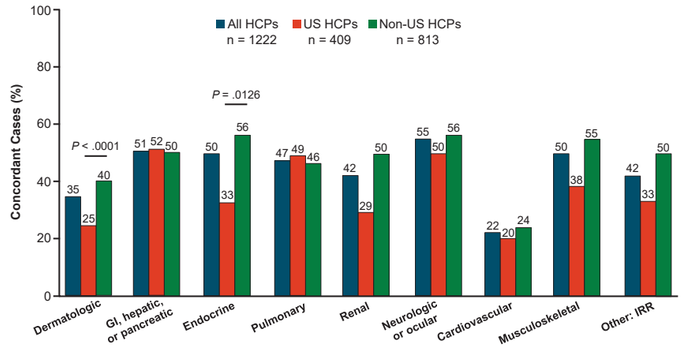
Planned Management of HCPs Compared With NCCN Guidelines® and Expert Recommendations

- Fewer cases in the US managed according to NCCN Guidelines® recommendations vs those outside the US (39% vs 48%, respectively; P = .0059)
- No improvement in cases managed concordant with NCCN/expert recommendations in 2019[3] vs 2017[1] versions of online tool





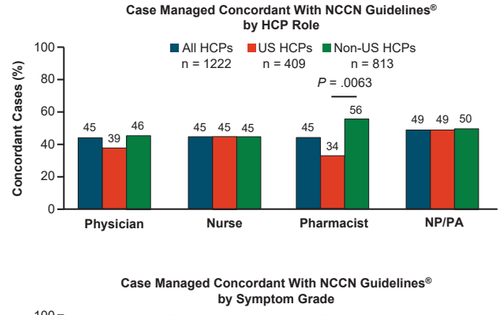
Patient Management Consistent With NCCN Guidelines® by Organ

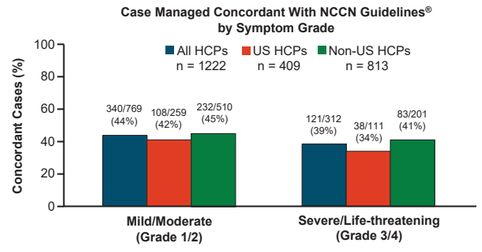


- Overall cardiovascular and dermatologic system symptoms managed according to NCCN Guidelines® (22% and 35% concordance, respectively)
- Significantly more HCPs outside the US managed dermatologic and endocrine system symptoms according to NCCN Guidelines® vs US HCPs (P < .0001 and P = .0126, respectively)

Self-Identified Impact on Practice (n = 257 cases)	Cases, %
Changed management plan to match NCCN Guidelines®	44
Confirmed management plan	50

Patient Management Consistent With NCCN Guidelines® by HCP Role and Symptom Grade





Conclusions

- These data suggest that many HCPs are not managing irAEs consistent with recommendations in the NCCN Guidelines®
  - Only 45% of HCPs planned management of specific irAEs were concordant with NCCN Guidelines® recommendations
  - Self-identified practice plans among HCPs outside of the US more consistent with NCCN Guidelines® vs US HCPs
  - Optimal management of irAEs has not significantly improved from 2017[1] to 2019[3]
  - The irAEs with the poorest concordance to NCCN Guidelines® recommendations were those affecting the dermatologic and cardiovascular systems
- Use of an online tool providing interactive and case-specific navigation of the NCCN Guidelines® recommendations can improve patient care and safety
  - Most HCPs treat < 20 patients/year with ICIs; given the relative rarity of many irAEs, clinicians are not experienced managing them in their practice
  - 44% of HCPs using the tool indicated intent to change practice to be concordant with the NCCN Guidelines® recommendation for their specific case

References:

1. Marcello K, Obholz KL, Quill TA, Weber JS. Variance from evidence-based management of immune-related adverse events among healthcare providers: analysis of an online management decision tool. 32nd Annual Meeting and Pre-Conference Programs of the Society for Immunotherapy of Cancer; November 8-12, 2017; National Harbor, Maryland. Abstract O33.
2. National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. V.1.2019 [http://www.nccn.org]. Accessed October 10, 2019.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Managing Immune Checkpoint Inhibitor–Related Toxicities: An Interactive Decision Support Tool [https://www.clinicaloptions.com/immuneAEtool]. Accessed July 16, 2019.

Evolution in Practice Patterns and Differences Among Experts and Community Healthcare Providers in the Treatment of Patients With Chronic Lymphocytic Leukemia

Bing-E Xu, PhD[1]; Kristen M. Rosenthal, PhD[1]; Krista Marcello[1]; Ryan P. Topping, PhD[1]; Farrukh T. Awan, MD, MS[2]; Steven E. Coutre, MD[3]; Nicole Lamanna, MD[4]; Jeff P. Sharman, MD[5]; Timothy A. Quill, PhD[1]; Kevin L. Obholz, PhD[1]; Andrew D. Zelenetz, MD, PhD[6]

1. Clinical Care Options. 2. Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center. 3. Stanford Cancer Center, Stanford University School of Medicine. 4. Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center. 5. Willamette Valley Cancer Institute, US Oncology Research. 6. Memorial Sloan Kettering Cancer Center.

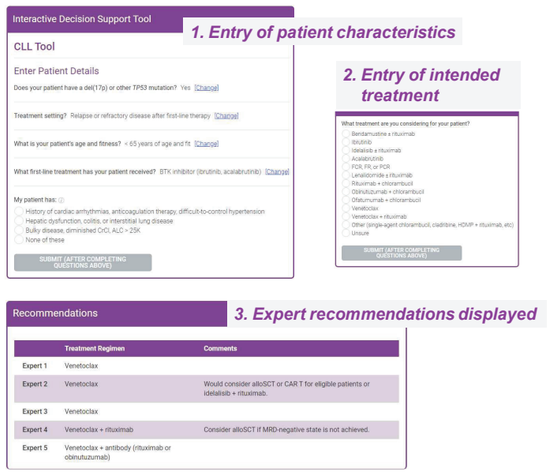
Background

- Targeted therapies are dramatically changing the treatment landscape for chronic lymphocytic leukemia (CLL)
- Given the rapid pace of new approvals and expanded indications for targeted agents in CLL, healthcare providers (HCPs), particularly those practicing in community settings with limited experience in CLL, can be challenged to make treatment decisions that optimize outcomes for their patients
- To assist HCPs in managing patients with CLL, we have developed and regularly updated an online treatment decision support tool in collaboration with CLL experts
- Here, we report an analysis of data from the 2 most recent CLL tool iterations capturing differences in practice patterns among HCPs compared with CLL experts over time and the impact of case-specific expert recommendations on HCP treatment decisions

Tool Design and Analysis

- 5 experts provided treatment recommendations for different case scenarios in the newly diagnosed and relapsed/refractory disease settings for each iteration of the tool:
  - Case scenarios based on factors experts considered important for treatment selection, including age, fitness, cytogenetic abnormalities, *IGHV* mutation status, and previous treatment
  - Expert recommendations compiled in March 2017 (2017 version) and September 2018 (2018 version)
- 2018 expert panel: Farrukh T. Awan, MD, MS; Steven E. Coutre, MD; Nicole Lamanna, MD; Jeff P. Sharman, MD; Andrew D. Zelenetz, MD, PhD
- To use the tool, HCPs enter their patients' information and their intended treatment plan; expert recommendations for their specific patient scenario are then provided
- Current tool available online at **clinicaloptions.com/CLLTool**

Tool Screenshot Examples

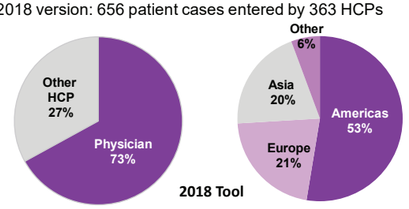


- This analysis compared the intended treatment of HCPs with expert recommendations for specific cases entered in the tool:
  - 2017 version: March to July 2017
  - 2018 version: October 2018 to July 2019

Results

Tool Participant Demographics

- 2017 version: 753 patient cases entered by 406 HCPs
- 2018 version: 656 patient cases entered by 363 HCPs

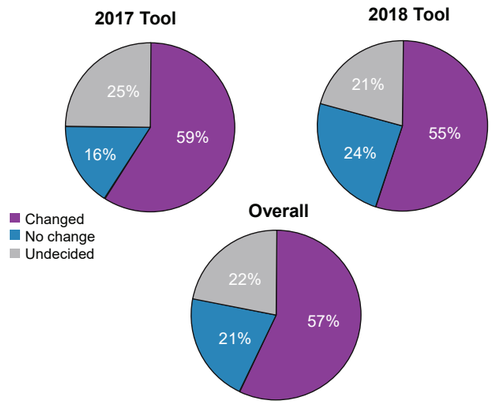


Characteristics of Patient Cases Entered by HCPs

Case Characteristics, n (%)	2017 Tool (n = 753)	2018 Tool (n = 656)
Treatment setting		
▪ Newly diagnosed	478 (63)	443 (68)
▪ Relapsed/refractory	275 (37)	213 (32)
Presence of del(17p) or *TP53* mutation		
▪ Yes	250 (33)	216 (33)
▪ No	468 (62)	440 (67)
▪ Unknown	35 (5)	0 (0)
Presence of *IGHV* mutation*	(n = 315)	(n = 310)
▪ Yes	97 (31)	99 (32)
▪ No	114 (36)	117 (38)
▪ Unknown	104 (33)	94 (30)

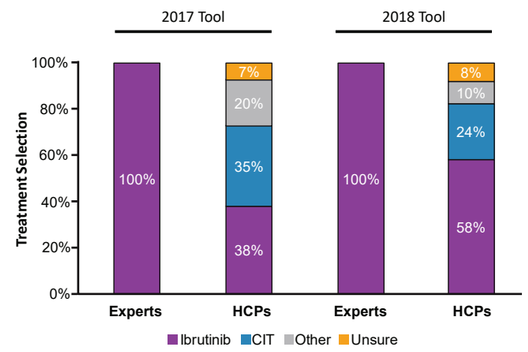
*Only asked for newly diagnosed patients without del(17p) and *TP53* mutation.

Impact of Expert Recommendations on Treatment Plan

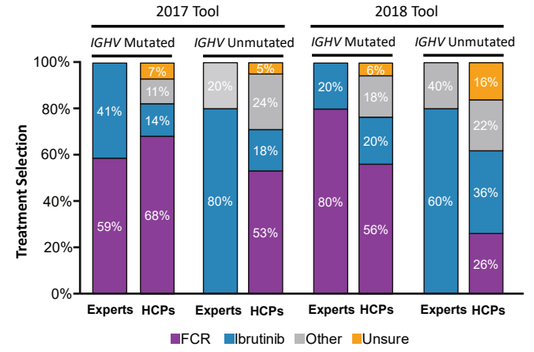


Tool impact questions were optional and available after users received expert recommendations.

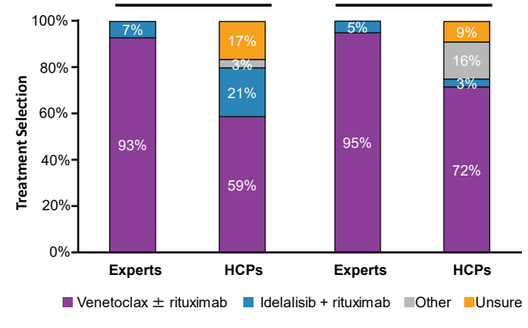
Patients With del(17p) or *TP53* Mutation: First-line Treatment



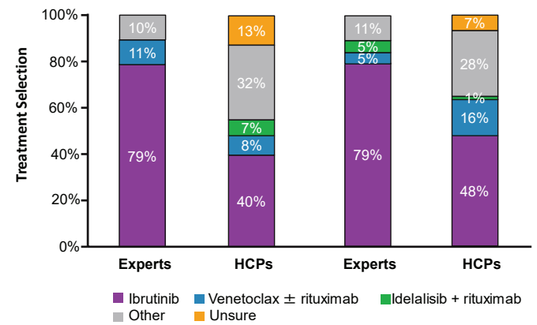
Patients Without del(17p) or *TP53* Mutation: First-line Treatment in Young and Fit Patients



Patients With del(17p) or *TP53* Mutation: Second-Line Treatment After Ibrutinib



Patients Without del(17p) or *TP53* Mutation: Second-line Treatment After Chemoimmunotherapy



Conclusions

- Practice patterns for the management of patients with CLL differ considerably between experts and community HCPs
- Expert recommendations were generally consistent in both the 2017 and 2018 tool iterations, and there was consensus for most cases
- There appears to be an increased alignment in treatment choice by HCPs and expert recommendations from 2017 to 2018
- Among HCPs who used this tool, more than one half indicated that the expert recommendations would change their intended treatment plan, suggesting that this online treatment decision support tool can help optimize the care of patients with CLL by aligning community practice with expert recommendations

Acknowledgments and Disclosures
The CME program that included this tool was supported by unrestricted educational grants from AbbVie, AstraZeneca, Genentech, Janssen, and Pharmacyclics.
Bing-E Xu, PhD; Kristen M. Rosenthal, PhD; Krista Marcello; Ryan P. Topping, PhD; Timothy A. Quill, PhD; and Kevin L. Obholz, PhD, have no relevant financial relationships to disclose. Farrukh T. Awan, MD, MS, has disclosed that he has received consulting fees from AbbVie, AstraZeneca, Genentech, Gilead, Janssen, Pharmacyclics, and Sunesis and funds for research support from Pharmacyclics. Steven E. Coutre, MD, has disclosed that he has received consulting fees from AbbVie, AstraZeneca, Astellas, BeiGene, Celgene, Genentech, Janssen, and Pharmacyclics and funds for research support from AbbVie, Acerta, Celgene, Gilead, and Janssen. Nicole Lamanna, MD, has disclosed that she has received consulting fees from AbbVie, AstraZeneca, BeiGene, Celgene, Genentech, Gilead, Janssen, Juno, and Pharmacyclics and funds for research support from AbbVie, Acerta, AstraZeneca, BeiGene, Genentech, Gilead, Infinity/Verastem, Juno, Ming, Oncternal, and TG Therapeutics. Jeff P. Sharman, MD, has disclosed that he has received consulting fees and funds for research support from AbbVie, Acerta, AstraZeneca, Celgene, Genentech, Gilead, Janssen, Pharmacyclics, Seattle Genetics, and TG Therapeutics. Andrew D. Zelenetz, MD, PhD, has disclosed that he has received consulting fees from Amgen, AstraZeneca, Bayer, BeiGene, Celgene, DAVA Oncology, Genentech/Roche, Gilead, Janssen, Karyopharm, MEI Pharma, MorphoSys, Novartis, Pfizer, Pharmacyclics/AbbVie, and Verastem.

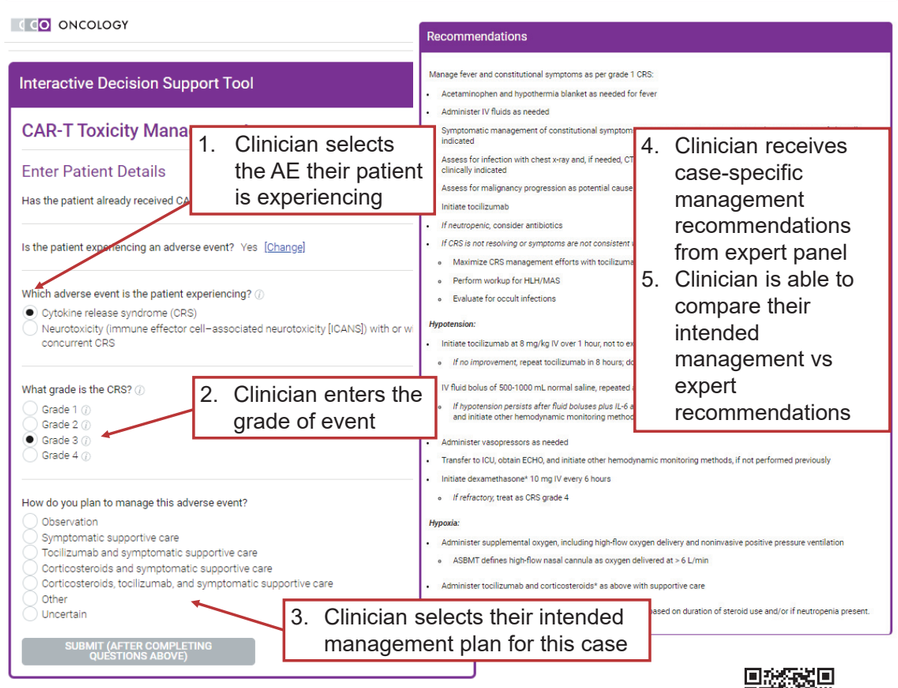
Management of CAR T-Cell Toxicities: Concordance and Divergence Between Healthcare Providers and Expert Consensus Recommendations

Matthew J. Frigault, MD[1]; Megan Cartwright, PhD[2]; Krista Marcello[2]; Timothy Quill, PhD[2]; Daniel J. DeAngelo, MD, PhD[3]; Ilene A. Galinsky, NP[3]; Shilpa Paul, PharmD, BCOP[4]; Jae H. Park, MD[5]
1. Massachusetts General Hospital; 2. Clinical Care Options, LLC; 3. Dana-Farber Cancer Institute; 4. MD Anderson Cancer Center; 5. Memorial Sloan Kettering Cancer Center.

Background

- Chimeric antigen receptor (CAR) T-cell therapy has been a major innovative breakthrough for hematologic malignancies with 2 currently FDA approved CAR T-cell products (tisagenlecleucel[1] and axicabtagene ciloleucel[2]) and several others in different stages of clinical investigation
- CAR T-cell therapies are associated with unique safety profiles and potentially serious toxicities, including
  - Cytokine-release syndrome (CRS)
  - Immune effector cell–associated neurotoxicity (ICANS)
- These adverse events (AEs) require vigilant monitoring and prompt recognition and management to ensure patient safety and optimal therapeutic benefit
- We developed an online Interactive Decision Support Tool to give healthcare providers (HCPs) case-specific, evidence-based consensus guidance from a panel of 5 interdisciplinary experts on the management of AEs due to CAR T-cell therapy
- Here, we report a comparison of planned CAR T-cell toxicity management among HCPs using the tool vs the expert consensus recommendations in the tool

Methods



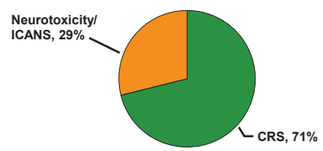
The tool is online at: clinicaloptions.com/carttool

Results

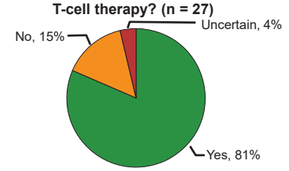
Demographics and Cases Entered

- N = 231 cases entered by HCPs over 132 days (5/9/19 - 9/18/19)
  - Most cases entered were for a patient who is planned to receive CAR T-cell therapy (n = 124; 53.7%)
  - Of remaining 107 cases where patient had already received CAR T-cell therapy, most concerned a patient experiencing an AE (n = 90; 84.1%)
- 50% of HCPs using the tool were physicians, 22% pharmacists, and 20% nurses
  - No significant difference in the type of HCP submitting a case for patient experiencing an AE vs submitting a case where CAR T-cell therapy was planned or patient not experiencing an AE (P = .1527)

Which adverse event is the patient experiencing? (n = 90)

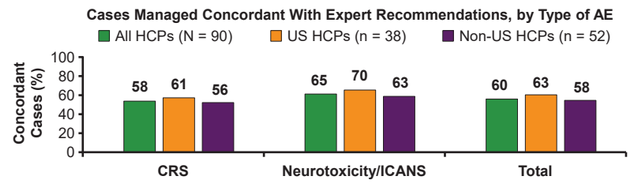


Do you practice at a treatment centerauthorized to administer CAR T-cell therapy? (n = 27)

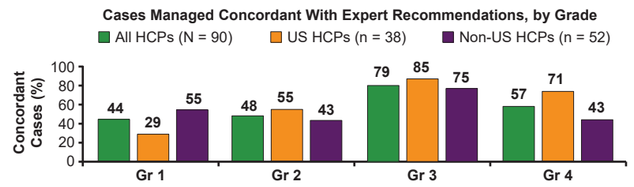


Concordance of HCP Toxicity Management With Expert Recommendations

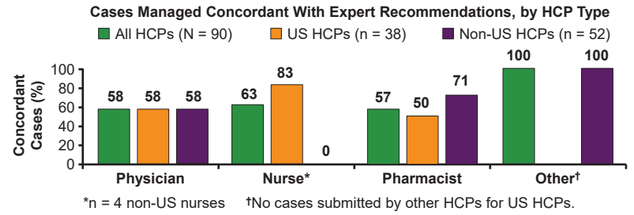
- Of 90 cases experiencing an AE entered into the tool by HCPs, 60% were managed concordant with expert recommendations (n = 54)
- No significant difference in concordance rates of US vs non-US HCPs for CRS (Chi-square P = .8625), ICANS (P = 1), or total cases (P = .7642)



- Significant difference in concordance rates by grade (P = .0417)



- Concordance rates differed significantly between HCP types for non-US HCPs (P = .0421)

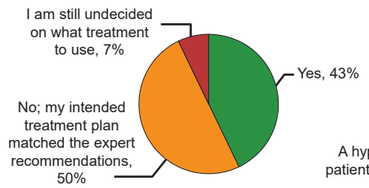


*n = 4 non-US nurses †No cases submitted by other HCPs for US HCPs.

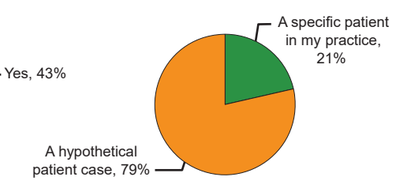
Impact of the Tool on Clinical Practice

- Of the 28 HCPs who answered the optional impact survey questions, 26 (93%) indicated that the tool recommendations either changed or confirmed their management plan
  - 21% reported that they were using the tool to manage a specific patient in their practice (no significant difference in answers for US vs non-US HCPs; Mann-Whitney U test P = .0767)

Did the expert recommendations change your treatment choice? (n = 28)



I used this tool to get recommendations on: (n = 28)



Conclusions

- These data suggest that many HCPs are not optimally managing AEs associated with CAR T-cell therapy administration
  - Only 60% of HCPs' planned management of specific AEs was concordant with expert recommendations provided in the tool
  - Self-identified practice plans among US and non-US HCPs were similar in concordance with expert recommendations
  - The highest concordance with expert recommendations occurred with grade 3 AEs and the least concordance occurred with grade 1 AEs
- Use of an online tool providing interactive, case-specific, evidence-based consensus recommendations can improve patient care and safety
  - 43% of HCPs using the tool indicated intent to change practice as a result of the expert recommendations provided for their specific case

References:
1. Tisagenlecleucel package insert. 2. Axicabtagene ciloleucel package insert

Treatment Trends and Variance Among Experts and Community Practitioners in Advanced Melanoma

Ryan P. Topping, PhD[1]; Michael B. Atkins, MD[2]; Adil Daud, MD[3]; Kim Margolin, MD[4]; Hussein Tawbi, MD, PhD[5]; Kevin L. Obholz, PhD[1]; Timothy A. Quill, PhD[1]; Michael Postow, MD[6]

1. Clinical Care Options, Reston, Virginia. 2. Lombardi Comprehensive Cancer Center, Georgetown University. 3. University of California, San Francisco. 4. City of Hope National Medical Center. 5. The University of Texas MD Anderson Cancer Center. 6. Memorial Sloan Kettering Cancer Center.

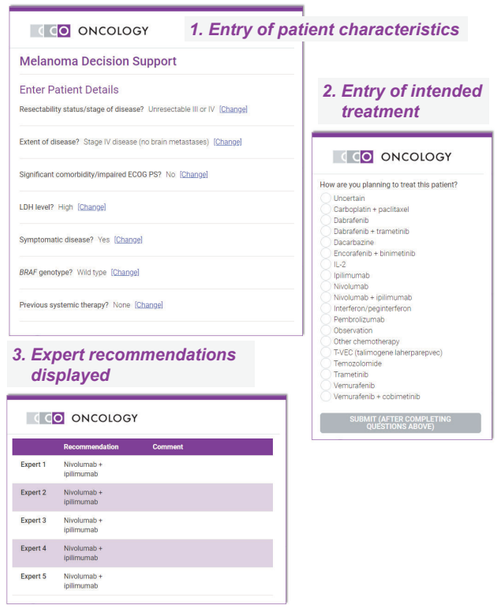
Background

- Best practices in the use of immune checkpoint inhibitors (ICIs) and targeted therapy in advanced melanoma continue to evolve. To assist with patient care and to help healthcare providers (HCPs) make informed decisions, we developed an online treatment decision support tool designed to provide community HCPs with case-specific treatment recommendations from 5 melanoma experts.
- In this study, cases entered into the tool by HCPs were analyzed to determine:
  - Variance between the planned treatment of HCPs and recommendations from melanoma experts
  - Impact of the tool on the subsequent treatment decisions of those who used it

Tool Design and Analysis

- 5 experts provided treatment recommendations in December 2018/January 2019 for 566 unique melanoma case scenarios based on key patient/disease factors defined by those experts
  - Experts: Michael B. Atkins, MD; Adil Daud, MD; Kim Margolin, MD; Michael Postow, MD; Hussein Tawbi, MD
- To use the tool, HCPs enter their patients' information and their intended treatment plan; expert recommendations for their specific patient scenario are then provided
- Tool available online at **clinicaloptions.com/MelanomaTool**

Tool Screenshot Examples

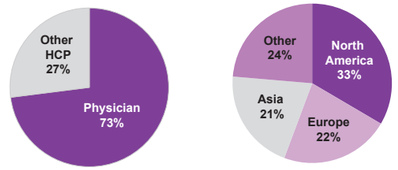


- This analysis compared the intended treatment of HCPs with expert recommendations for specific cases entered in the tool from February 5, 2019, through November 5, 2019
- A secondary analysis compared 2019 treatment patterns with those observed in a 2016 version of this online tool (Quill TA, et al. Pigment Cell Melanoma Res. 2017;30:134.)

Results

Tool Participant Demographics

- 571 patient cases entered by 305 HCPs

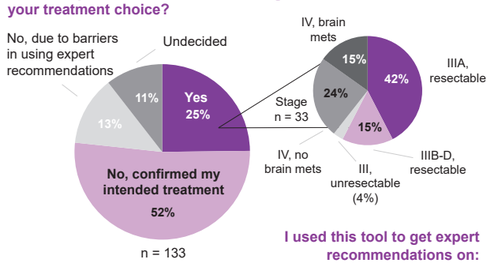


Characteristics of Patient Cases Entered by HCPs

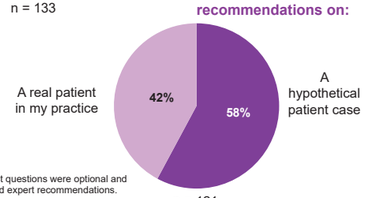
Case Characteristic	n (%)
Treatment setting	
▪ Adjuvant therapy for resectable disease	286 (50)
▪ Treatment for unresectable disease	285 (50)
Adjuvant setting	286
BRAF mutation status	
▪ Wild type	141 (49)
▪ V600 mutant	145 (51)
Significant comorbidity/ECOG PS ≥ 2	
▪ Yes	38 (13)
▪ No	248 (87)
Unresectable setting	285
Disease stage	
▪ Stage III	29 (10)
▪ Stage IV, no brain metastases	157 (55)
▪ Stage IV, brain metastases	99 (35)
Previous systemic therapy	
▪ None	203 (71)
▪ First line	82 (29)
BRAF mutation status	
▪ Wild type	150 (53)
▪ V600 mutant	135 (47)
Significant comorbidity/ECOG PS ≥ 2	
▪ Yes	57 (20)
▪ No	228 (80)

Use of the Tool and Impact on Treatment Plan

Did the expert recommendations change your treatment choice?



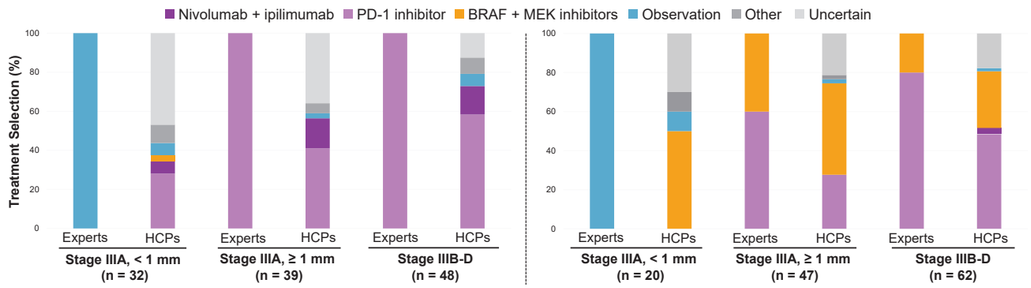
I used this tool to get expert recommendations on:



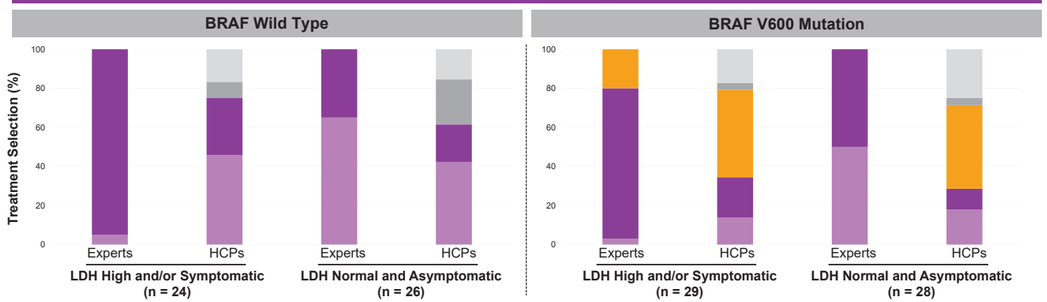
Intended use and tool impact questions were optional and available after users received expert recommendations.

Acknowledgments
The CME program that included this tool was supported by unrestricted educational grants from Merck & Co., Inc. and Novartis Pharmaceuticals Corporation.

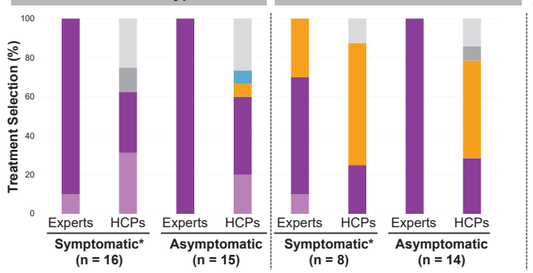
Adjuvant Treatment for Stage III Resectable Disease



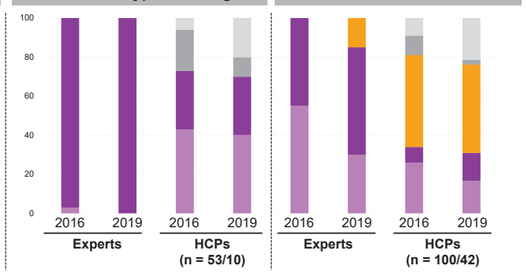
Treatment for Unresectable/Metastatic Disease (Stage III or IV, No Brain Metastases)



Treatment for Stage IV Disease With Brain Metastases



Treatment for Stage IV Disease, 2019 vs 2016



Analyzed case scenarios for which there were no significant comorbidities and ECOG performance status was 0 or 1. *Describes systemic therapy choices when these would be appropriate; per the experts, local radiotherapy would also be a consideration for some scenarios depending on patient and disease characteristics.

Conclusions

- Analysis of data from an online treatment decision support tool for melanoma revealed significant variance between expert recommendations and the intended treatment of HCPs for numerous scenarios
- *Adjuvant therapy*: Evidence of potential overtreatment by HCPs for pts with stage IIIA disease and LN metastases < 1 mm was evident; most HCPs recommended adjuvant therapy in this setting vs observation by experts; experts were more likely to recommend PD-1 inhibitor adjuvant therapy vs HCPs for pts requiring treatment
- *Unresectable disease*: Compared with experts, HCPs were less likely to recommend more aggressive combination ICI therapy for pts with symptomatic disease or those with poorer prognosis; HCPs were more likely to recommend BRAF + MEK inhibitors for all pts with BRAF mutations
  - For pts with brain metastases and BRAF mutations, HCPs were more likely to use BRAF + MEK inhibitors vs experts
- From 2016 to 2019, HCP treatment choices for select pts with metastatic melanoma were similar and consistently differed from expert recommendations, suggesting an ongoing need for education
- Online tools that provide customized, patient-specific expert advice can increase the number of clinicians who make optimal treatment decisions for pts with advanced melanoma

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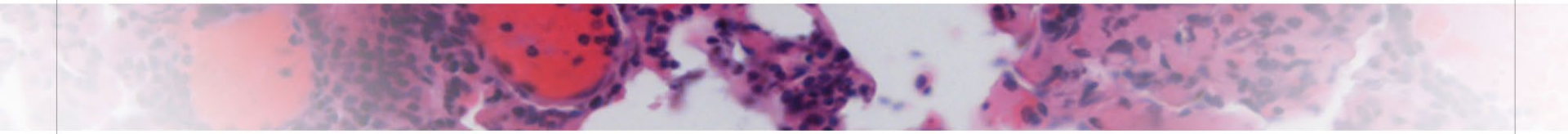


Management of BTK Inhibitor Associated Adverse Events: Current Practice Trends Among Healthcare Providers and Concordance With Expert Recommendations

Kristen Rosenthal, PhD[1]*; Jeremy S Abramson, MD, MMSc[2]; Farrukh T Awan, MD[3]; John P. Leonard, MD[4,5]; Julie M. Vose, MD, MBA[6]; Timothy A Quill, PhD[1]*; and Christopher Flowers, MD[7]

[1]Clinical Care Options, LLC, Reston, VA; [2]Massachusetts General Hospital Cancer Center, Boston, MA; [3]University of Texas Southwestern Medical Center, Dallas, TX; [4]Weill Cornell Medical College, New York, NY; [5]Weill Cornell Medical College, Pelham Manor, NY; [6]University of Nebraska Medical Center Fred & Pamela Buffett Cancer Center, Omaha, NE; [7]The University of Texas MD Anderson Cancer Center, Houston, Texas

Disclosures

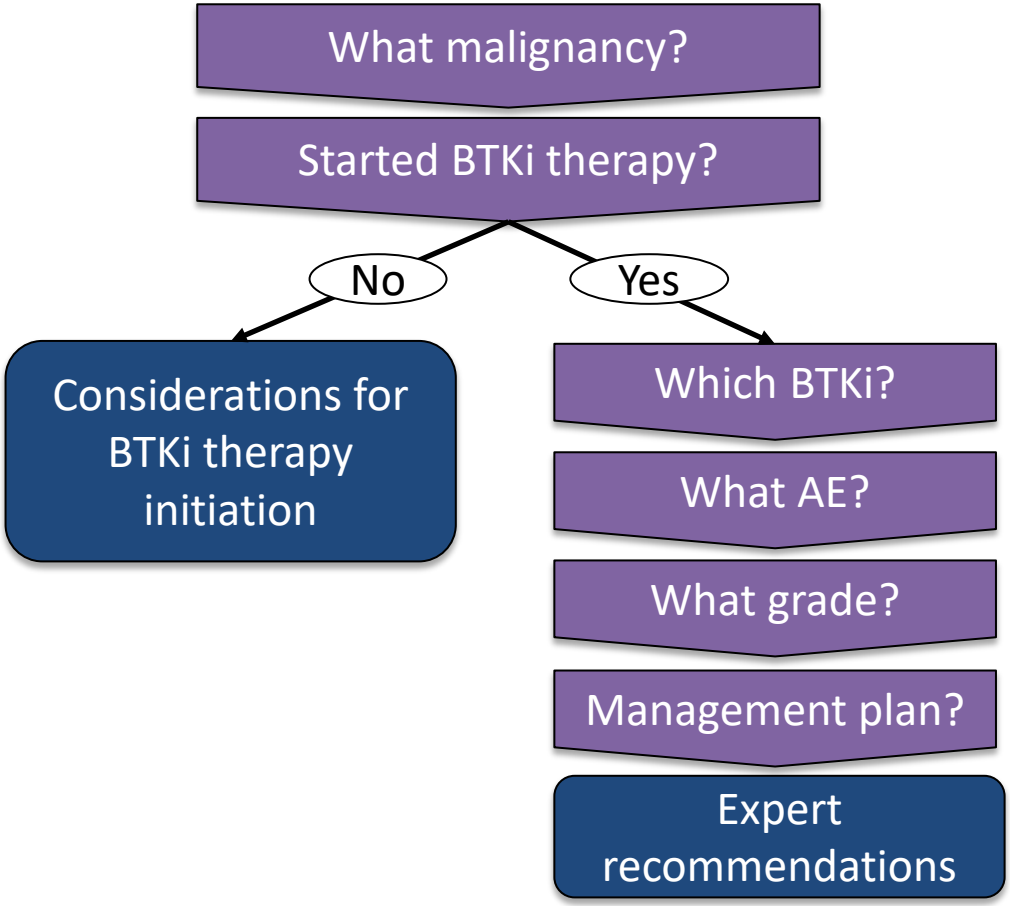
- **Kristen M. Rosenthal, PhD,** has no relevant financial relationships to disclose.
- **Jeremy S. Abramson, MD, MMSc,** has no relevant financial relationships to disclose.
- **Farrukh T. Awan, MD,** has served as consultant for AbbVie, AstraZeneca, Blueprint Medicines, Celgene, Dava Oncology, Genentech, Gilead Sciences, Janssen, Karyopharm, Kite, MEI Pharma, Pharmacyclics, and Sunesis.
- **John P. Leonard, MD,** has served as consultant for ADC Therapeutics, AstraZeneca, Bayer, Bristol-Myers Squibb/Celgene, Epizyme, Genmab, Gilead Sciences/Kite, Karyopharm, MEI Pharma, Miltenyi, Sutro, Regeneron, and Roche/Genentech.
- **Julie M. Vose, MD, MBA,** has served as consultant for AbbVie, AstraZeneca, Karyopharm, Loxo, Roche/Genentech, and Verastem; has received honoraria from AbbVie, Allogene, AstraZeneca, Celgene, Epizyme, Janssen, Karyopharm, Miltenyi Biotech, Loxo, Roche/Genentech, Wugen, and Verastem; and has received funds or research support from AstraZeneca, Bristol-Myers Squibb, Epizyme, Incyte, Kite/Gilead, Loxo, Novartis, and Seattle Genetics.
- **Timothy A. Quill, PhD,** has no relevant financial relationships to disclose.
- **Christopher Flowers, MD,** has served as consultant for AbbVie, Bayer, BeiGene, Celgene, Denovo, Genentech/ Hoffmann-La Roche, Gilead Sciences, Karyopharm, Pharmacyclics/Janssen, OptumRx, and Spectrum and has received funds for research support from AbbVie, Acerta, Burroughs Wellcome Fund, Celgene, Eastern Cooperative Oncology Group, Genentech/ Hoffmann-La Roche, Gilead Sciences, Millennium/Takeda, National Cancer Institute, TG Therapeutics, and V Foundation.

Background

- The advent of BTK inhibitors (BTKi; ibrutinib, acalabrutinib, zanubrutinib) has dramatically improved outcomes for many patients with B-cell malignancies
- To ensure optimal patient outcomes with BTKi therapy, it is essential to maintain both ongoing therapy and patient quality of life
  - These dual goals require prompt recognition and management of the unique adverse events (AEs) associated with BTKi therapy
- In 2019, we developed an online decision support tool to provide case specific guidance on managing BTKi AEs
- Here, we report data from this tool comparing expert recommendations and community HCPs management plans for defined patient scenarios

Tool Development

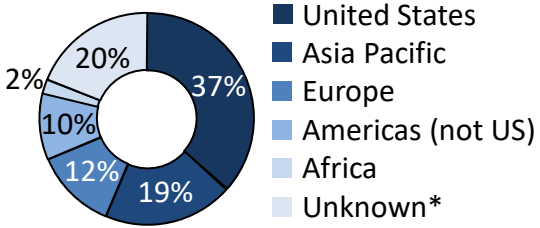
- 5 experts identified a simplified set of key questions on BTKi AEs
  - Experts: Jeremy S. Abramson, MD, MMSc; Farrukh T. Awan, MD; John P. Leonard, MD; Julie M. Vose, MD, MBA; and Christopher Flowers, MD
- In July 2019, these experts provided recommendations for managing distinct AE scenarios arising from the different combinations of the chosen characteristics



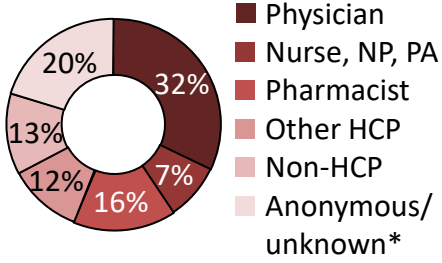
Demographics of Tool Participants: September 2019 - October 2020

- 970 complete cases entered by 532 distinct individuals

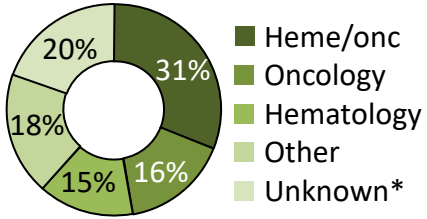
Geographic Distribution



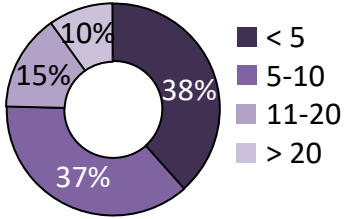
Role/Degree



Specialty



How many patients do you treat with a BTK inhibitor per year ?



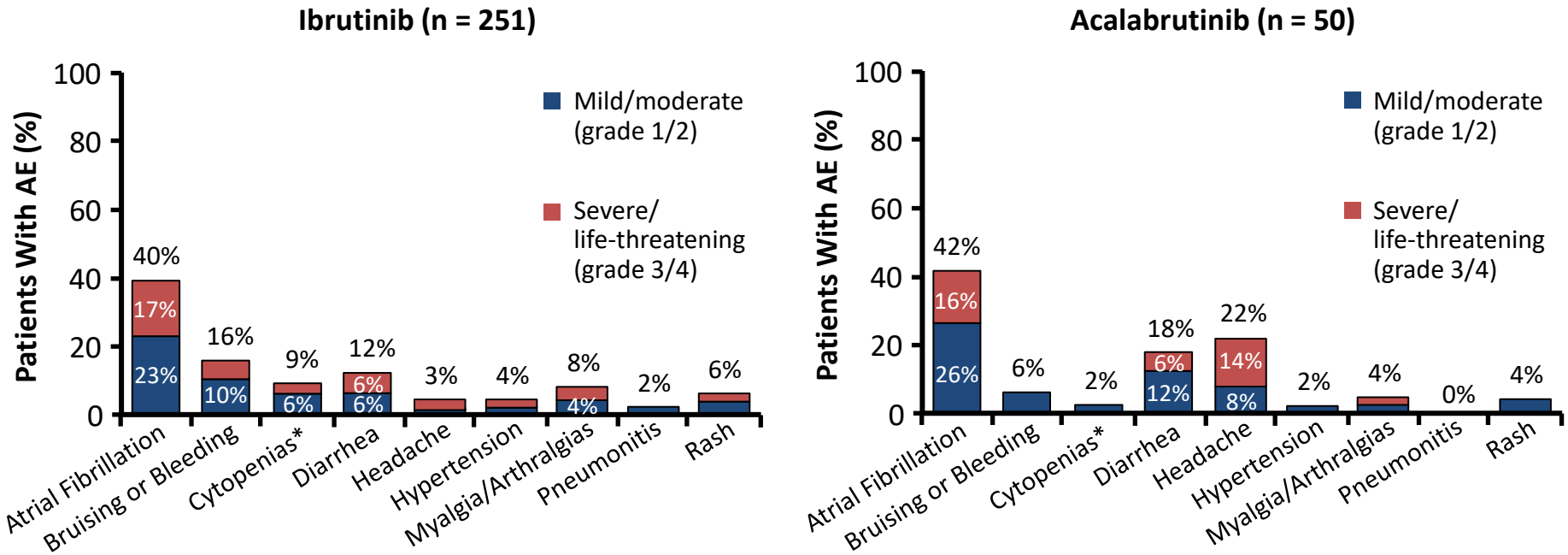
Optional survey (N = 100)

Disease Entered	Cases From All Participants, n (%)	Cases From HCP Participants, n (%)
CLL	679 (70)	485 (73)
MCL	159 (16)	100 (16)
MZL	58 (6)	33 (6)
WM	71 (7)	45 (7)

Begun BTKi Tx?	Cases From All Participants, n (%)	Cases From HCP Participants, n (%)
No, Tx is planned	450 (47)	306 (46)
Yes • Experiencing AE • Planning medical procedure	517 (53) 429 88	357 (54) 301 56

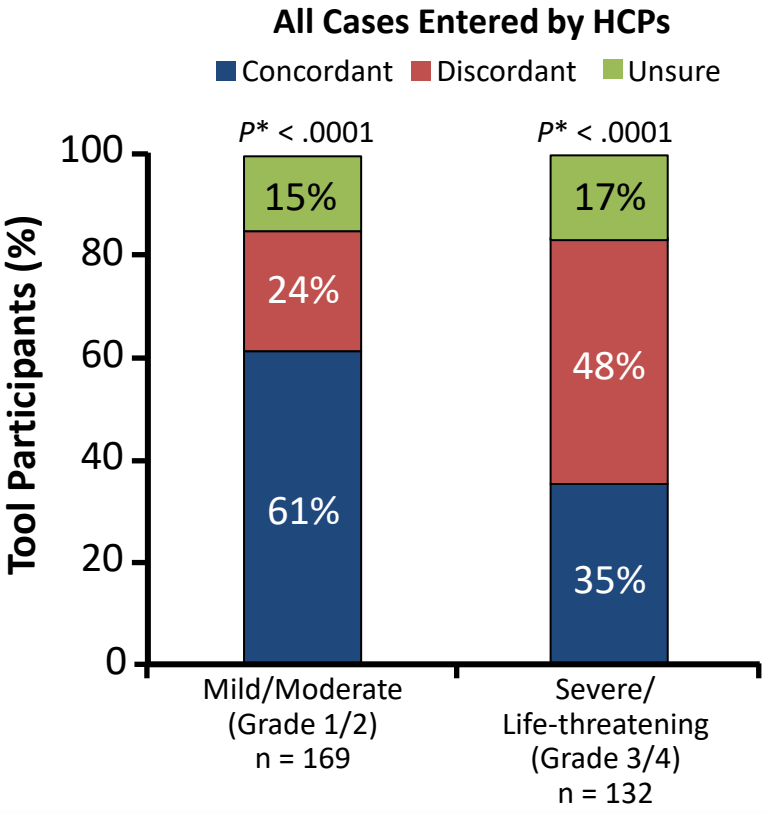
*Includes anonymous mobile access

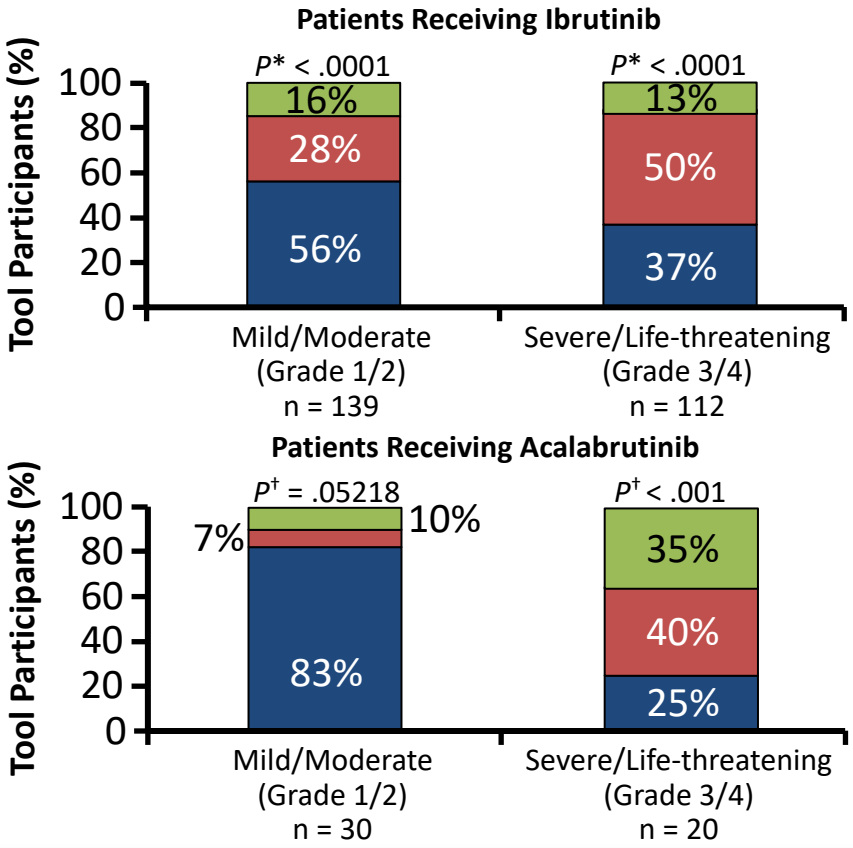
Patient Cases Entered Into Tool by HCPs: Type of AE (N = 301)



*Mild/moderate includes grade 1-3 cytopenias and severe/life-threatening includes grade 3 neutropenia with infection or fever or grade 4 cytopenias. †Severe/life-threatening includes grade 3 thrombocytopenia with bleeding, grade 4 thrombocytopenia, and grade 4 neutropenia lasting longer than 7 days and mild/moderate includes any other cytopenias.

HCP Agreement With Expert Recommendations

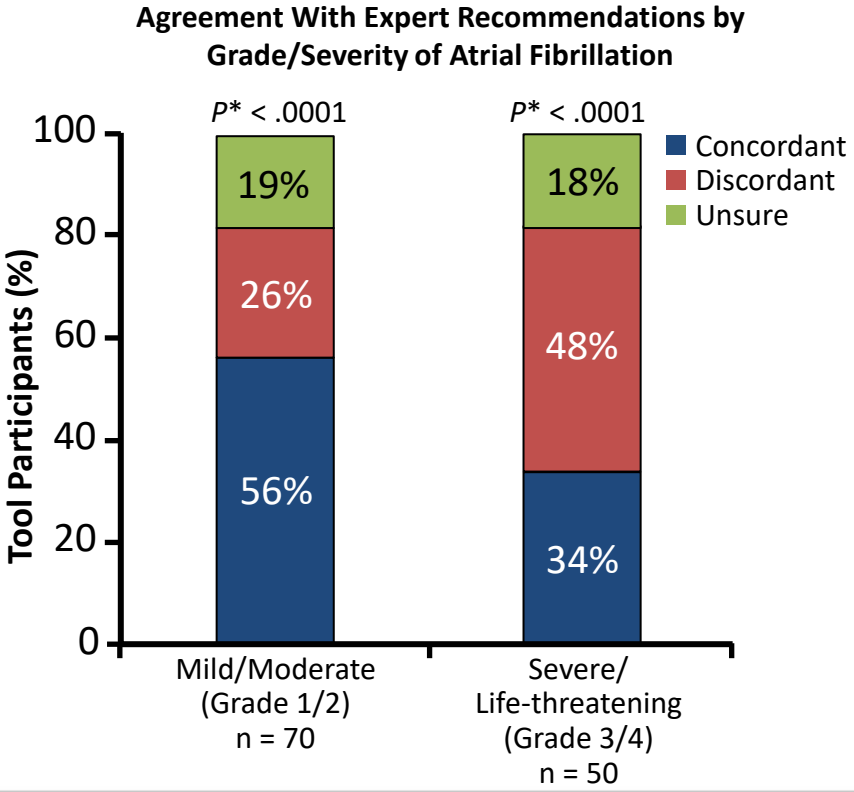




*Chi-square P value for HCP selection vs expert recommendations.
‡Fisher exact probability test (two-tailed) for HCP selection vs expert recommendations.

Example: Management of Atrial Fibrillation

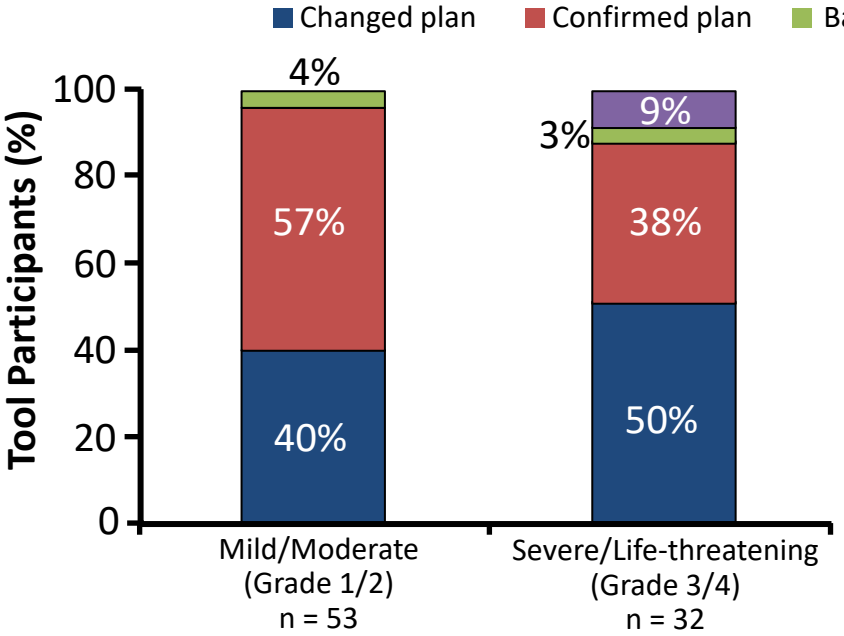
Expert Recommendations	Summary
Grade 1/2	• Cardiology consult • Treatment with BTKi can generally be continued while rate control–directed therapeutic interventions are initiated • Use of concurrent anticoagulant therapy needs to be assessed on a case-by-case basis
Grade 3/4	• Cardiology consult • Hold BTKi until symptoms resolve and there is adequate rate control • After clinical resolution to grade < 3 or baseline, BTKi can be resumed at the same dose for the first occurrence or can be dose reduced for recurrences • Discontinue for recurrence after dose reductions (per package insert)



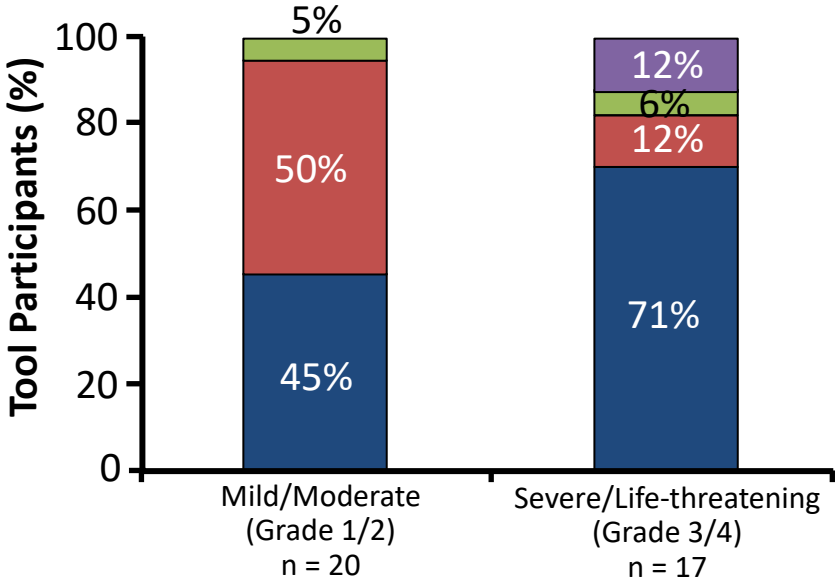
*Chi-square P value for HCP selection vs expert recommendations.

Impact of Tool on Planned HCP Clinical Practice

Optional Survey: Did the Expert Recommendations Change Your Management Approach?



HCPs Whose Management Plan Was Different Than Expert Recommendations



Conclusions

- In our online tool on managing BTKi AEs, 75% of clinicians indicated that they treat ≤ 10 patients/yr with a BTKi
- Most common AEs (≥ 10%) entered regardless of BTKi choice were atrial fibrillation, diarrhea, and bruising or bleeding
  - Headache was also a commonly entered for acalabrutinib
- Management of BTKi AEs by HCPs often diverges from evidence-based expert recommendations, especially grade 3/4 AEs
  - For grade 1/2 AEs, 24% did not match expert recommendations and 15% were unsure
  - For grade 3/4 AEs, 48% did not match expert recommendations and 17% were unsure
- Use of an online tool providing easy access to BTKi AE management recommendations may improve patient care and safety
  - For HCPs whose plans differed from expert recommendations, 71% would change their management approach for grade 3/4 AEs based on the information from this tool

Management of CAR T-Cell Toxicities: Concordance Between Healthcare Providers and Expert Consensus Recommendations in 2019 and 2020

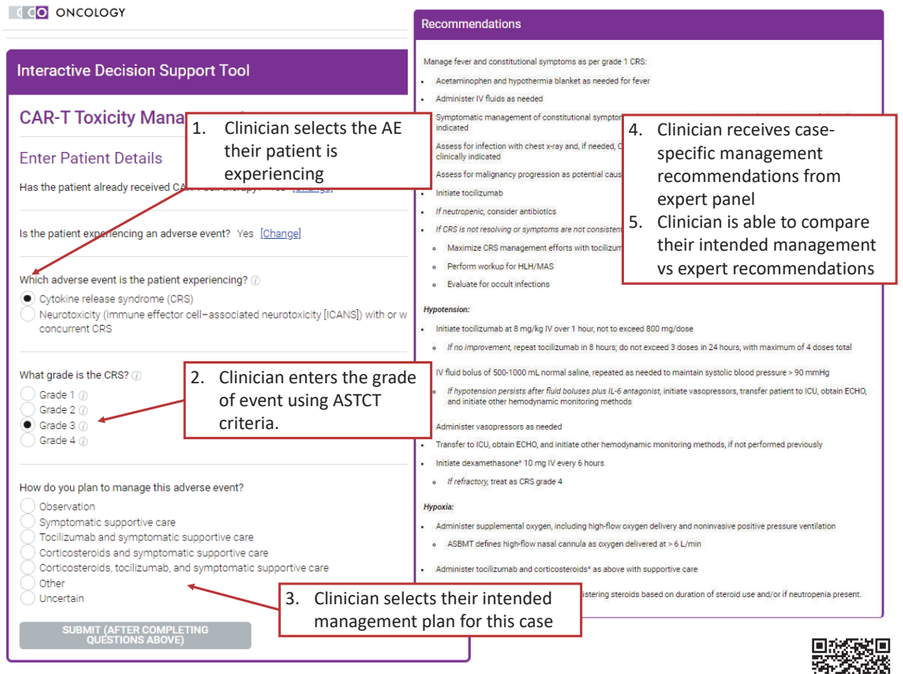
Matthew J. Frigault, MD[1]; Megan Cartwright, PhD[2]; Krista Marcello[2]; Timothy Quill, PhD[2]; Daniel J. DeAngelo, MD, PhD[3]; Ilene A. Galinsky, NP[3]; Shilpa Paul, PharmD, BCOP[4]; Jae H. Park, MD[5]

1. Massachusetts General Hospital; 2. Clinical Care Options, LLC; 3. Dana-Farber Cancer Institute; 4. MD Anderson Cancer Center; 5. Memorial Sloan Kettering Cancer Center.

Background

- CAR T-cell therapy has been a major innovative breakthrough for hematologic malignancies with 2 currently FDA-approved CAR T-cell products (tisagenlecleucel[1] and axicabtagene ciloleucel[2]) and several others in different stages of clinical investigation
- CAR T-cell therapies are associated with unique safety profiles and potentially serious toxicities, including cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity (ICANS)
- These adverse events (AEs) require vigilant monitoring and prompt recognition and management to ensure patient safety and optimal therapeutic benefit
- CCO developed an online Interactive Decision Support Tool to give healthcare providers (HCPs) case-specific, evidence-based consensus guidance from a panel of 5 interdisciplinary experts on the management of AEs due to CAR T-cell therapy
- Here, we report an updated comparison of planned CAR T-cell toxicity management among HCPs using the tool vs the expert consensus recommendations in the tool between the first 231 cases entered from 5/9/2019 through 9/18/2019 (Cohort 1) and the next 200 cases entered from 9/19/2019 through 7/31/2020 (Cohort 2)

Methods



The tool is online at: clinicaloptions.com/carttool

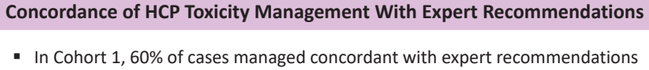
Results

Demographics and Cases Entered

- N = 431 cases entered by HCPs over 64 weeks (5/9/19 - 7/31/2020)
  - Majority of cases had already received CAR T-cell therapy (n = 227)
  - CRS was the most common AE case entered (n = 126; 67%)
    - In Cohort 1 71% of cases were CRS and 29% were ICANS vs 63% and 37%, respectively, in Cohort 2
- The proportion of the type of HCPs using the tool was comparable in both Cohorts, with 55% physicians, 22% nurses, and 23% pharmacists overall

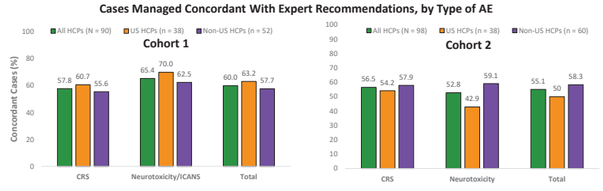
Impact of the Tool on Clinical Practice

- Of the 53 HCPs who answered the optional impact survey questions, 50% in Cohort 1 and 76% in Cohort 2 indicated that the tool recommendations confirmed their management plan

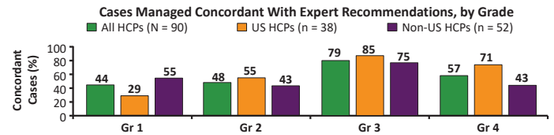


Concordance of HCP Toxicity Management With Expert Recommendations

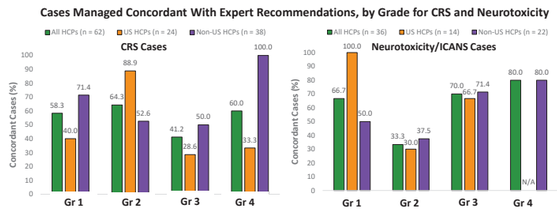
- In Cohort 1, 60% of cases managed concordant with expert recommendations (n = 54)
- In Cohort 2, 55% of cases managed concordant with expert recommendations (n = 54)



- **Cohort 1:** Significant difference in concordance by grade (*P* = .0417)

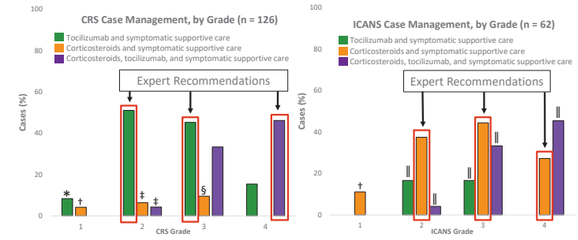


- **Cohort 2:** No significant difference in concordance by type of AE, grade of AE, or by region (US vs non-US HCPs)



Case Management by HCPs by AE and Grade

- Pooled data from both cohorts: HCPs reported initiating corticosteroids more often than recommended by experts (eg, Grade 3 CRS and all grades of ICANS)



*Tocilizumab not recommended for grade 1 CRS except for persistent or refractory fever. †Corticosteroids not recommended for grade 1 CRS or grade 1 ICANS. ‡Corticosteroids recommended only for hypotension or hypoxia in patients at high risk for severe CRS and with continued hypotension/hypoxia after IL-6 antagonist, hypoperfusion signs, or rapid deterioration. § Corticosteroids recommended for hypotension or hypoxia. ‖Tocilizumab only recommended if ICANS occurs concurrently with CRS necessitating intervention. The tool did not differentiate cases of ICANS that were concurrent with CRS

Conclusions

- These data suggest that many HCPs continue to suboptimally manage AEs associated with CAR T-cell therapy administration
  - Only 60% of HCPs' planned management of specific AEs was concordant with expert recommendations provided in the tool in cohort 1 vs 55% in Cohort 2
  - In cohort 1, there was a significant difference in concordance with expert recommendations by grade, however, no significant difference was found in cohort 2 by grade, type of AE (CRS vs ICANS), or by region (US vs non-US HCPs)
    - Tocilizumab used more frequently by HCPs than expert recommendations for management of ICANS
    - Corticosteroids were used earlier in CRS (lower grades)
  - Use of an online tool providing interactive, case-specific, evidence-based consensus recommendations can improve patient care and safety
  - A greater proportion of HCPs in Cohort 2 indicated that the expert recommendations confirmed/matched their intended management plan (76% vs 50% in Cohort 1) indicating potentially improved confidence in CAR T cell therapy toxicity management over time

References:

1. Tisagenlecleucel package insert. 2. Axicabtagene ciloleucel package insert

Variance Between Experts and Community Practitioners in Treating Soft Tissue Sarcomas: Analysis of an Online Decision Support Tool

Ryan P. Topping, PhD[1]; Vicki L. Keedy, MD[2]; Shreyaskumar R. Patel, MD[3]; Richard F. Riedel, MD[4]; Brian A. Van Tine, MD, PhD[5]; Timothy A. Quill, PhD[1]; William Tap, MD[6]

1. Clinical Care Options, Reston, Virginia. 2. Vanderbilt-Ingram Cancer Center, Nashville, Tennessee. 3. The University of Texas MD Anderson Cancer Center, Houston, Texas. 4. Duke Cancer Institute, Durham, North Carolina.
5. Washington University School of Medicine, St Louis, Missouri. 6. Memorial Sloan Kettering Cancer Center, New York, New York.

Background

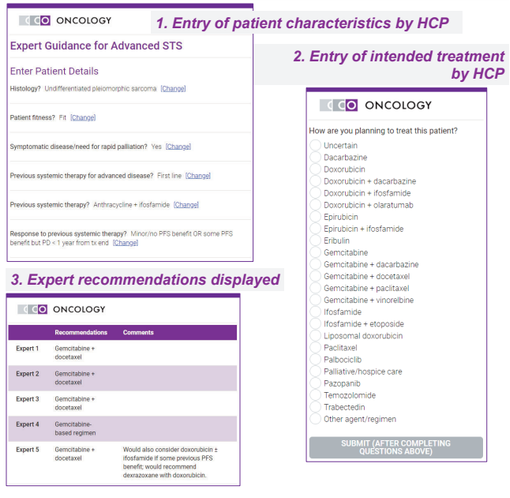
Soft tissue sarcomas (STSs) are rare cancers comprising > 50 histologic subtypes, each of which has unique management considerations. Current clinical practice guidelines note numerous targeted and chemotherapy options for patients with advanced STSs but generally lack specificity in providing recommendations for individual STS subtypes. As such, it is recommended that patients with STSs be treated at high-volume centers; however, this is not always possible.

We developed an online treatment decision support tool designed to provide oncology healthcare providers (HCPs) with case-specific systemic treatment recommendations from 5 STS experts. Here, we report an analysis of cases entered into the tool by HCPs, comparing their planned treatment with expert recommendations and assessing the impact of those recommendations on intended HCP treatment decisions.

Tool Design and Analysis

- 5 experts provided treatment recommendations in February 2019 for 272 distinct case scenarios of patients with unresectable or metastatic STS
  - Case scenarios were defined by factors the expert panel considered important for treatment selection, including histologic STS subtype, patient fitness, and previous treatment
  - Experts: Vicki L. Keedy, MD; Shreyaskumar R. Patel, MD; Richard F. Riedel, MD; Brian A. Van Tine, MD, PhD; William Tap, MD
  - 7 of the most common chemotherapy-sensitive histologic STS subtypes were selected for the tool (see Table)
- To use the tool, HCPs enter their patients' information and their intended treatment plan; expert recommendations for their specific patient scenario are then provided
- Tool available at **clinicaloptions.com/SarcomaTool**
- This analysis compared the intended treatment of HCPs with expert recommendations for specific cases entered in the tool from April 10, 2019 to May 20, 2020

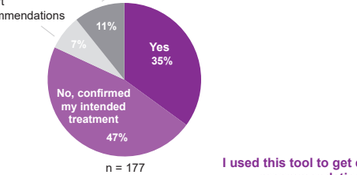
Tool Use and Screenshot Examples



Results

Tool Participant Demographics

- 605 patient cases entered by 349 HCPs



- Of 166 responding treaters, 61% reported treating ≤ 10 patients with STS per year

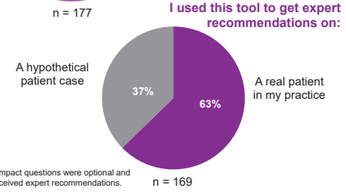
Characteristics of Patient Cases Entered by HCPs

Case Characteristic, n (%)	N = 605
Histology	
▪ Leiomyosarcoma	213 (35)
▪ Undifferentiated pleiomorphic sarcoma	89 (14)
▪ Synovial sarcoma	77 (13)
▪ Dedifferentiated liposarcoma	74 (12)
▪ Angiosarcoma	61(10)
▪ Myxoid/round cell liposarcoma	49 (8)
▪ Malignant peripheral nerve sheath tumor	42 (7)
Patient fitness	
▪ Fit	545 (90)
▪ Unfit	60 (10)
Symptomatic disease	
▪ Yes	339 (56)
▪ No	266 (44)
Previous systemic therapy	
▪ None	407 (67)
▪ First line	198 (33)
Extent of disease (n = 407 with no previous systemic therapy)	
▪ Locally advanced unresectable with potential for conversion to resectable disease	201 (49)
▪ Metastatic or locally advanced unresectable with no potential for conversion to resectable disease	206 (51)

Use of the Tool and Impact on Treatment Plan

Did the expert recommendations change your treatment choice?

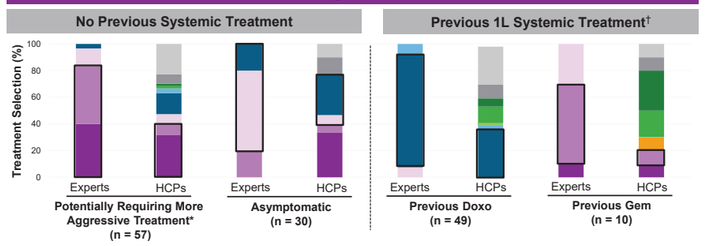
I used this tool to get expert recommendations on:



Intended use and tool impact questions were optional and available after users received expert recommendations.

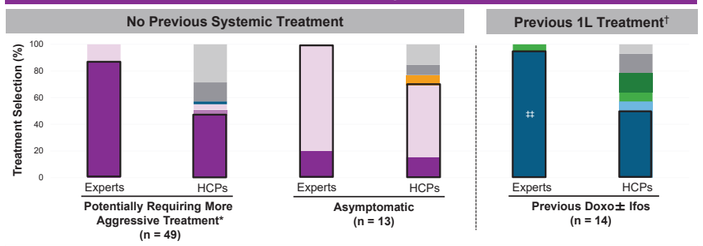
Doxo + ifos | Doxo + dac | Doxo | Gem + doc | Other gem-based | Ifos | Eribulin | Pazopanib | Trabectedin | Other | Uncertain | Foremost/key expert tx recommendations

Leiomyosarcoma



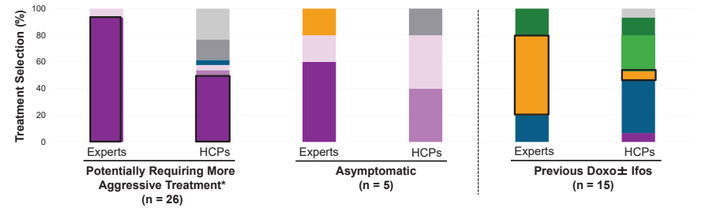
Key observations: For previously untreated pts, HCPs less frequently planned more aggressive tx for pts who might benefit vs experts; conversely, HCPs more frequently planned more aggressive tx for pts with asymptomatic disease vs experts. Substantial tx variability was observed between HCPs and experts in the 2L setting, with HCPs more likely to plan tx with novel agents like trabectedin.

Undifferentiated Pleiomorphic Sarcoma



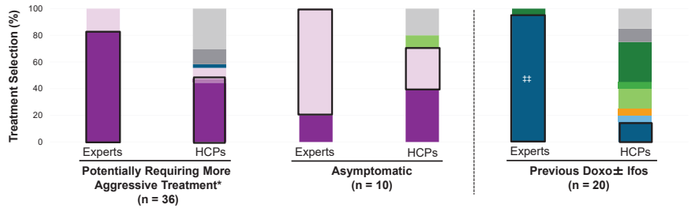
Key observations: For previously untreated pts, HCPs less frequently planned more aggressive tx for pts who might benefit vs experts; HCP plans and expert recommendations more closely aligned for pts with asymptomatic disease. For pts who did not respond to doxo ± ifos, experts almost exclusively recommended gem + doc; the planned tx of HCPs was more variable.

Synovial Sarcoma



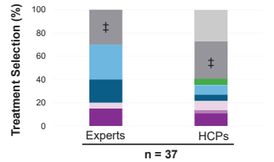
Key observations: For previously untreated pts, HCPs less frequently planned more aggressive tx for pts who might benefit vs experts; for asymptomatic pts, there was variability between experts in optimal tx recommendations. Notably, experts most frequently recommended ifos (most often in a high-dose regimen) following doxo ± ifos; this regimen was infrequently planned by HCPs.

Dedifferentiated Liposarcoma

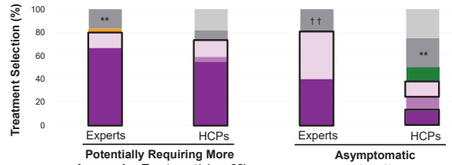


Key observations: For previously untreated pts, HCPs less frequently planned more aggressive tx for pts who might benefit vs experts; conversely, HCPs more frequently planned more aggressive tx for pts with asymptomatic disease vs experts. Following doxo ± ifos, experts almost exclusively recommended gem + doc; HCPs most often planned tx with a novel agent like trabectedin or eribulin.

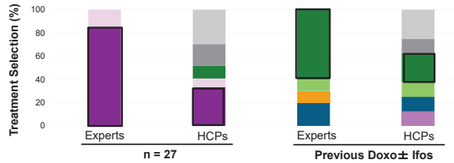
Angiosarcoma



Malignant Peripheral Nerve Sheath Tumor (MPNST)



Myxoid/Round Cell Liposarcoma



Key observations: For 1L tx for angiosarcoma, expert recommendations varied considerably. Expert and HCP tx selections generally aligned for 1L MPNST cases where more aggressive treatment would potentially be required. For myxoid/round cell liposarcoma cases with previous doxo ± ifos, experts most frequently recommended a novel agent like trabectedin.

Analyzed cases in which pts had no significant comorbidities and ECOG performance status was 0/1. *Symptomatic disease/need for rapid palliation or locally advanced unresectable disease with potential for conversion to resectable disease. †Case scenarios for which no/minor PFS response was observed with previous tx. ‡Experts, 30% paclitaxel; HCPs, 25% paclitaxel, 8% other. §Expert tx differences largely unaffected by symptomatic vs asymptomatic disease. **20% epirubicin ± ifos. †† 17% epirubicin + ifos. ‡‡n = 4 expert choices defined as "gem-based tx." *1L, first-line treatment; 2L, second-line treatment; dac, dacarbazine; doc, docetaxel; dox, doxorubicin; gem, gemcitabine; ifos, ifosfamide; pts, patients; tx, treatment.*

Conclusions

- Analysis of data from an online treatment decision support tool suggested differences in how experts and community providers manage patients with advanced STS of varied histologic subtypes
- Cases of leiomyosarcoma or liposarcoma were most frequently entered into the tool; however, a significant number of cases were entered for relatively rarer subtypes, including synovial sarcoma and angiosarcoma
- Expert recommendations in the tool changed the intended treatment plan of many HCPs, suggesting that online treatment decision tools that provide customized, patient-specific expert advice may increase implementation of optimal therapeutic decisions for advanced STS

Acknowledgment: The CME program that included the online treatment decision support tool was supported by an unrestricted educational grant from Lilly.

Contemporary Management of Advanced Hepatocellular Carcinoma: Treatment Patterns Among HCPs and Concordance With Expert Recommendations

Ryan P. Topping, PhD[1]; Timothy A. Quill, PhD[1]; Thomas A. Abrams, MD[2]; Amit G. Singal, MD, MS[3]; Mark Yarchoan, MD[4]; Andrew X. Zhu, MD, PhD, FACP[5]; Richard S. Finn, MD[6]

1. Clinical Care Options, Reston, Virginia. 2. Dana-Farber Cancer Institute, Boston, Massachusetts. 3. UT Southwestern Medical Center, Dallas, Texas. 4. The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, Maryland. 5. Massachusetts General Hospital Cancer Center, Boston, Massachusetts, and Jiahui International Cancer Center, Shanghai, China. 6. UCLA Jonsson Comprehensive Cancer Center, Los Angeles, California.

Scan me

Background

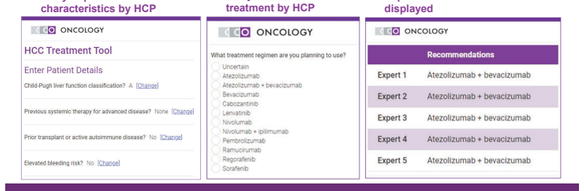
Healthcare professionals (HCPs) who manage patients with advanced hepatocellular carcinoma (HCC) are challenged to maintain a knowledge of contemporary treatment paradigms for these patients, but this field has evolved rapidly over the past few years. Prior to 2017, sorafenib was the only approved systemic therapy for advanced HCC; today, 9 regimens are approved. Given this new therapeutic landscape, we developed an online treatment decision support tool designed to provide HCPs with case-specific treatment recommendations from 5 HCC experts. Here, we report an analysis of cases entered into the tool by HCPs, comparing their planned treatment with expert recommendations.

Tool Design and Analysis

- 5 experts provided treatment recommendations in January 2021 for 71 distinct case scenarios of patients with advanced HCC who were assumed to be candidates for systemic therapy; case patients were also assumed to have good performance status
  - Case scenarios were defined by factors the expert panel considered important for treatment selection, including Child-Pugh liver function classification, the presence of key contraindications to immune checkpoint inhibitor or multikinase inhibitor therapy, AFP level, and previous treatment
  - Experts: Thomas A. Abrams, MD; Richard S. Finn, MD; Amit G. Singal, MD, MS; Mark Yarchoan, MD; Andrew X. Zhu, MD, PhD, FACP
- To use the tool, HCPs entered their patients' information and their intended treatment plan; expert recommendations for their specific patient scenario were then provided
  - **Tool is available at: clinicaloptions.com/HCCTool**
- This analysis compared the intended treatment of HCPs with expert recommendations for specific cases entered in the tool from April 1, 2021, to September 30, 2021

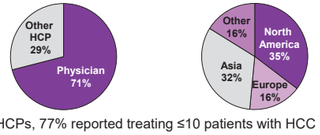
Tool Use and Screenshot Examples

1. Entry of patient characteristics by HCP
2. Entry of intended treatment by HCP
3. Expert recommendations displayed



Tool Participant Demographics

- 318 patient cases entered by 165 HCPs



- Of 39 responding HCPs, 77% reported treating ≤10 patients with HCC per month

Characteristics of Patient Cases Entered by HCPs, n (%)	Responses
Child-Pugh liver function	N = 318
▪ A	222 (70)
▪ B	96 (30)
Previous systemic therapy for advanced disease (Child-Pugh A)	n = 222
▪ None	146 (66)
▪ First line	56 (25)
▪ First and second line	20 (9)
First-line regimen if previous systemic therapy (Child-Pugh A)	n = 56
▪ Atezolizumab + bevacizumab	22 (39)
▪ Lenvatinib	16 (29)
▪ Sorafenib	13 (23)
▪ PD-1 inhibitor monotherapy	5 (9)

Conclusions

Analysis of data entered by HCPs into an online treatment decision support tool suggests significant differences among experts and HCPs in contemporary management of patients with advanced HCC

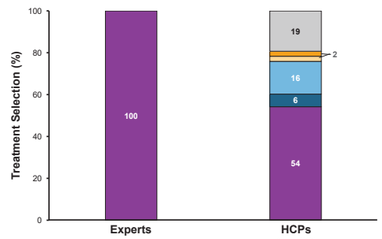
Data suggest that a decision support tool can affect HCP treatment decisions in a rapidly evolving therapeutic landscape, potentially improving patient care

Results

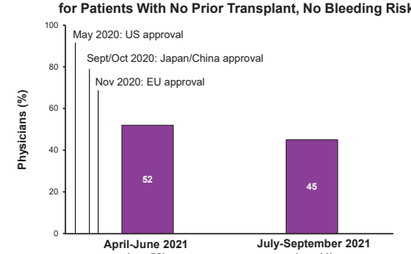
Atezolizumab + bevacizumab | Sorafenib | Lenvatinib | Cabozantinib | Regorafenib | Ramucirumab | Nivolumab | Nivolumab + ipilimumab | Pembrolizumab | Other | Uncertain

Expert and HCP Treatment Selections: No Previous Systemic Therapy

No Prior Transplant, No Bleeding Risk

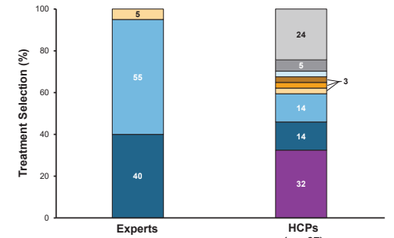


Timing of HCP Physicians Selecting Atezolizumab + Bevacizumab for Patients With No Prior Transplant, No Bleeding Risk

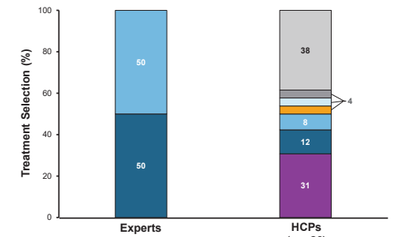


Key observations: For patients with no prior transplant or elevated bleeding risk, all experts would recommend atezolizumab + bevacizumab; HCPs planned this treatment in ~half of cases, and the proportion of physicians planning atezolizumab + bevacizumab for this population did not appear to increase over time, suggesting an ongoing educational need.

No Prior Transplant, Elevated Bleeding Risk*



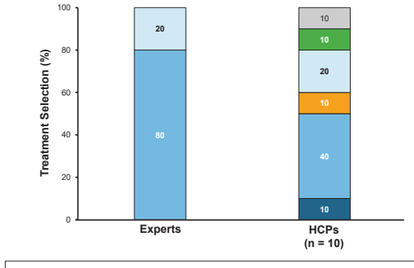
Prior Transplant†



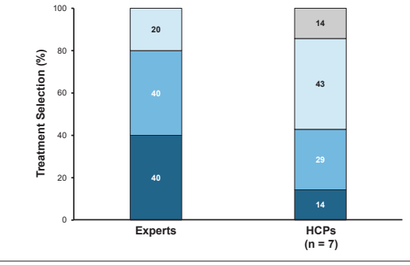
Key observations: For patients for whom the experts would not consider atezolizumab + bevacizumab to be optimal (prior transplant or elevated bleeding risk), sorafenib and lenvatinib were favored; notably, a substantial proportion of HCPs would select atezolizumab + bevacizumab for these patients, and few selected sorafenib and lenvatinib.

Expert and HCP Treatment Selections: Previous Systemic Therapy

PD With Atezolizumab + Bevacizumab, *Aggressive/Bulky Disease*, No Proteinuria/Hypertension

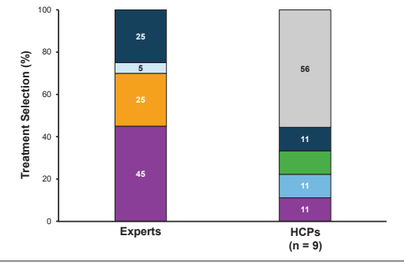


PD With Atezolizumab + Bevacizumab, *No Aggressive/Bulky Disease*, No Proteinuria/Hypertension

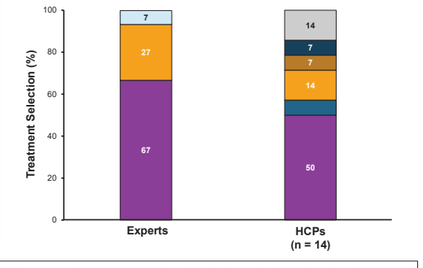


Key observations: For patients experiencing disease progression with atezolizumab + bevacizumab, experts favored lenvatinib (particularly for patients with aggressive/bulky disease). Despite low n values, the planned treatment of HCPs generally aligned with expert treatment recommendations for these patients.

PD With Sorafenib, No Prior Transplant, No Bleeding Risk, Any AFP Level



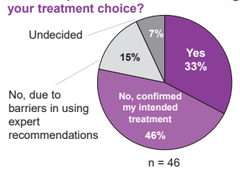
PD With Lenvatinib, No Prior Transplant, No Bleeding Risk, Any AFP Level



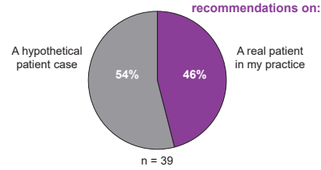
Key observations: For patients experiencing disease progression with sorafenib and lenvatinib, there was variance among experts, with atezolizumab + bevacizumab and nivolumab + ipilimumab predominantly recommended; HCPs appeared to be less certain of treatment in this setting, with low n values.

Use of the Tool and Impact on Treatment Plan‡

Did the expert recommendations change your treatment choice?



I used this tool to get expert recommendations on:



Key observation: One-third of responding HCPs changed their treatment choice based on expert recommendations, suggesting that a decision support tool can affect HCP treatment decisions.

*Additional variables (yes or no) included aggressive/bulky disease, persistent significant proteinuria or hypertension, and contraindication to a VEGF-targeted TKI. †Additional variables (yes or no) included aggressive/bulky disease and persistent significant proteinuria or hypertension. Patients with an increased bleeding risk may include those with uncontrolled gastroesophageal varices or recent significant bleeding episodes or surgery. ‡Intended use and tool impact questions were optional and available after users received expert recommendations.
AFP, alpha-fetoprotein; PD, progressive disease.

Acknowledgment: The CME program that included the online treatment decision support tool was supported by unrestricted educational grants from AstraZeneca, Genentech, a member of the Roche Group, and Lilly.

Disclosures: Ryan P. Topping, PhD, and Timothy A. Quill, PhD, have no relevant conflicts of interest to report. Thomas A. Abrams, MD, has disclosed that he has received consulting fees from Eisai, Exelixis, Genentech, Lilly, Merck, and Servier, and has ownership interest in Biogen. Richard S. Finn, MD, has disclosed that he has received consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, CStone, Eisai, Lilly, Merck, Pfizer, and Roche/Genentech. Amit G. Singal, MD, MS, has disclosed that he has received consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Exact Sciences, Exelixis, Genentech/Roche, Glycotest, GRAIL, Merck, and Wako. Mark Yarchoan, MD, has disclosed that he has received consulting fees from AstraZeneca, Eisai, Exelixis, and Genentech. Andrew X. Zhu, MD, PhD, FACP, has disclosed that he has received consulting fees from Bayer, Bristol-Myers Squibb, Eisai, Exelixis, Lilly, Merck, and Roche/Genentech.

Variance in Practice Between Experts and Oncology Healthcare Professionals for Follicular Lymphoma: Analysis of an Online Treatment Decision Tool

Rachael M. Andrie, PhD[1]; John M. Burke, MD[2]; Ian W. Flinn, MD, PhD[3]; John P. Leonard, MD[4]; Jeff P. Sharman, MD[5], Kristen M. Rosenthal, PhD[1]; Timothy A. Quill, PhD[1]; Christopher R. Flowers, MD, MS[6]

[1]Clinical Care Options, Reston, VA. [2]Rocky Mountain Cancer Centers, US Oncology Hematology Research, Aurora, CO. [3]Sarah Cannon Research Institute, Nashville, TN. [4]Weill Cornell Medicine, New York, NY. [5]Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR. [6]The University of Texas MD Anderson Cancer Center, Houston, TX.

Abstract #1922

Background and Aim

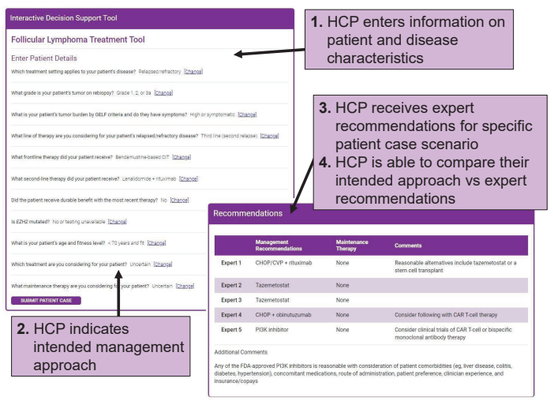
Follicular lymphoma (FL) is an incurable disease with a persistent risk of relapse and shorter durations of response with each line of therapy. As a result, management of patients with FL is complex, requiring multiple lines of therapy using various regimens with different mechanisms of action.

We developed an online treatment decision tool designed to provide oncology healthcare professionals (HCPs) with case-specific, individual management recommendations from experts in FL care in both the newly diagnosed and relapsed/refractory (R/R) disease settings. Here, we report an analysis of cases entered into this tool by HCPs comparing their planned treatment with expert recommendations and assessing the impact of those recommendations on intended HCP treatment decisions.

Tool Design and Analysis

- 5 lymphoma experts provided therapy recommendations in November 2020 for 264 unique case scenarios in newly diagnosed and R/R FL
- Case scenarios were defined by key patient and disease characteristics considered by the expert panel to be important for treatment decisions, including disease stage, tumor grade, tumor burden, presence of symptoms, age, and fitness as well as previous therapy, duration of response, and *EZH2* mutation status for relapsed disease
- To use the tool, HCPs entered their patient's information along with their intended treatment plan. Expert treatment recommendations were then shown to the HCP for that specific patient case scenario
  - **Tool available at:** www.clinicaloptions.com/FLtool
- HCPs were then asked to indicate if the expert recommendations affected their planned treatment approach

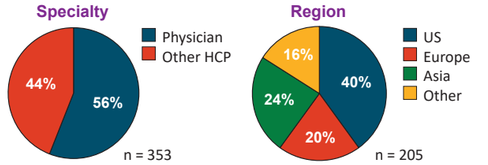
Tool Screenshots (Examples)



Results

Tool Participant Demographics

- 353 patient cases were entered by 235 HCPs from March 2021 to November 2021



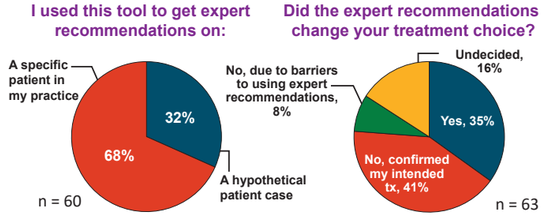
- Most responding HCPs (n = 60) were from academic medical centers (43%) and community practice/hospitals (33%). Of responding HCPs, 74% reported being in practice for ≥5 years (n = 57) and 66% reported treating >5 patients with lymphoma per month (n = 56)

Characteristics of Patient Cases Entered by HCPs

Case Characteristics, n (%)	N = 353
Newly diagnosed	**182 (51)**
▪ Stage I/II contiguous	55 (30)
▪ Stage II noncontiguous or III/IV FL	127 (70)
R/R	**172 (49)***
▪ Grade 1, 2, 3a/low tumor burden/asymptomatic	35 (20)
• Second line	17 (49)
• Third line	16 (46)
▪ Grade 1, 2, 3a/high tumor burden/symptomatic	89 (52)
• Second line	34 (38)
• Third line	48 (54)

*n = 48 (28%) of R/R cases were grade 3b, had suspected transformation, or the grade was unknown because rebiopsy was not done.

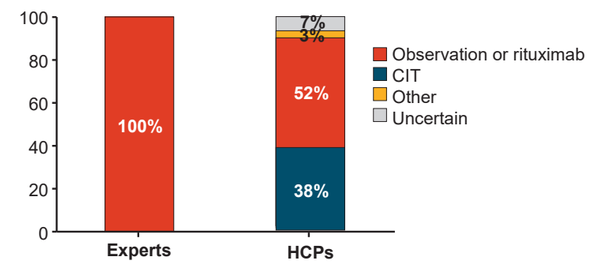
Use of Tool and Impact on Treatment Plan



- For HCPs reporting on the tool's clinical impact, 60% who initially selected another treatment option or who were uncertain indicated that they would change their intended therapy to match the experts

Treatment Decisions for Newly Diagnosed, Grade 1-3a, Stage II Noncontiguous* or III/IV FL

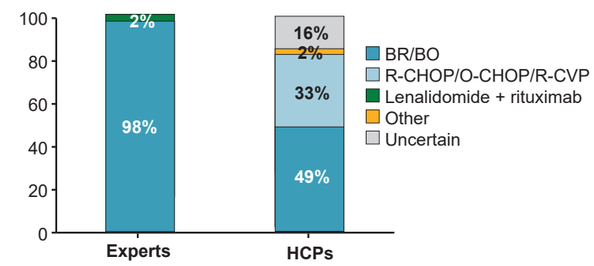
Low tumor burden,† asymptomatic (n = 29)



- **Key Observations:** For patients with newly diagnosed FL with low tumor burden and no symptoms, all experts recommended observation or single-agent rituximab whereas 38% of HCPs chose chemoimmunotherapy (CIT) in this setting

*Or not within a clinically acceptable radiation field. †By GELF criteria.

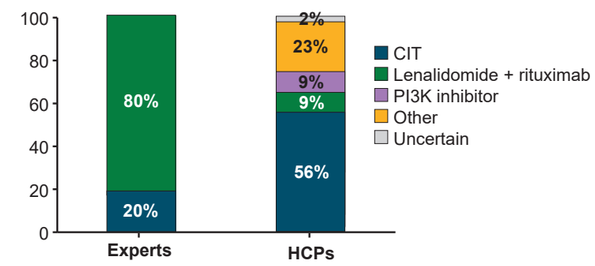
High tumor burden,† symptomatic (n = 51)



- **Key Observations:** For patients with newly diagnosed FL with high tumor burden and symptoms, 82% of HCPs chose CIT in agreement with expert consensus in this setting; however, experts exclusively recommended a bendamustine-based CIT regimen whereas 33% of HCPs chose a CHOP- or CVP-based CIT regimen

Treatment Decisions for R/R, Grade 1-3a, High Tumor Burden, Symptomatic FL

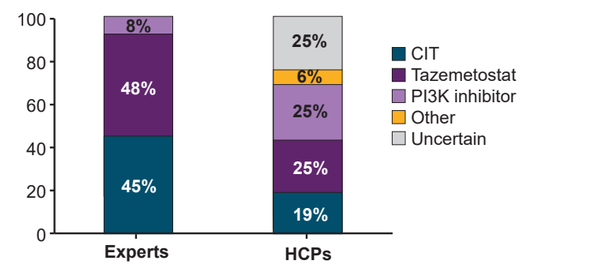
Second-line after relapse on first-line CIT‡ (n = 43)



- **Key Observations:** In the second-line setting for R/R FL with high tumor burden and symptoms, experts recommended lenalidomide plus rituximab for the majority of patients with relapse on frontline CIT whereas only 9% of HCPs chose this regimen, with over two-thirds instead selecting another CIT regimen or a PI3K inhibitor

‡Bendamustine-, CHOP-, or CVP-based CIT.

Third-line after relapse on first-line CIT‡ and second-line lenalidomide + rituximab (n = 16)



- **Key Observations:** For symptomatic cases with high tumor burden and relapse on first-line CIT and second-line lenalidomide plus rituximab, experts favored tazemetostat, regardless of *EZH2* mutation status, or another CIT regimen; by contrast, HCPs were fairly evenly split between tazemetostat, a PI3K inhibitor, or another CIT regimen

B, bendamustine; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CVP, cyclophosphamide/vincristine/prednisone; O, obinutuzumab; R, rituximab.

Conclusions

- Data from this tool suggest differences in clinical practice between experts and HCPs for cases of newly diagnosed and R/R FL, including examples of potential overtreatment such as the use of CIT in asymptomatic patients with newly diagnosed FL and low tumor burden
  - Of note, treatment options in the third-line setting continue to evolve, with experts recommending clinical trial enrollment if available
- In most cases, HCPs who initially selected treatment options that diverged from expert recommendations or were uncertain about treatment choice changed their intended therapy to match the experts
- Online support tools with expert guidance, like this decision support tool, may help to increase the number of HCPs making optimal management decisions for patients with FL

For correspondence regarding this poster, please contact Rachael M. Andrie, PhD (randrie@clinicaloptions.com).

COI: Rachael M. Andrie, PhD, has no relevant conflicts of interest to report.

Acknowledgement: The CME program that included the online treatment decision support tool was supported by unrestricted educational grants from Bayer HealthCare Pharmaceuticals Inc., Celgene Corporation, and Epizyme Inc.

Variance Between Experts and Community Clinicians in Treatment of Chronic Hepatitis B Infection

Zachary Schwartz, MSc, ELS[1]; Robert S. Brown Jr., MD, MPH[2]; Natalie H. Bzowej, MD, PhD[3]; Jordan J. Feld, MD, MPH[4]; Jenny Schulz, PhD[1]; Edward King, MA[1]; Norah Terrault, MD, MPH[5]

1. Clinical Care Options, LLC, Reston, VA. 2. Weill Cornell Medicine, New York, NY. 3. Ochsner Health System, New Orleans, LA. 4. Toronto Centre for Liver Disease, Toronto, ON, Canada. 5. UCSF, San Francisco, CA.

1. Background

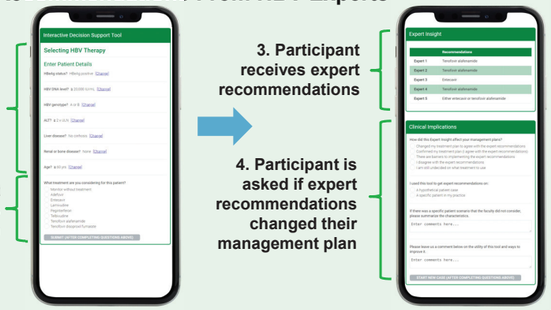
- Recent updates to the AASLD practice guidelines for chronic HBV infection—and the approval in 2016 of the first new HBV therapy since 2008—require clinicians to reappraise their treatment plans for patients with HBV infection
- We developed an online decision support tool based on recommendations from multiple experts for select HBV patient scenarios based on key criteria

2. Methods

- 5 HBV experts provided first-line management recommendations for 433 unique HBV case scenarios based on a simplified set of patient variables:
  - HBeAg status
  - HBV genotype
  - HBV DNA level
  - ALT level
  - Liver histology
  - Renal or bone disease
  - Age
  - Pregnancy plans
- We then developed an online decision support tool that enabled participants to specify a patient scenario using these variables and then select their intended first-line management plan

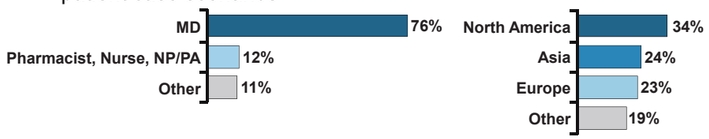
Online Decision Support Tool Provides Patient-Specific Recommendations From HBV Experts

1. Participant enters patient and disease factors
2. Participant indicates management plan
3. Participant receives expert recommendations
4. Participant is asked if expert recommendations changed their management plan



3. Participant Demographics

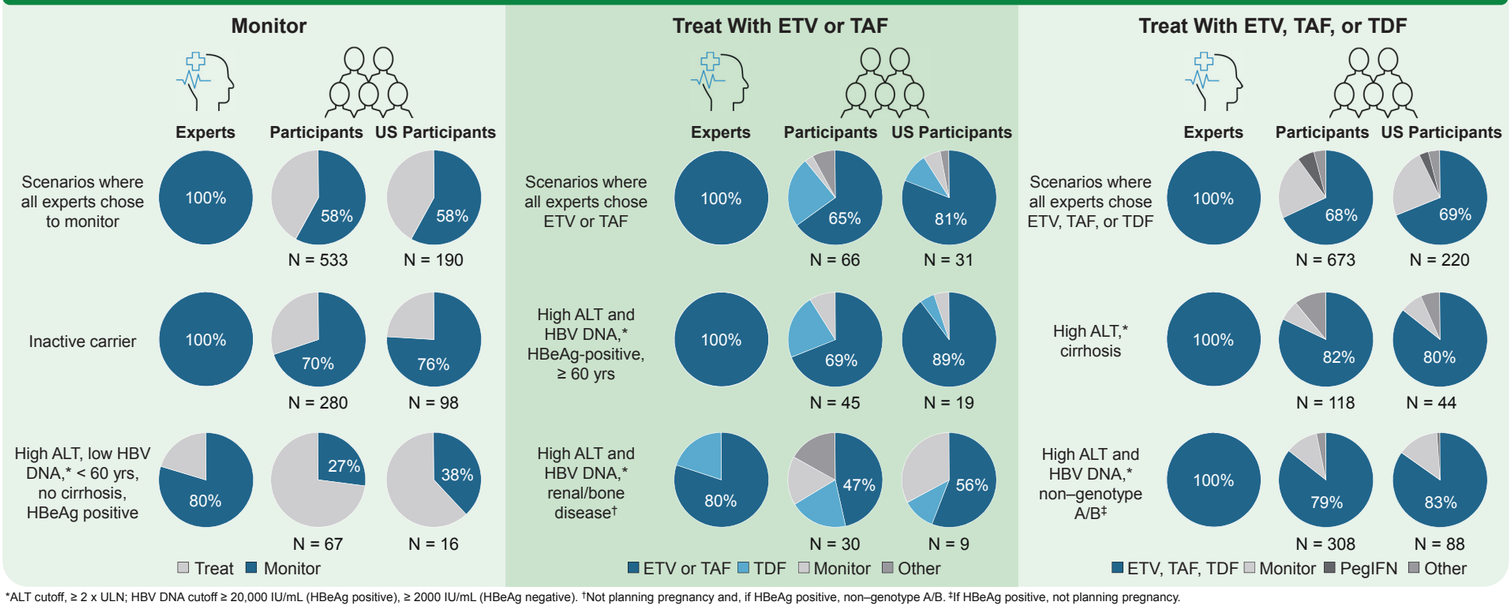
- Between November 2017 and September 2018, N = 902 participants (79% hepatology, gastroenterology, ID, IM, FP/GP) entered 1820 patient case scenarios



4. Comparison of Expert and Community Clinicians' First-line Management Choices

- Overall, in 29% (534/1820) of cases entered, the participant planned a first-line management approach that differed from the experts (28% [165/581] for US participants)

5. Comparison of First-line Management Choices by Patient Scenario



*ALT cutoff, ≥ 2 x ULN; HBV DNA cutoff ≥ 20,000 IU/mL (HBeAg positive), ≥ 2000 IU/mL (HBeAg negative). †Not planning pregnancy and, if HBeAg positive, non–genotype A/B. ‡If HBeAg positive, not planning pregnancy.

6. Impact

Intent to Change Among Participants Differing From Expert Consensus

"This is great! Like having a panel of experts in your back pocket!!"

"I love the tool and when I see 5 people [with] the same opinion it does make me feel better."

7. Conclusions

- This online decision support tool showed substantial **variability** in first-line management strategies for chronic HBV infection **between experts and community clinicians**
- In many cases, participants chose an approach that no expert chose
  - Participants would often treat patients that experts would monitor
  - Where experts chose ETV or TAF, 24% of participants chose TDF (10% in US)
  - Where experts chose any recommended nucleos(t)ide analogue (ETV, TAF, or TDF), 32% of participants did not
  - In 5% of all cases, participants chose agents not recommended by guidelines (adefovir, lamivudine, telbivudine)
- Expert recommendations **changed the intended treatment plan for most participants,** suggesting the tool's use can help optimize care of patients with chronic HBV infection

Acknowledgements: This research is based on activities supported by an independent educational grant from Gilead Sciences.

Disclosures: 1. None. 2. Consulting fees from Bristol-Myers Squibb and Gilead Sciences and funds for research support from Gilead Sciences. 3. Consulting fees from Gilead Sciences and funds for research support from Allergan, Cirius Therapeutics, and Gilead Sciences. 4. Consulting fees from AbbVie, ContraVir, Gilead Sciences, and Merck and funds for research support from AbbVie, Gilead Sciences, Janssen, Merck, and Wako Life Sciences. 5. Consulting fees from Dynavax Technologies, Gilead Sciences, and Novartis and funds for research support from Gilead Sciences.

Differences Between Experts and Community Clinicians in Selecting HIV Switch Regimens for Patients With Viral Suppression

Jennifer Blanchette, PhD[1]; Jenny Schulz, PhD[1]; Edward King, MA[1]; Brian Wood, MD[2]; Joseph J. Eron, MD[3]; Paul E. Sax, MD[4]

1. Clinical Care Options, LLC, Reston, VA. 2. University of Washington, Seattle, WA. 3. University of North Carolina at Chapel Hill, Chapel Hill, NC. 4. Brigham and Women's Hospital, Boston, MA

1. Background

- Patients may consider switching suppressive HIV regimens for a variety of reasons, including simplification, improved safety and tolerability, drug interactions, or cost
- Because switching treatment is a common clinical dilemma in current HIV care, we developed an online treatment decision support tool to assist providers in selecting a new regimen in a variety of patient scenarios

2. Methods

- In March 2018, 5 HIV experts provided treatment recommendations for 1360 unique HIV switch case scenarios based on a simplified set of patient variables:
  - HLA-B*5701 status
  - ARV drug resistance
  - Presence of or high risk for CVD
  - HBV coinfection
  - Current ART regimen and component requiring a switch
- We then developed an online decision support tool that enabled clinicians to specify a patient scenario using these variables and then see the experts' recommendations for that specific case. Users' treatment intentions were captured before and after recommendations were displayed

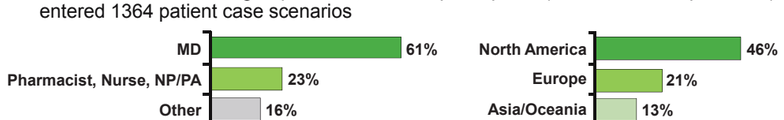
Online Decision Support Tool Provides Patient-Specific Recommendations From 5 HIV Experts

1. Participant enters patient and disease factors
2. Participant indicates management plan
3. Participant receives expert recommendations
4. Participant is asked if expert recommendations changed his/her management plan

www.clinicaloptions.com/hiv/programs/hiv-switch/interactive-decision-support-tool/

3. Participant Demographics

- From March 2018 through April 2019, N = 835 participants (69% ID or HIV specialists) entered 1364 patient case scenarios



Disclosures: 1. None. 2. None. 3. Funds for research support from Gilead Sciences, Janssen, and ViiV Healthcare and consulting fees from Gilead Sciences, Janssen, Merck, and ViiV Healthcare 4. Funds for research support from Gilead Sciences and ViiV Healthcare and fees for advisor or review panel member from Gilead Sciences, Janssen, and Merck.

4. Comparison of Switch Regimen Choice by Patient Scenario

All Cases in Which Users' Baseline Switch Intentions Inconsistent With Expert Recommendations

Patient Characteristics

Case	Treatment Inconsistent With Expert Selections	Participants Choosing Treatment Inconsistent With Expert Selections
CVD, high risk for CVD, and/or HLA-B*5701+/unknown	ABC (13% vs 0% experts), boosted PIs (30%),* DTG/RPV (31%)*	64%, N = 430
History of resistance	Boosted PIs (40%),* DTG/RPV (24%)*	69%, N = 306
Resistance unknown, but no history of VF	Boosted PIs (35%),* DTG/RPV (26%)*	62%, N = 249

Type of Resistance

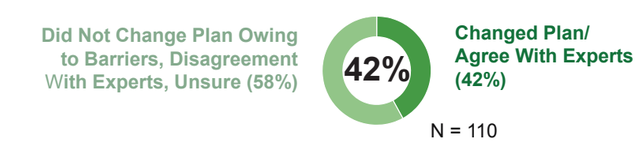
Case	Treatment Inconsistent With Expert Selections	Participants Choosing Treatment Inconsistent With Expert Selections
M184V/I or a single TAM	Boosted PIs (38%),* DTG/RPV (24%)*	66%, N = 141
K103N	Boosted PIs (22%),* DTG/RPV (26%)*	68%, N = 40
(M184V/I or a single TAM) and K103N	Boosted PIs (48%),* DTG/RPV (23%)*	74%, N = 125

Combined Characteristics

Case	Treatment Inconsistent With Expert Selections	Participants Choosing Treatment Inconsistent With Expert Selections
(CVD, high risk for CVD, and/or HLA-B*5701+/unknown) AND history of resistance	ABC (11% vs 0% experts), boosted PIs (45%),* DTG/RPV (24%)*	73%, N = 117
(CVD, high risk for CVD, and/or HLA-B*5701+/unknown) AND (M184V/I or a single TAM) and K103N	ABC (12% vs 0% experts), boosted PIs (50%),* DTG/RPV (25%)*	78%, N = 51

*Percentage of cases in which users selected this ART option but experts did not, or vice versa.

5. Intent to Change Among Participants Differing From Experts



"This is a very useful tool and it is always important to have the advice of an expert; thanks for the support"

"This was fun, easy to use, and quite helpful!"

6. Conclusions

- This online decision support tool showed that clinicians' initially planned switch regimen for patients requiring a change in ART for reasons other than virologic failure differed from HIV experts for 64% of case scenarios; rate of difference increased as cases became more complex
- Scenarios where clinicians' treatment plan was inconsistent with expert selections were:
  - Users more often selected boosted regimens overall, particularly boosted PIs
  - Users and experts differed in their use of dual therapy option DTG/RPV
  - TDF-containing regimens: never selected by experts vs 11% of participant cases
- Using an online tool changed the intended treatment plan for many participants, suggesting the tool's use can help optimize the selection of a switch regimen in patients with virologic suppression on their current ART regimen

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Gilead Sciences.

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Poster 477

Hep B Consult: A Point-of-Care Interactive Decision Support Tool Delivers Real-Time, Personalized, HBV Guideline-Based Teaching

Produced in collaboration with:

American Liver Foundation — Your Liver. Your Life.® · PCE · AHF Asian Health Foundation

Zachary Schwartz, MSc, ELS*; Jenny Schulz, PhD*; Jennifer M. Blanchette, PhD*; Edward King, MA*; Kosh Agarwal, MD†; Grace L. Wong, MD‡, Paul Y. Kwo, MD §

*Clinical Care Options, LLC. †Institute of Liver Studies, King's College Hospital NHS Trust. ‡Institute of Digestive Disease, Department of Medicine and Therapeutics, The Chinese University of Hong Kong. §Stanford University School of Medicine.

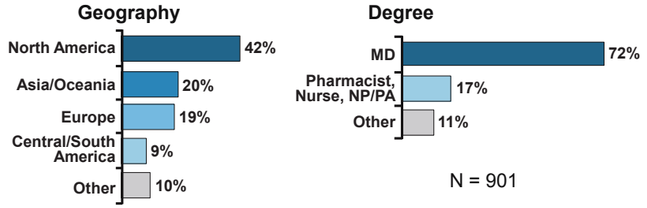
1. Background

- We previously identified variance in HBV management strategies between community clinicians and experts[1]
- Here, we developed a comprehensive online decision support tool based on **American, European, and Asian Pacific guideline recommendations**
- Tool is available as an app and on the CCO Web site

2. Participant Demographics

- From March through October 2019, **N = 3371** participants entered cases into the tool
  - n = 2470 participants via the app (anonymous)
  - n = 901 participants via the CCO site (authenticated)

Authenticated Participants



N = 901

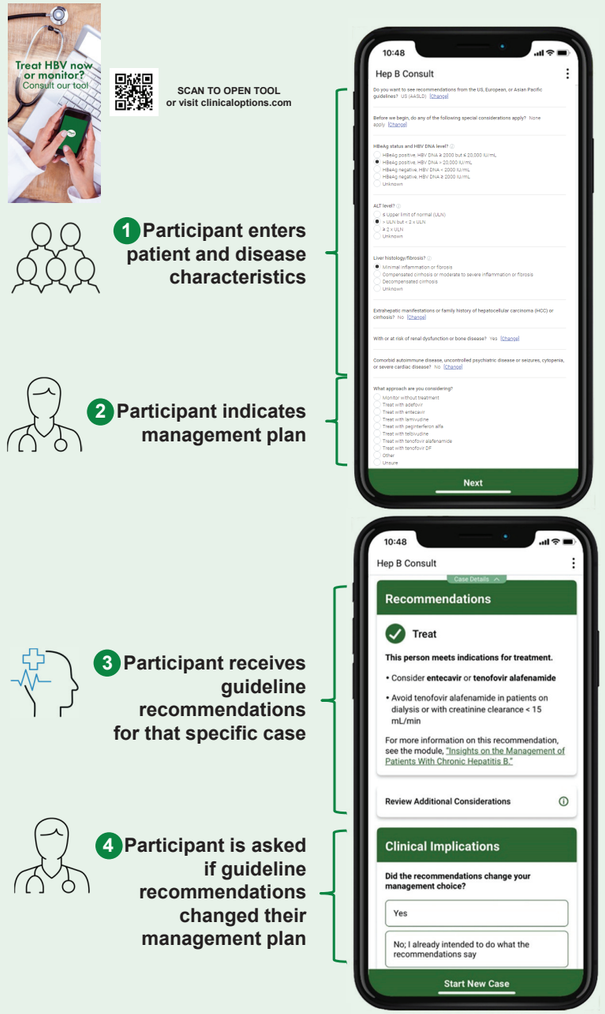
3. Cases Entered

8015 Total Cases Entered → **5067** Cases Entered by Clinicians → **4310** Cases With Clear Guidelines

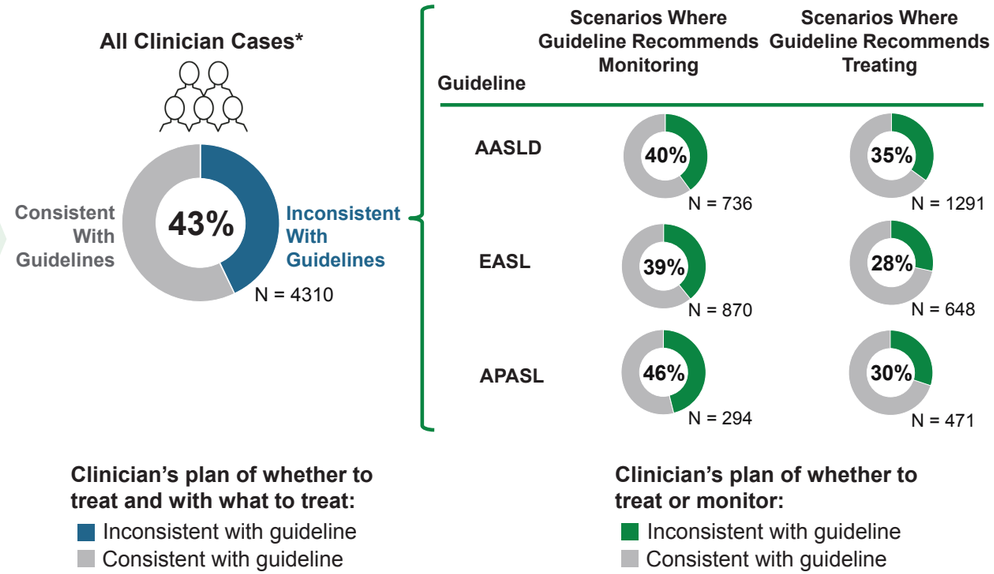
Of 2478 cases where participants specified:
- **55% were real patients**
- 45% were hypothetical cases

- In **28%** of all cases, participants selected a management plan without knowing one of the following factors:
  - HBeAg status
  - ALT and HBV DNA
  - Liver histology/fibrosis
  - Extrahepatic manifestations
  - Bone or renal disease
  - Other comorbidities
- In these cases, the tool provided education on why these patient characteristics are needed before deciding how to manage the patient

4. Online Decision Support Tool Provides Patient-Specific Recommendations



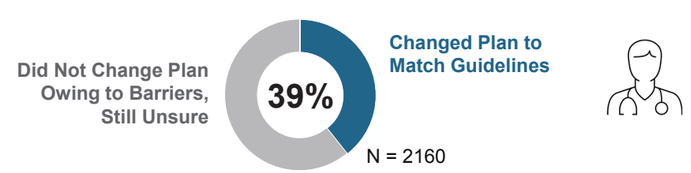
5. Baseline Management Plan



*Excludes scenarios where guideline recommendation is indeterminate.

6. Posteducation Impact

Subset of Clinician Cases Where Baseline Plan Differed From Guidelines and Clinician Identified Future Plan



7. Conclusions

- This online decision support tool showed that clinicians' initial HBV management plans of whether to treat and what to treat with **differed from guidelines** for 43% of case scenarios
- Using an online tool **changed the intended treatment plan for many participants,** suggesting the tool's use can help optimize care of patients with chronic HBV infection

Reference: 1. Schwartz. AASLD 2018. Poster 406. https://www.clinicaloptions.com/publications/2018/11_2018_san_francisco_hbv_poster

Disclosures: *None. †Funds for research support from Gilead Sciences and Merck Sharp & Dohme; consulting fees from Arbutus, Gilead Sciences, and Vir Biotechnology. ‡Consulting fees from AbbVie, Arrowhead, Bristol-Myers Squibb, Gilead Sciences, and Quest; funds for research support from Assembly, Bristol-Myers Squibb, and Gilead Sciences; served on a data and safety monitoring board for Johnson & Johnson. §Consulting fees from Gilead Sciences and Janssen; funds for research support from Gilead Sciences; speaker bureaus for Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche.

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Gilead Sciences.

Variance Between Clinicians and Guidelines in the Management of HIV/HCV Infection

Zachary Schwartz, MSc, ELS[1]; Jenny Schulz, PhD[1]; Edward King, MA[1]; Susanna Naggie, MD, MHS[2]; Mark S. Sulkowski, MD[3]

1. Clinical Care Options, LLC, Reston, VA. 2. Duke University School of Medicine, Durham, NC. 3. Johns Hopkins University School of Medicine, Baltimore, MD.

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1. Background

- Simultaneous treatment for both HIV and HCV infection requires consideration of multiple factors beyond drug interactions
- In May 2018, we developed an online decision support tool based on recommendations from the AASLD/IDSA and DHHS guidelines for HIV/HCV patient scenarios

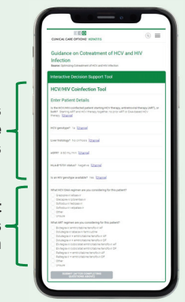
2. Methods

- Guidelines were applied to first-line management recommendations for 304 unique HIV/HCV coinfection case scenarios based on a simplified set of patient variables:
  - Current ART/HCV therapy
  - HIV and HCV genotypes
  - Liver histology
  - Renal function
  - HLA-B*5701 status
- Next, we developed an online decision support tool that enabled users to define a patient scenario using these variables and then see recommendations for that specific case. Users' treatment intentions were captured before and after recommendations were displayed

Online Decision Support Tool Provides Patient-Specific Recommendations From HIV and HCV Guidelines

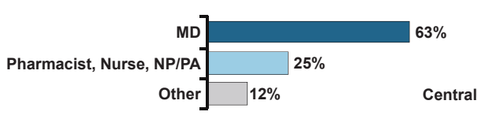
SCAN TO OPEN TOOL

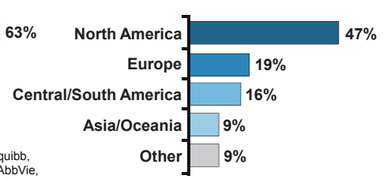
1. Participant enters patient and disease factors
2. Participant indicates management plan
3. Participant receives guideline recommendations
4. Participant is asked if guideline recommendations changed their management plan



3. Participant Demographics

- From August 2018 through August 2019, N = 683 participants (61% ID or HIV specialists) entered **972** patient case scenarios

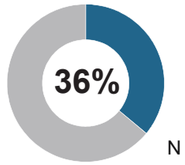




Disclosures: 1. None. 2. Funds for research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Tacere. 3. Funds for research support from AbbVie, Gilead Sciences, and Proteus Digital Health and consulting fees from AbbVie, Gilead Sciences, and Merck.

4. Comparison of First-line Management Choices by Patient Scenario

All Cases in Which Users' Baseline Treatment Intentions Inconsistent With Guidelines



Patient Characteristics

Case	Treatment Inconsistent With Guidelines	Participants Choosing Treatment Inconsistent With Guidelines
eGFR < 60 mL/min	SOF/LDV, SOF/VEL, or TDF	41% (N = 158)
HLA-B*5701 Positive	DTG/ABC/3TC	6% (N = 53)

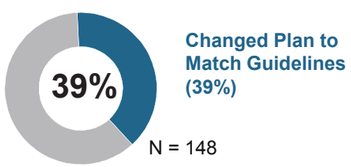
Drug Interactions

Case	Treatment Inconsistent With Guidelines	Participants Choosing Treatment Inconsistent With Guidelines
Receiving EVG/COBI	GRZ/ELB	14% (N = 147)
Receiving GRZ/ELB	EVG/COBI	11% (N = 27)
Receiving SOF/LDV	EVG/COBI/ 3TC/TDF	6% (N = 69)

HIV or HCV Genotype

Case	Treatment Inconsistent With Guidelines	Participants Choosing Treatment Inconsistent With Guidelines
HIV Genotype Unavailable	EVG or RAL	20% (N = 152)
HCV Genotype 2, 3	SOF/LDV	16% (N = 212)
HCV Genotype 2, 3, 5, 6	GRZ/ELB	7% (N = 226)

5. Intent to Change Among Participants Differing From Guidelines



"Excellent simple review and confirmation of my choice"

"This tool could be a help when we don't have all the regimens available in our setting"

6. Conclusions

- This online decision support tool showed that clinicians' initial treatment plans for HIV/HCV coinfection **differed from HIV and HCV guidelines** for 36% of case scenarios
- Scenarios where clinicians' treatment plan was inconsistent with guidelines were:
  - SOF or TDF in patients with eGFR < 60 mL/min
  - DAAs and ART with drug–drug interactions
  - SOF/LDV or GRZ/ELB in unapproved HCV genotypes
  - EVG or RAL without knowing HIV genotype, or ABC in HLA-B*5701-positive patients
- Using an online tool **changed the intended treatment plan for many participants,** suggesting the tool's use can help optimize care of patients with HIV/HCV coinfection

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Gilead Sciences.

Variance Between Clinicians and Guidelines in the Management of HIV/HCV Infection: Results by Specialty

Zachary Schwartz, MSc, ELS*; Jenny Schulz, PhD*; Edward King, MA*; Susanna Naggie, MD, MHS†; Mark S. Sulkowski, MD‡
*Clinical Care Options, LLC, Reston, VA. †Duke University School of Medicine, Durham, NC. ‡Johns Hopkins University School of Medicine, Baltimore, MD.

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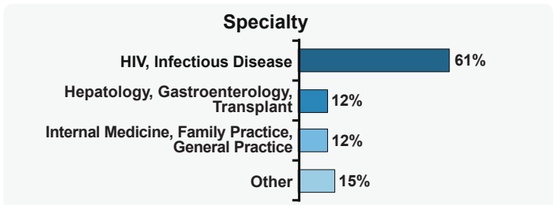
Poster 1579

1. Background

- In May 2018, we developed an online decision support tool based on recommendations from the AASLD/IDSA and DHHS guidelines for HIV/HCV patient scenarios
- This tool showed that clinicians' initial treatment plans **differed from HIV and HCV guidelines for 36% of case scenarios,**[1] based on:
  - Drug interactions
  - HIV or HCV genotype
  - Renal function
  - HLA-B*5701 status
- Current subanalysis examines treatment plans by specialty

2. Participant Demographics

- From August 2018 through August 2019, N = 683 participants entered **972** patient case scenarios



3. Methods

Online Decision Support Tool Provides Patient-Specific Recommendations From HIV and HCV Guidelines

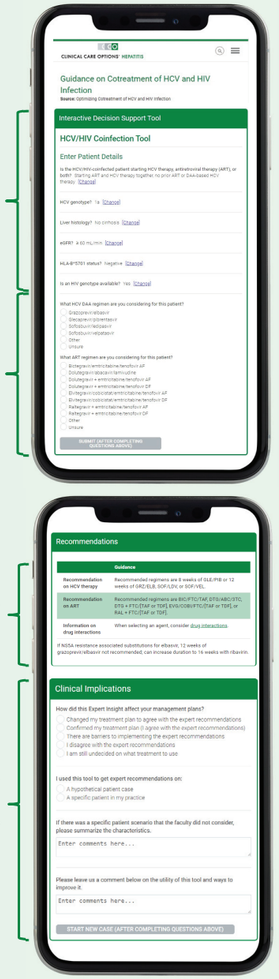
SCAN TO OPEN TOOL or visit clinicaloptions.com

1 Participant enters patient and disease characteristics:
- Current ART/HCV therapy
- HIV and HCV genotypes
- Liver histology
- Renal function
- HLA-B*5701 status

2 Participant indicates management plan

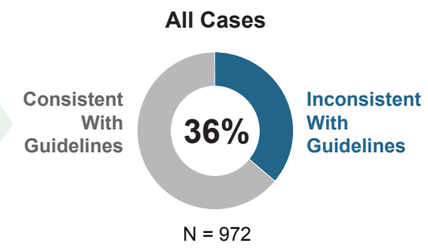
3 Participant receives guideline recommendations for that specific case

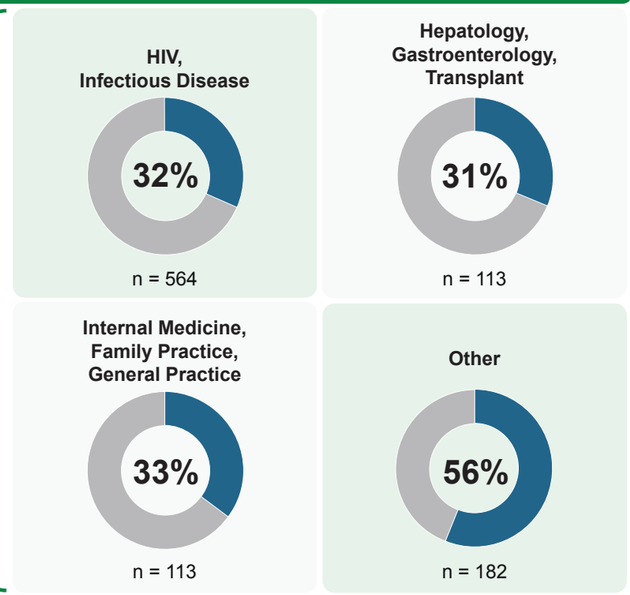
4 Participant is asked if guideline recommendations changed their management plan



Acknowledgements: This research is based on CME activities supported by an independent educational grant from Gilead Sciences.

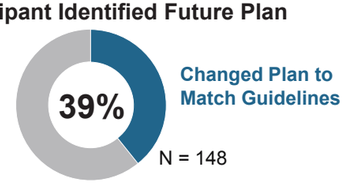
4. Baseline Management Plan by Specialty





5. Posteducation Impact

Subset of Cases Where Baseline Plan Differed From Guidelines and Participant Identified Future Plan



"Excellent simple review and confirmation of my choice"

"This tool could be a help when we don't have all the regimens available in our setting"

6. Conclusions

- Discordance between guidelines and clinicians' initial treatment plans for HIV/HCV coinfection was **consistent across key specialties of HIV/infectious disease, hepatology/gastroenterology/transplant, and internal medicine/family practice/general practice**
- Using an online tool **changed the intended treatment plan for many participants,** suggesting the tool's use can help optimize care of patients with HIV/HCV coinfection

Reference: 1. Schwartz. IDWeek 2019. Poster 2549. www.clinicaloptions.com/publications/2019/10_2019_hcvhivcoinfection

Disclosures: *None. †Funds for research support from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Tacere. ‡Funds for research support from AbbVie, Gilead Sciences, and Proteus Digital Health and consulting fees from AbbVie, Gilead Sciences, and Merck.

Point-of-Care Interactive Decision Support Tool Demonstrates Discordance Between Healthcare Practitioner Approaches and APASL Guideline Recommendations in the Management of HBV Infection

Tiffany Hensley-McBain, PhD[1]; Zachary Schwartz, MS[1]; Jennifer Blanchette, PhD[1]; Jenny Schulz, PhD[1]; Edward King, MA[1]; Grace LH Wong, MD[2]

[1]Clinical Care Options, LLC. [2]The Chinese University of Hong Kong.

CLINICAL CARE OPTIONS® HEPATITIS

APASL 2021 COLLABORATION AND CURE 4 - 6 FEB 2021

Produced in collaboration with: PCE, AHF Asian Health Foundation, American Liver Foundation — Your Liver. Your Life.

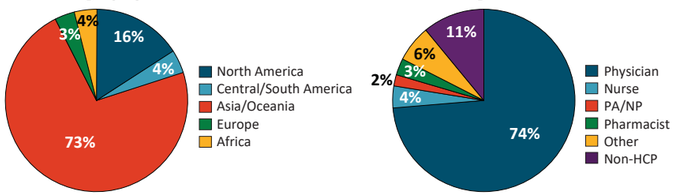
1. Background

Patient variables that inform HBV treatment candidacy and treatment selection are complex and interconnected. To aid healthcare practitioners (HCPs) in aligning management decisions with practice guidance, we developed a decision support tool. The tool enables users to specify a guideline (AASLD, EASL, or APASL) and enter patient variables: HBV DNA/ALT levels, liver fibrosis, etc. Users select their intended approach, after which the tool displays case-specific guideline recommendations.

2. Tool Users

- From March 2019 through November 2020, **N = 20,052** cases were entered into the tool, of which **n = 3511 specified APASL guidelines**
  - n = 2997 cases via the app (anonymous)
  - n = 514 cases via the CCO site (authenticated)

Authenticated Participants (n = 514)



3. Cases Entered

3511 Cases Selected APASL Guidelines → **2416** Cases With Clear Guideline Recommendation Reached → **1721** Cases Entered by Healthcare Practitioners

Of 1010 cases where participants specified:

- **58% were real patients**
- 42% were hypothetical cases

Of 1885 cases where HBeAg status and HBV DNA level were known:

40% HBeAg Positive	60% HBeAg Negative
50% HBV DNA ≤ 20,000	**47%** HBV DNA < 2000
50% HBV DNA > 20,000	**53%** HBV DNA > 2000

4. Online Decision Support Tool Provides Patient-Specific Recommendations

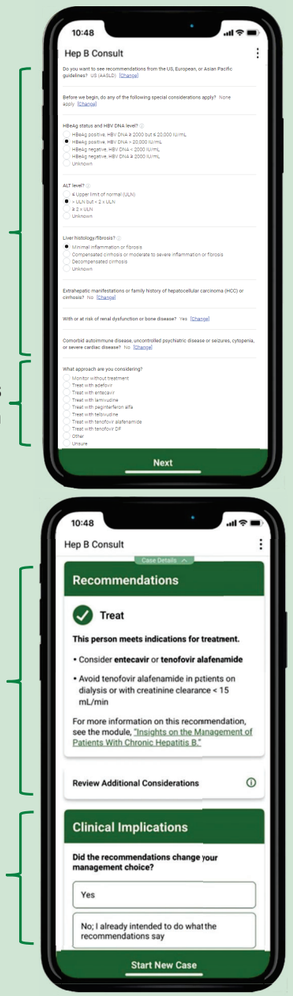
SCAN TO OPEN TOOL or visit clinicaloptions.com

1 **Participant enters patient and disease characteristics**

2 **Participant indicates management plan**

3 **Participant receives guideline recommendations for that specific case, including link to CME-certified module**

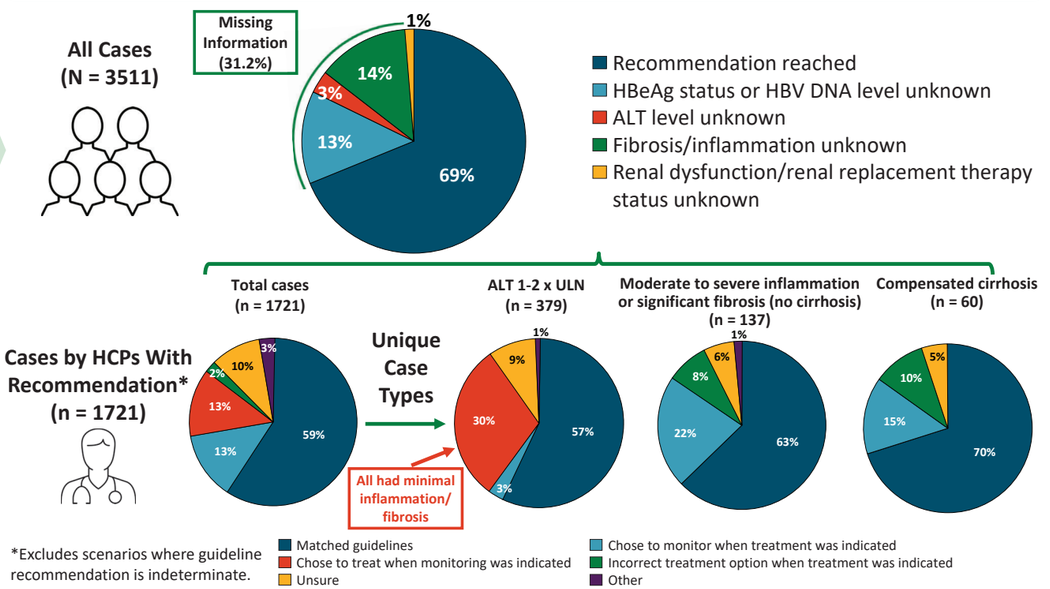
4 **Participant is asked if guideline recommendations changed his/her management plan**



Acknowledgements: This research is based on CME activities supported by an independent educational grant from Gilead Sciences.

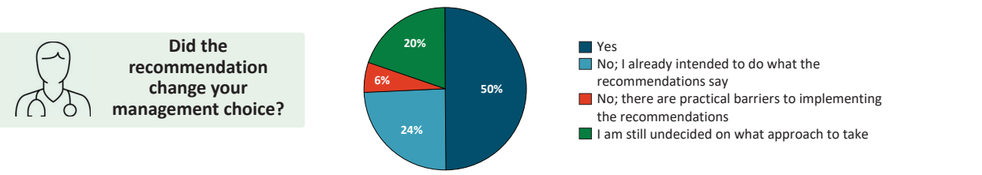
Disclosures: [1]None. [2]Consulting fees from Gilead Sciences and Janssen; funds for research support from Gilead Sciences; speaker bureaus for Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, and Roche.

5. Case Outcome and Intended Management Approach



6. Posteducation Impact

Subset of Cases Where Baseline Plan Differed From Guidelines and HCP Identified Future Plan (n = 307)



7. Conclusions

- This decision support tool showed that **users selected "unknown" for a variable necessary to reach a guideline recommendation for 31.2% of cases** → the information most often missing was the level of fibrosis/inflammation
- HCPs' initial HBV management plans **differed from guidelines for 41% of case scenarios** → cases in which the HCP chose to treat when monitoring was indicated and those in which the HCP chose to monitor when treatment was indicated were equally represented (13% each)
- Of cases in which the HCPs' intentions were inconsistent with guidelines, **49.8% indicated that they planned to change their approach** after being provided the recommendation by the tool

CLINICAL CARE OPTIONS®

A Point-of-Care Decision Support Tool Reveals Variance Between Clinicians and Experts in Selecting Among GLP-1 RAs in Type 2 Diabetes

ENDO 2021
Poster 4181

Zachary Schwartz, MSC, ELS[1]; Kiran Mir-Hudgeons, PhD[1]; Anne Roc, PhD[1]; Robert S. Zimmerman, MD[2]; Anne Peters, MD[3]
[1]Clinical Care Options, LLC. [2] Cleveland Clinic [3]Univesirty of Southern California

1. Background

To help clinicians understand GLP-1 receptor agonist (GLP-1 RA) therapies and their novel characteristics and to help them choose among GLP-1 RAs for patients with T2D, we developed an online tool where choice of treatment among GLP-1 RAs is guided by a panel of experts.

The goal was to provide real-time recommendations based on patient-specific characteristics and to identify variances between the treatment strategies of experts and community clinicians.

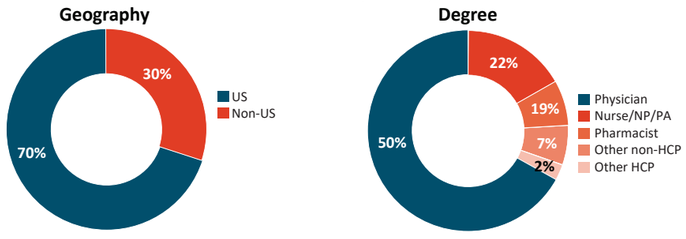
Five diabetes experts provided treatment recommendations for a combination of patient variables totaling 48 possible scenarios based on:

- A1C level
- CVD
- CKD
- Need for weight loss
- Retinopathy

2. Cases

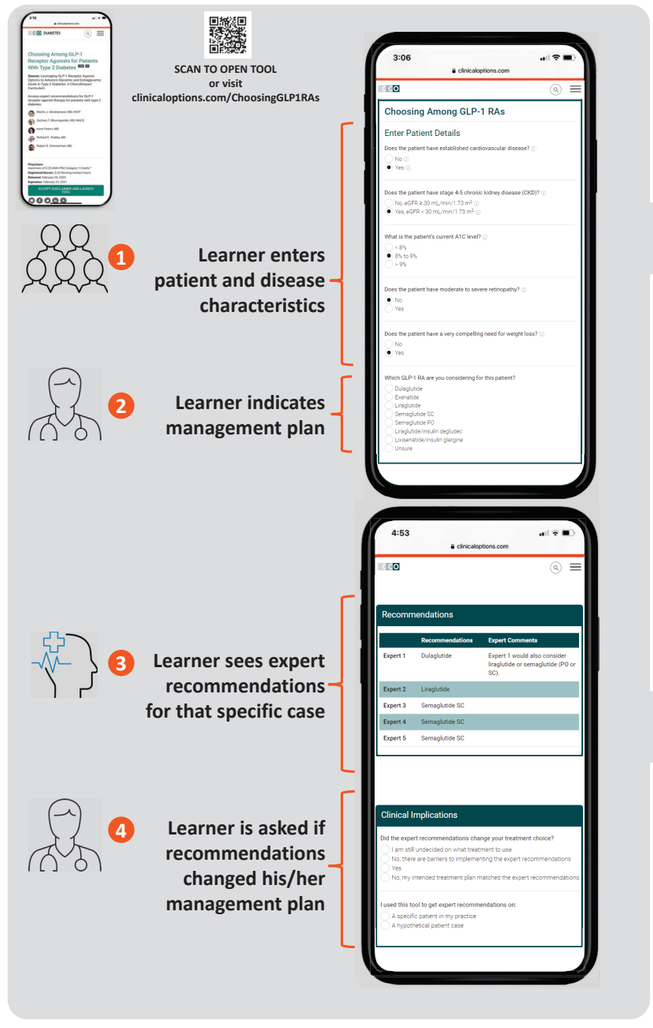
- From February through October 2020, **983 learners** entered **N = 1433** cases into the tool
  - n = 365 cases via the app (anonymous)
  - n = 623 cases via the CCO site (authenticated)

Authenticated Cases (n = 623)



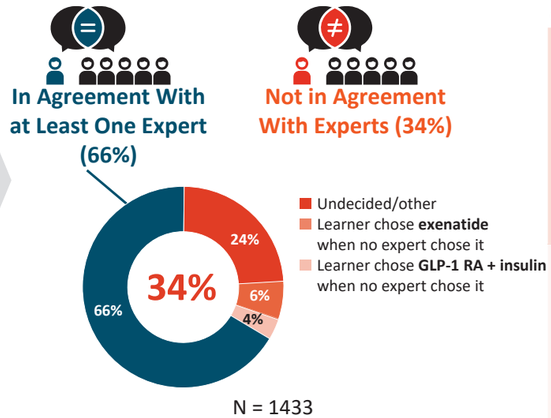
Of 584 cases where learners specified:
- **38% were real patients**
- 62% were hypothetical cases

3. Online Decision Support Tool Provides Patient-Specific Recommendations



4. Learners' Initial Choice of GLP-1 RA

All Cases

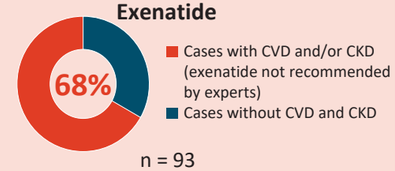


N = 1433

By Treatment

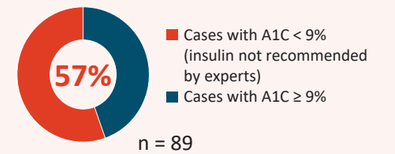
To explore this variance between learners and experts, we examined all cases where learners chose **exenatide** or chose a **GLP-1 RA + insulin**

All Cases Where Learner Chose Exenatide



n = 93

All Cases Where Learner Chose GLP-1 RA + Insulin

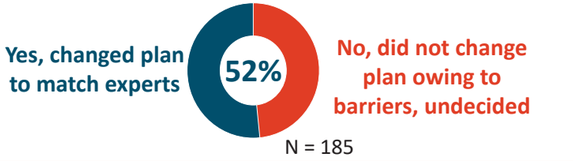


n = 89

5. Posteducation Impact

Subset of Learner Cases Where Baseline Plan Differed From Experts and Learner Identified Future Plan

Did the recommendation change your management choice?



N = 185

6. Conclusions

- Learners' initial choice of GLP-1 RA **differed from experts for 34% of case scenarios,** highlighted continuing gaps in clinicians' ability to select among GLP-1 RAs for T2D
- These cases of variance included:
  - Use of **exenatide** in patients with **CVD and/or CKD**
  - Use of GLP-1 RA + **insulin** in patients with **A1C < 9%**
- Of cases in which the learners' intentions differed from expert recommendations, **52% indicated that they planned to change their approach** after being provided the recommendation by the tool, suggesting the tool's use can help optimize care of patients with T2D

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Novo Nordisk Inc.

Disclosures: [1]None. [2]Consulting Fee; Self; Novo Nordisk. Grant Recipient; Self; Bayer, Inc., Merck, Novo Nordisk. Speaker; Self; LifeScan, Merck. [3]Consulting Fee; Self; Abbott Laboratories, Biorad, Eli Lilly & Company, Mannkind Corporation, Merck, Novo Nordisk, Zealand. Grant Recipient; Self; Dexcom, VTV Therapeutics. Stock Owner; Self; Omada Health, Stability Health, Pend.

CLINICAL CARE OPTIONS®

Diabetes Consult: Can an App Improve Healthcare Professionals' Selection of T2D Treatment for High-Risk Patients?

ADCES21

Zachary Schwartz, MSC, ELS[1]; Martin Abrahamson, MD, FACP[2]; Anne Peters, MD[3]

[1]Clinical Care Options, LLC. [2] Harvard Medical School. [3]Univesirty of Southern California.

1. Background

T2D management is shifting toward treating patients with therapies that align with their level of CV and end-organ risk. These shifts create gaps in knowledge and competence, especially as they relate to managing patients with comorbid CV and/or renal disease.

To measure how healthcare professionals choose among diabetes treatments in practice and to help them choose such treatments appropriately, we developed a decision support app in which healthcare professionals enter the characteristics of their patient and receive guidance on choice of treatment by a panel of experts.

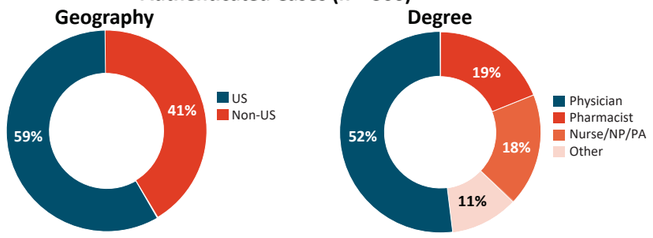
Five diabetes experts provided therapy recommendations for 18 unique patient case scenarios based on patient variables including:

- ASCVD
- Heart failure
- CKD
- Need for weight loss
- A1C
- eGFR
- Urine albumin level

2. Cases

- From December 2020 through April 2021, **434 learners** entered **673** cases into the tool
  - 313 cases via the app (anonymous)
  - 360 cases via the CCO site (authenticated)

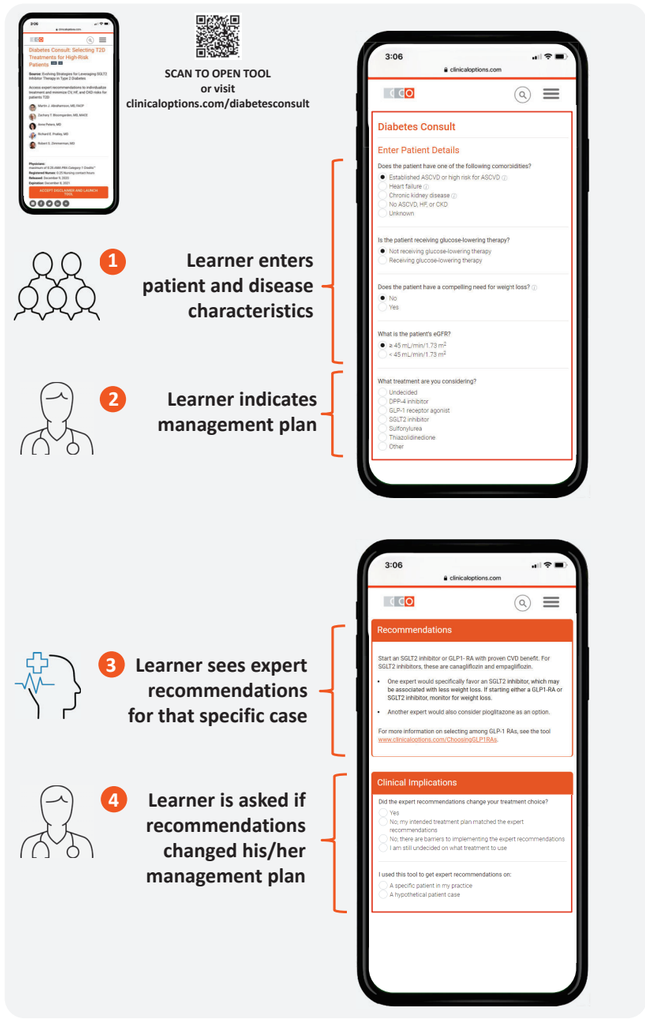
Authenticated Cases (n = 360)



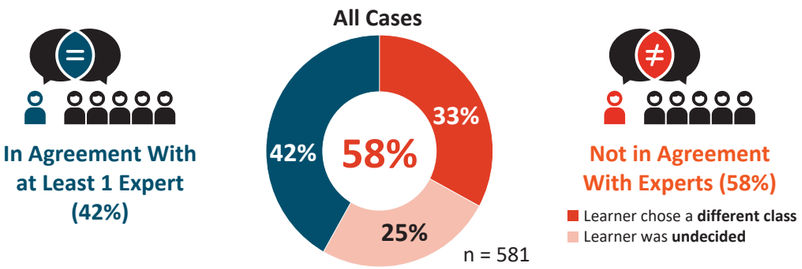
In 14% (n = 92) of all cases, learners selected a treatment before evaluating whether a patient had ASCVD, HF, or CKD

- **In these instances, learners were taught the importance of considering comorbid CV and/or renal disease**

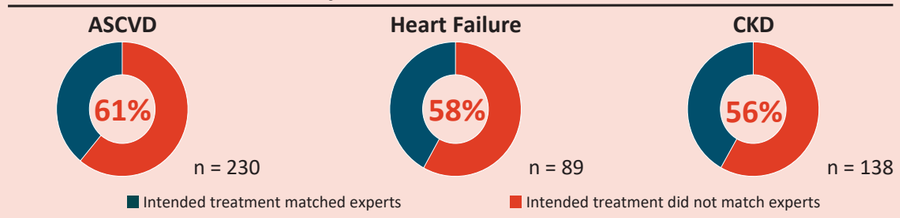
3. Online Decision Support Tool Provides Patient-Specific Recommendations



4. Learners' Initial Choice of Diabetes Treatment



By Comorbid Disease State



5. Posteducation Impact

Subset of Learner Cases Where Baseline Plan Differed From Experts and Learner Identified Future Plan

6. Conclusions

- Learners' initial choice of therapy **differed from experts for 58% of case scenarios,** highlighting continuing gaps in healthcare professionals' consideration of patient factors in choosing diabetes treatment and their ability to optimize treatment options for multiple patient scenarios.
- Of cases in which the learners' intentions differed from expert recommendations, **47% indicated that they planned to change their approach** after being provided the recommendation by the tool, suggesting the tool's use can help optimize care of patients with T2D.
- A point-of-care app can be part of an implementation strategy to positively influence practice behaviors.

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

Disclosures: [1]None. [2]Novo Nordisk, WebMD Health Services. [3]Abbott Diabetes Care, AstraZeneca, Dexcom, Insulet, Lilly, Medscape, Novo Nordisk, Omada Health (stock options), Teladoc (stock options), Vertex, Zealand.

Expert Advice on Managing Severe Asthma: An Interactive Decision Support Tool Provides Real-Time Expert Recommendations

AAAAI 2021
Poster 122

Zachary Schwartz, MSC, ELS[1]; Carolyn Skowronski, PharmD[1]; Anne Roc, PhD[1]; Bradley E. Chipps, MD[2]; Nicola A. Hanania, MD, MS[3]; Linda Rogers, MD[4]; Eileen Wang, MD, MPH[5]; and Michael E. Wechsler, MD, MMSc[6]

[1]Clinical Care Options, LLC. [2]Capital Allergy & Respiratory Disease Center. [3]Baylor College of Medicine. [4]Mount Sinai Health System. [5]University of Colorado School of Medicine. [6]National Jewish Hospital.

1. Background

To help clinicians make personalized recommendations for patients with severe asthma, we developed an online tool based on treatment choices from 5 experts for customizable patient scenarios.

The goal was to provide real-time recommendations for severe asthma based on patient-specific characteristics and to identify variances between the treatment strategies of experts and community clinicians.

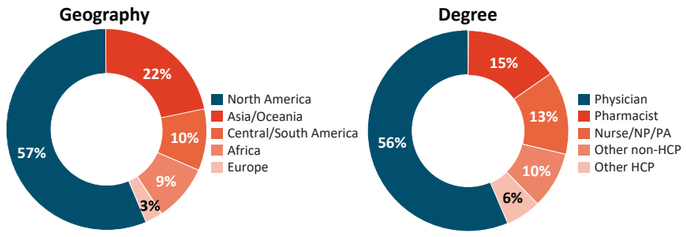
Five asthma experts provided treatment recommendations for a combination of patient variables totaling 70 possible scenarios based on:

- Oral corticosteroid use
- Exhaled nitric oxide
- Blood eosinophils
- Allergic phenotype
- IgE
- Other allergies/comorbidities
- Body weight
- Childbearing potential

2. Learners

- From August 2020 through January 2021, **458 learners** entered **N = 866** cases into the tool
  - n = 215 cases via the app (anonymous)
  - n = 651 cases via the CCO site (authenticated)

Authenticated Cases (n = 651)



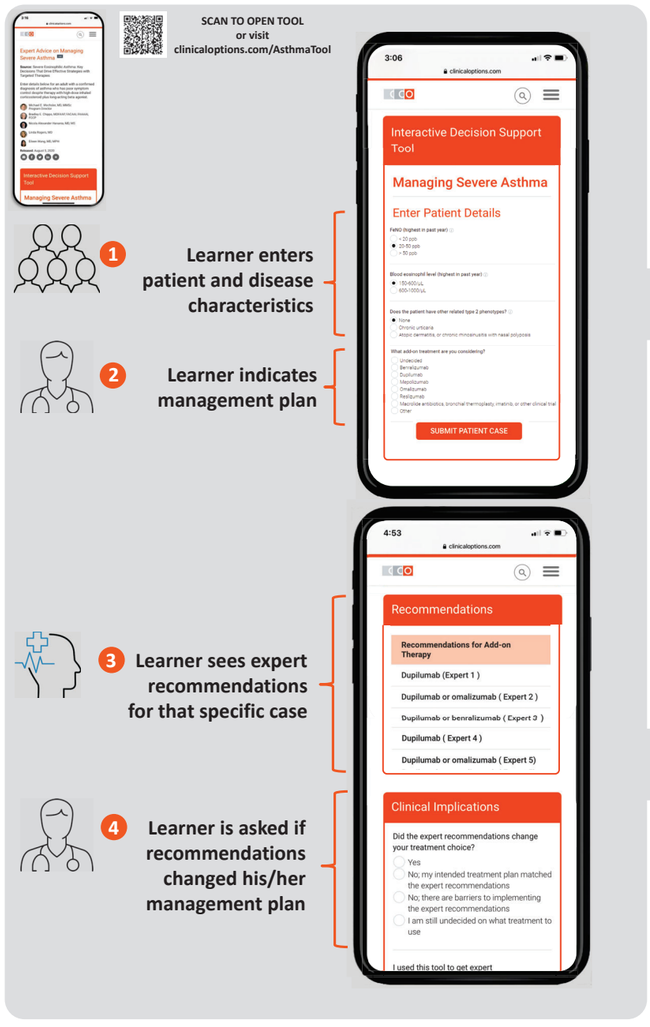
3. Cases Entered

866 Cases → **220** Cases With Severe Asthma

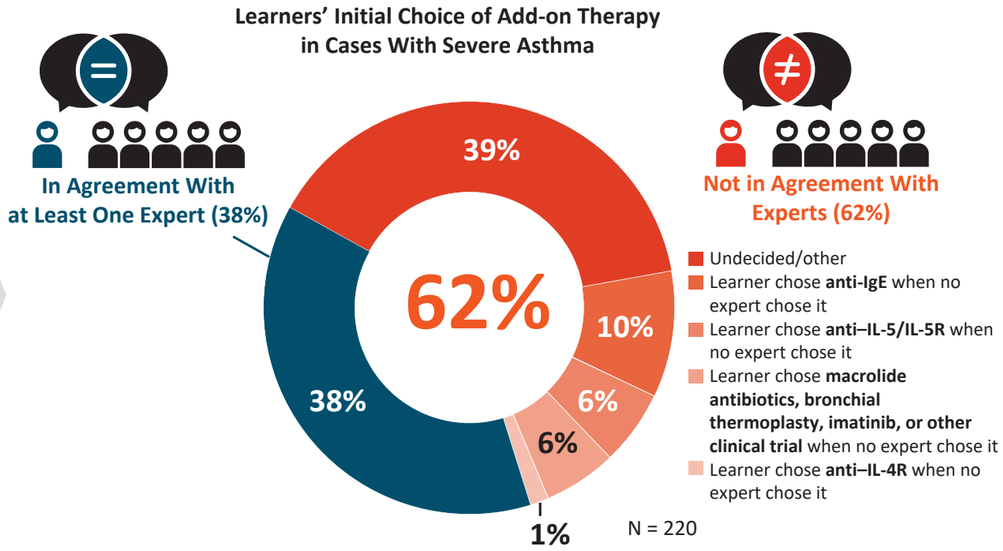
Of 96 severe asthma cases where learners specified:

- **34% were real patients**
- 66% were hypothetical cases

4. Online Decision Support Tool Provides Patient-Specific Recommendations

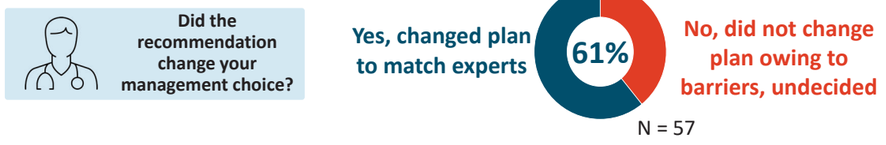


5. Intended Management Approach



6. Posteducation Impact

Subset of Learner Cases Where Baseline Plan Differed From Experts and Learner Identified Future Plan



7. Conclusions

- This online decision support tool showed that learners' initial choice of add-on therapy for severe asthma **differed from experts for 62% of case scenarios**
- Of cases in which the learners' intentions differed from expert recommendations, **61% indicated that they planned to change their approach** after being provided the recommendation by the tool, suggesting the tool's use can help optimize care of patients with severe asthma

Acknowledgements: This research is based on CME activities supported by independent educational grants from Novartis Pharmaceuticals Corporation and from Sanofi Genzyme and Regeneron Pharmaceuticals.

Disclosures: [1]None. [2]Consulting fees and fees for non-CME/CE services from AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi Genzyme. [3]Funds for research support from AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Gossamer Bio, Novartis, and Sanofi Genzyme; consulting fees from Boehringer Ingelheim, GlaxoSmithKline, Mylan Novartis, and Sanofi Genzyme; and fees for non-CME/CE services from GlaxoSmithKline, Mylan, and Sanofi Genzyme. [4]Funds for research support from AstraZeneca and Sanofi; consulting fees from AstraZeneca, Novartis, and Sanofi; and other financial or material support from AstraZeneca. [5]Fees for non-CME/CE services from AstraZeneca and funds for research support from Genentech and GlaxoSmithKline. [6]Funds for research support from AstraZeneca, Regeneron, Sanofi Genzyme, and Teva and consulting fees from AstraZeneca, Cohero, Equillium, Genentech, GlaxoSmithKline, Novartis, Regeneron, resTORbio, Sanofi Genzyme, and Teva.

Add or Switch? Major Depressive Disorder Interactive Decision Support App Reveals Discordance Between Expert and Community Clinicians

CLINICAL CARE OPTIONS®

APA 2021
Abstract 5354

Zachary Schwartz, MSC, ELS[1]; Kiran Mir-Hudgeons, PhD[1]; Anne Roc, PhD[1]; Leslie Citrome, MD, MPH[2]; Christoph U. Correll, MD[3]; Rakesh Jain, MD, MPH[4]; Roger McIntyre, MD, FRCPC[5]; Michael E. Thase, MD[6]

[1]Clinical Care Options, LLC. [2]New York Medical College. [3]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell.
[4]Texas Tech Health Sciences Center, School of Medicine.[5]University of Toronto. [6]Perelman School of Medicine at the University of Pennsylvania

1. Background

In many patients with major depressive disorder (MDD), remission is not achieved with the initial antidepressant. Most guidelines recommend switching to or adding another treatment for residual symptoms, but healthcare professionals (HCPs) often fail to measure response or adjust treatment.

To address this practice gap and to help HCPs make individualized treatment recommendations for such patients, we developed a decision support app based on recommendations from 5 experts.

2. Methods

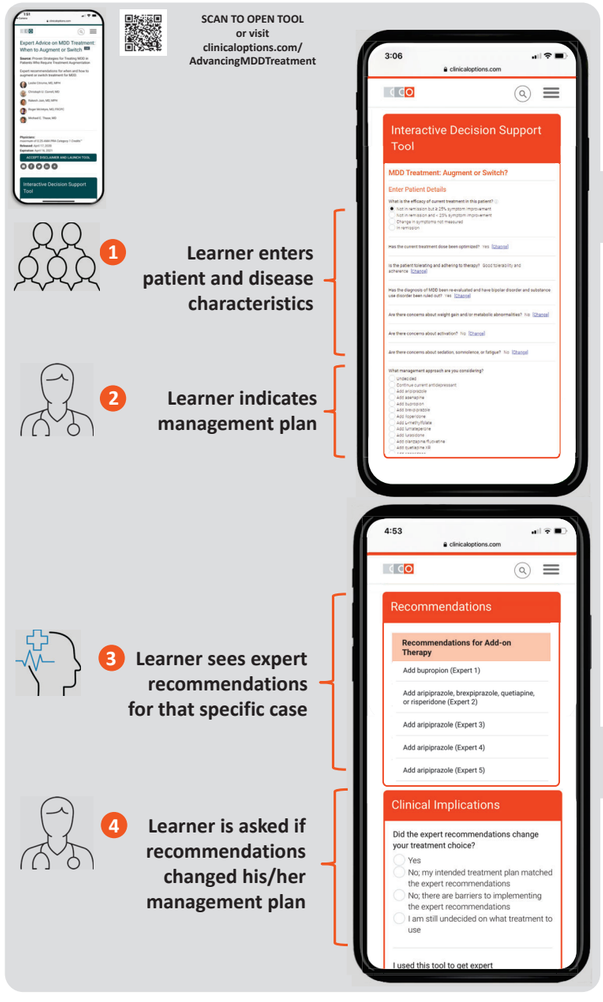
In March 2020, 5 depression experts provided treatment recommendations for 45 unique MDD case scenarios based on an agreed upon, simplified set of patient variables:

- Efficacy of current treatment
- Tolerability of/adherence to current treatment
- Concerns about sexual dysfunction, weight gain/metabolic abnormalities, activation/sedation

3. Cases

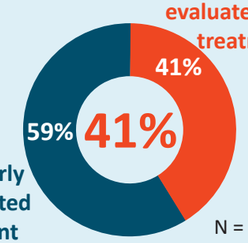
- From April 2020 to March 2021, **534 learners** entered **781 unique patient case scenarios**
  - n = 394 cases via the CCO site (authenticated)
  - n = 140 cases via the app (anonymous)
- **87% of learners were US-based** and 13% were from outside the US
- **62% of learners were physicians,** 20% were nurses/NP/PA, 11% were pharmacists

4. Online Decision Support Tool Provides Patient-Specific Recommendations



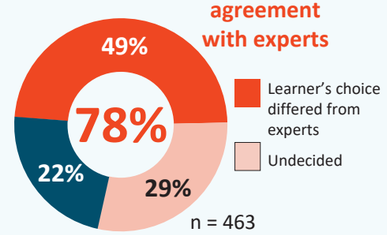
5. Intended Management Approach

Did Learners Properly Evaluate Need for Treatment Adjustment?



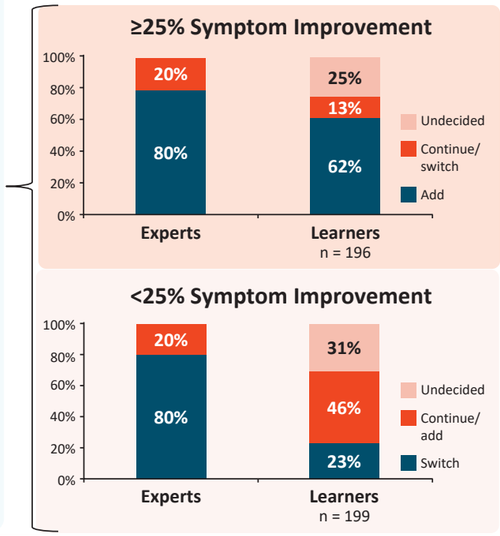
- In **41% of all cases,** participants selected a treatment plan **before evaluating the need for treatment adjustment** via the following strategies:
  - Measure change in symptoms
  - Dose optimization
  - Assess adherence/tolerability
  - Re-evaluate MDD diagnosis

Did Learners' Treatment Decisions Align With Experts?



- In **78% of cases,** where a treatment decision was made, participants selected a treatment plan that differed from experts

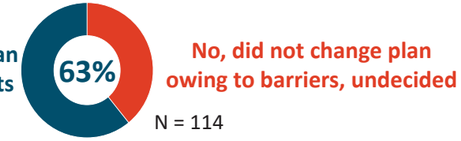
In Patients Not in Remission, Did Experts and Learners Add or Switch?



6. Posteducation Impact

Subset of Learner Cases Where Baseline Plan Differed From Experts and Learner Identified Future Plan

Did the recommendation change your treatment choice?



7. Conclusions

- This point-of-care app can be part of an implementation strategy to positively influence practice behaviors: Clinicians can see if their intended treatment choice is congruent with a panel of experts and reconsider their plans as appropriate. The app revealed—and helped learners correct—key gaps:
  - Learners often failed to practice measurement-based care by **neglecting to evaluate the need for treatment adjustment** in 41% of case scenarios
  - Of cases where a treatment decision was made, learners' intentions **differed from experts** in 78% of case scenarios

Acknowledgements: This research is based on CME activities supported by an independent educational grant from Otsuka and Lundbeck Alliance.

Disclosures: [1]None. [2]Consulting Fees: Acadia, Alkermes, Allergan, Avanir, BioXcel, Eisai, Impel, Indivior, Intra-Cellular Therapies, Janssen, Lundbeck, Luye, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Sage, Shire, Sunovion, Takeda, Teva, and Vanda; Speaker Bureau: Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Sage, Shire, Sunovion, Takeda, and Teva; Ownership Interest: Bristol-Myers Squibb, Johnson & Johnson, Lilly, Merck, and Pfizer. [3]Research Grants: Janssen/Johnson & Johnson and Takeda; Consulting Fees: Alkermes, Allergan, Angelini, Gedeon Richter, Gerson Lehrman Group, Intra-Cellular Therapies, Janssen/Johnson & Johnson, LB Pharma, Lundbeck, MedAvante-ProPhase, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva; Non-CME/CE services: Alkermes, Allergan, Angelini, Gedeon Richter, Janssen/Johnson & Johnson, Lundbeck, MedAvante-ProPhase, Otsuka, Pfizer, Recordati, Sumitomo Dainippon, Sunovion, and Takeda. [4]Consulting Fees: Acadia, Alfasigma, Alkermes, Allergan, Eisai, Evidera, Impel, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine, Osmotica, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Supernus, Takeda and Teva; Non-CME/CE Services: Alkermes, Allergan, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Takeda, Teva and Tris Pharmaceuticals; Research Grants: Allergan, Lilly, Lundbeck, Otsuka, Pfizer, Shire, and Takeda; Spouse/partner Consulting Fees: Lilly, Otsuka, Pamlab, and Sunovion; Spouse/partner Non-CME/CE services: Lilly. [5]Research Grants: CIHR/GACD/Chinese National Natural Research Foundation; Speaker/Consulting Fees: Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Eisai ,Intra-Cellular, AbbVie; CEO: Champignon. [6]Research Grants: Acadia, Allergan, Axsome, Intracellular, Johnson & Johnson, Otsuka, and Takeda; Consulting Fees: Acadia, Akili, Alkermes, Allergan, H. Lundbeck, Jazz, Johnson & Johnson, Merck, Otsuka, and Pfizer.

Educational Impact of the Flipped Classroom Model in the Setting of Hepatitis C

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CLINICAL CARE OPTIONS® HEPATITIS

PIM Postgraduate Institute for Medicine

Background

- The rapid pace of drug development has created 2 parallel challenges for clinicians treating patients with chronic hepatitis C virus (HCV) infection: *synthesizing* the data on new treatments and *applying* these data to clinical practice
- To meet these challenges, Clinical Care Options (CCO) used a "flipped classroom" educational approach, where learners reviewed online homework in advance (prework) and then spent their live classroom time applying knowledge and skills through the use of case scenarios. Reinforcing didactic material was also presented in the live classroom

Methods

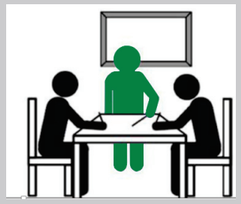
- We compared learning for individuals who completed homework before the live workshop or Webinar (flipped learners) vs those who did not complete homework (live-only learners)

Synthesis: Foundational Homework

Self-directed review of didactic education

- Online, text-based, CME-certified activity on hepatitis C management with slide thumbnails and level 4 outcomes assessment, including reinforcement after posttest
  - Core faculty: Mark S. Sulkowski, MD; Nancy Reau, MD
- To increase completion, preregistrants were reminded to complete this foundational homework to get the most out of the upcoming live education

Application: Live Workshop or Webinar



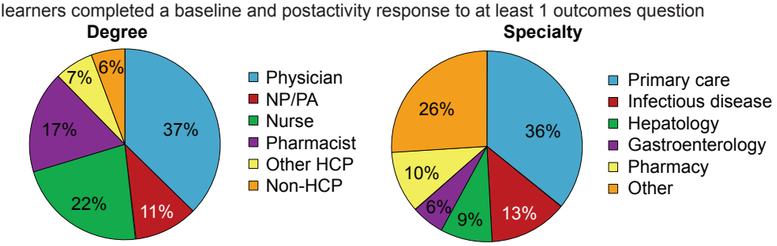
Faculty-led skill development, discussion, and interaction with peers

- Case-based CME-certified workshops, including polling audience questions and level 4 outcomes assessment, held as in-person, local and regional meetings across the United States, as well as live Webinars for learners unable to attend in person
  - Core faculty: Mark S. Sulkowski, MD; Nancy Reau, MD; Ira M. Jacobson, MD

- Learning was assessed using objective level 4 outcomes with questions measuring competence immediately before and immediately after the live workshop or Webinar
  - Competence was assessed for each of 3 learning objectives; results were pooled among 2 cohorts who participated in a live workshop or Webinar in either the spring (cohort 1) or fall (cohort 2)
- Learning was also compared among individuals who participated live in-person vs those who participated in live Webinars

Participant Demographics

- 879 US clinicians, mostly physicians, attended one of the live in-person workshops or Webinars (May-October 2015)
- 639 of these learners completed a baseline and postactivity response to at least 1 outcomes question

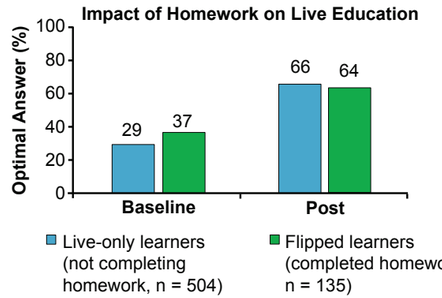


- 21% of the live in-person workshop or Webinar participants indicated they had completed the online foundational homework
  - In a similar CCO flipped classroom activity for oncology nurses, 45% of learners completed self-directed homework comprising 4 interactive, CE-certified online video segments[1]

Acknowledgments: This research is based on activities supported by an educational grant from Bristol-Myers Squibb.
Disclosures: The authors of this presentation have no financial relationships or conflicts of interest to report.
Reference: 1. Obholz KL, Brady ED, DeMeyer ES, Bowser AD. Using a flipped classroom design to educate oncology nurses. Alliance for Continuing Education in the Health Professions (ACEHP) Conference; Alexandria, Virginia; January 13-16, 2016.

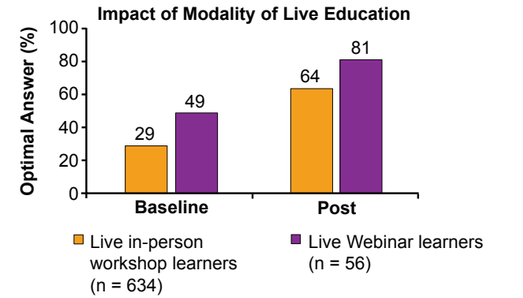
Impact of Foundational Homework

- Learners who completed foundational homework were better prepared to answer questions related to program objectives at the start of the live workshop or Webinar
  - Higher baseline competence at live events in flipped learners vs live-only learners
- No substantial difference in immediate posteducation scores among flipped learners vs live-only learners



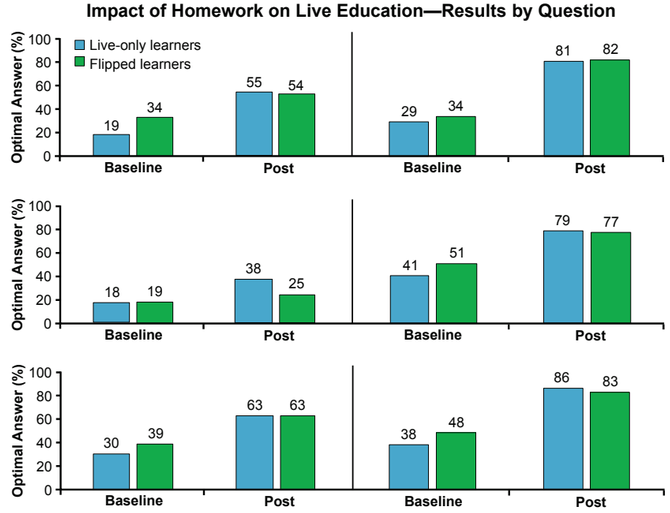
Impact of In-Person Workshop vs Webinar

- Learners who participated in live Webinars demonstrated higher competence both before and immediately after the live education than did learners who participated in live in-person workshops



Results by Learning Objective and Cohort

Learning Objective	Cohort 1	Cohort 2
Integrate data from clinical trials, approved indications, and expert guidance to select optimal HCV regimens for harder-to-treat HCV patients	Impact of Homework on Live Education—Results by Question	
Modify HCV management strategies in specific populations to reflect practice-changing developments in a timely manner		
Implement practical on-treatment management strategies to manage adverse events and optimize outcomes with HCV therapy in difficult-to-treat HCV patients		



Conclusions

- Flipped classroom homework better prepared clinicians for live education
  - Future studies could examine persistence of competence in flipped learners vs live-only learners
- Participants in live Webinars had higher competence post education than did participants in live in-person workshops
  - Live Webinars may be a good option for flipped classroom education or standard education
  - Future studies could examine whether live Webinar learners are more likely to complete online foundational homework
- Demographics showed higher rate of homework completion in CCO oncology flipped classroom program (*video-based* homework and *nursing* audience) than current CCO hepatology flipped classroom program (*text-based* homework and *physician* audience)
  - Among physicians, different approaches may be needed to increase completion of foundational homework, such as incentives, competitions/leaderboards, or scheduled time to complete homework before the live education

Social Media Behavior and Attitudes of US Physicians: Implications for Continuing Education Providers

January 2017

A Clinical Care Options (CCO) White Paper

Social media is making greater inroads into both the formal and informal education that physicians seek out and receive online. In a recent survey conducted by CCO, more than 50% of the US physician learners stated they have accessed social media for professional purposes, and among those, 61% have used it to learn about and access new CME opportunities. Meanwhile, CME activities are becoming better integrated with social media via alerts about activities, posting of news and clinical information, and related opinions and advice. However, not all physicians use social media for education or other purposes related to their occupation, citing concerns and barriers such as privacy, appropriateness, and time constraints as reasons for abstaining. In this white paper, we outline key points of interest to the CME community, and propose an approach to further the integration of social media with CME that is pragmatic, is practical, and takes into account the need for further research and innovation as online CME evolves.

How Social Media is Changing Physician Education

It has been 20 years since the first so-called social media platforms emerged online, allowing users to share content and opinions while interacting with other participants in ways that were never before possible. Today, social media is part of the everyday fabric of society, from Millennials who are "digital natives" (ie, they have had computers since the crib) to members of the Greatest Generation, who remember life without TV but now might use Facebook to remain connected with their great grandchildren. Eight years ago, only 24% of Americans had a social media profile; today, that number has ballooned to 78%.[1]

Physicians are no different from the average online citizen; they have taken to social media just like everyone else. What is unique, however, is how the education of physicians is being transformed via social media, sometimes in subtle ways and sometimes in ways that are transformative. Today, a well-timed tweet can help direct a physician to conference coverage or spur participation in a new certified online activity. Clinicians who are active on social media sites report that they not only appreciate finding relevant medical information but also enjoy the ongoing opportunities to engage directly with peers and experts to learn how that information applies to clinical practice.[2]

Social media platforms can be the delivery mechanism for an educational activity, but in some respects, participating in the social media platform is itself becoming the education. Participants can learn by tracking other participants' statements, queries, and responses; they can provide their own ideas or treatment approaches and get immediate feedback; and in many cases, they can receive near instantaneous fulfillment of tailored responses related to a specific gap in their ability to diagnose or treat a patient.

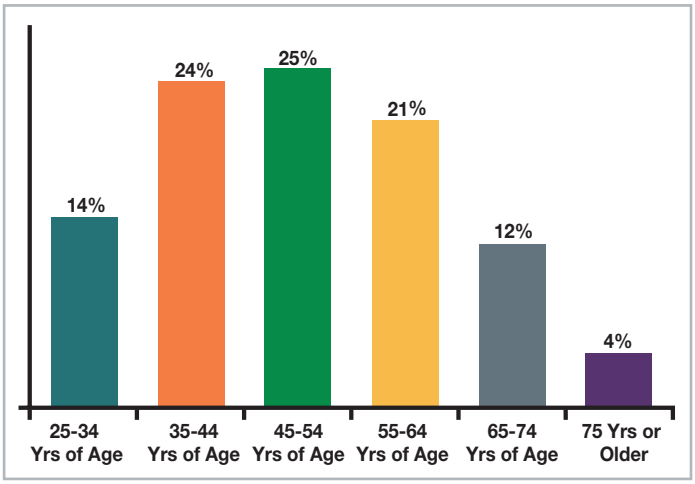
Social media networks are the conduit that allows physicians to create these "personal learning networks"[3]—that is, a constellation of people and resources that can be accessed to answer very specific queries related to patient care. For example, some physicians are connecting with one another though social media groups, particularly on Facebook, establishing bonds and connections that facilitate not only networking and socialization but also the sharing of information that helps group members diagnose and treat challenging cases. Most of these communities are built around a forum where physicians can share knowledge relevant to their specialty and discuss professional issues with like-minded peers whom they consider credible.[4]

U.S. Physician Survey: Social Media

With that backdrop, CCO sought to study the evolution and adoption of social media and its utility in medical education among our physician membership. We sought to take stock of current social media utilization and trends. We also wanted to listen carefully to our physician learners in order to understand how medical educators could fine-tune and evolve existing social media initiative and, of importance, do so in a way that is sensitive to physicians' concerns about privacy and appropriateness of social media for professional purposes. The results, as described in this white paper, were eye-opening and may have important implications for the CME community at large.

To learn more about the social media behaviors and attitudes of the learner population, a 29-question survey was sent to US physicians who are members of the Clinical Care Options (CCO) Web site. More than 200 responses were received. Survey respondents tended to be mid-career, with 25% reporting they were in the range of 45-54 years of age, although many younger and older physicians responded as well (Figure 1).

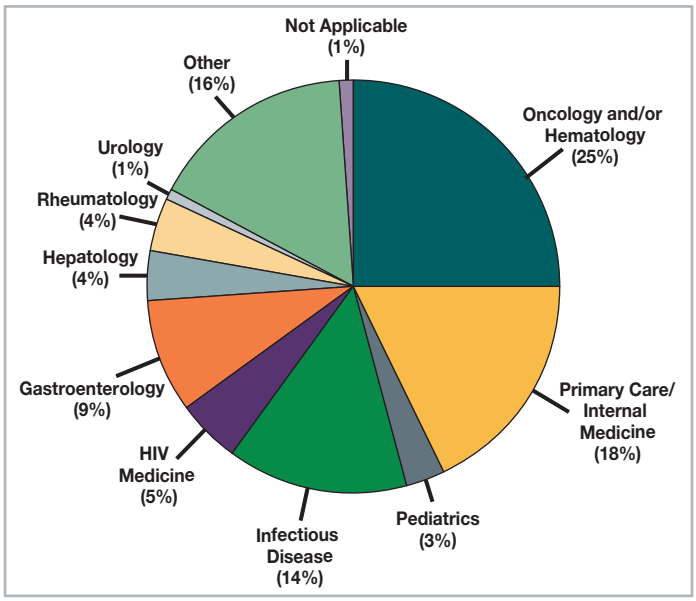
Figure 1. Survey respondents by age.



Respondents reported a wide variety of specialties, reflecting the diverse CCO membership attracted through specialty-specific portals. The largest group was hematology/oncology, which accounted for 25% of the overall survey takers (Figure 2) and represents one of the most rapidly changing medical specialties. Approximately one third of the physicians indicated their practice setting as an academic medical center, whereas the rest reported a variety of community (and some public/government) affiliations. Most work in an urban practice setting (65%), and others worked in suburban (26%) and rural (5%) settings.

The survey sample also skewed more heavily male, at 63% of respondents, which has been seen in other surveys and may in part reflect the demographic breakdown to be expected given the age range of respondents; that is, male physicians tend to be overrepresented in older age ranges.[5]

Figure 2. Survey respondents by specialty.



Social Media Usage: Personal vs Professional

One key point evaluated through the study was how many physician members use social media for *personal engagement vs occupational or professional purposes,* such as accessing CME, seeking medical/conference information and news, or engaging in discussions with colleagues.

Overall, 71% of physicians reported using social media for personal reasons, with women more likely to use it in this manner compared with men (76% vs 68%, respectively); usage was very high among 25-34 year olds (90%) and, as might be expected, trended downward for older age groups. Even among physicians 65 years of age or older, however, usage was still fairly high at 56%.

More than one half (54%) also use social media professionally, with use again skewing more heavily to younger members (63% of 25-34 year olds). In fact, there seems to be somewhat of a "digital divide" in the learner population, with 64% of 25-44 year olds reporting using social media in this way vs just 48% of those 45 years of age or older (Table).

Table. Self-Reported Use of Social Media for CME and Other Occupational/Professional Purposes

	Aged 25-44 Yrs		Aged 45+ Yrs	
	n	%	n	%
Yes	52	64	59	48
No	25	32	63	52
Unsure	4	5	2	2

This social media age gap was even more dramatic in a survey of Canadian oncologists reported in the *Journal of Oncology Practice,* with social media use at 93% for respondents aged 25-34 years and just 39% for those aged 45-54 years.[6] The authors warned that such a dramatic rift could lead to "critical gaps in communication, collaboration, and mentorship."[7]

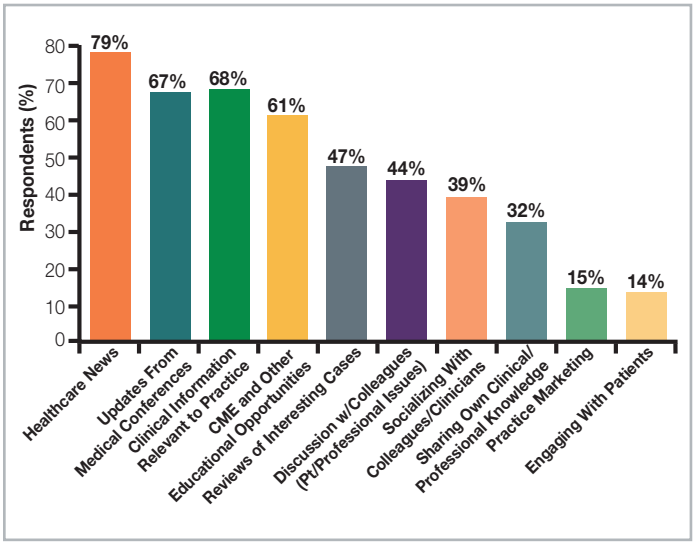
In addition, we observed a significant gender difference whereby 67% of our female respondents reported occupational social media use compared with just 46% of male respondents. At first glance, this should not be surprising as, in the population at large, women have traditionally been more likely to use social media than men. However, this social media gender gap has now narrowed to the point where men today are participating in social media almost as frequently as women,[8] but hints of differential participation by gender remain in these data.

Professional use of social media by physicians varies by platform. Facebook, the most popular platform, skews more toward personal use: Among those physicians in the survey who said they do frequent social media, 46% reported they used Facebook for personal reasons, only 3% used it strictly for professional purposes, but a fairly substantial 29% said they use it for both. LinkedIn, the networking site designed for business, is frequented by 67% of social media–savvy physicians, most of whom (not surprisingly) cite professional reasons for using it. Twitter, although not as popular overall, has a respectable number of physicians who report using it for professional purposes.

What Do Physicians Get From Social Media, Professionally?

The clear winners are news, conference updates, CME notifications, and other *passive* forms of participation. Although many people mistakenly believe that social media is defined by social interaction,

Figure 3. Professional benefits of social media as reported by physicians.



the vast majority of social media use is all about passively consuming news feeds and browsing friends' profiles rather than sharing or promoting original content.[9] Moreover, the informal "90-9-1 Rule" for online communities states that 90% of users "lurk" and never contribute, 9% occasionally contribute, and 1% account for the vast majority of contributions.[10]

This study reflects that rule of thumb, to some degree. A full 61% of our study participants said they used social media to find out about new CME opportunities, 66% cited medical conference information as a key benefit, and 79% said reading healthcare news was a key part of their social media experience. By contrast, discussion, sharing, and networking activities ranked much lower (Figure 3).

Content is not randomly dumped into social networks for physicians to stumble upon. It is fairly well established now that the most powerful forms of social media "advertising" are recommendations from a friend or trusted colleague.[11] The same principle applies to the recommendation of clinical content. One physician who responded to the survey put it this way: "Sometimes on Twitter, or via my personal use of Facebook (by being friends with people I went to medical school/residence/fellowship with), I'll find interesting articles, especially regarding the more policy/social/general news aspects of medicine."

CME-Focused and Physician-Focused Social Media Sites

Clinically focused social networks like Doximity, SERMO, and QuantiaMD have offered CME in various forms. For example, Doximity offers *AMA PRA Category 1 Credit* to clinicians who read CME-eligible articles and submit a credit claim request. QuantiaMD offers access to a library of online CME programs produced and accredited by third parties. HealthTap, a smaller and somewhat lesser known network, offers CME credit to physicians who collaboratively discuss and solve challenging medical cases in a "Global Rounds" virtual space.

Although most of the physicians in the survey do not regularly use these clinically focused social networks, many have at least tried them, and small subsets of physicians who do access social media are regular users of SERMO (23%), Doximity (24%), and QuantiaMD (20%). Keep in mind, however, that one half of the physicians in the survey said that they did not access social media at all for professional purposes, and therefore, the actual percentage of physicians who regularly use these services likely is much smaller.

Regarding those physicians who have not used social media professionally, a substantial minority stated they had interest in trying some in the near future, particularly those with a clinical focus, such as Doximity (39%), SERMO (30%), and QuantiaMD (26%), which were ranked much higher than Facebook (16%) and Twitter (7%).

What have you learned via social media?

Based on physician responses to the CCO Social Media Survey

- Blood pressure management in the elderly
- The method to morcellate fibroids in a bag
- Current updates on the Zika virus
- Resistant bacteria
- Just read about the new quadrivalent flu vaccine
- The validity of liquid biopsy
- Learning the astrocytes in brain take glucose actively
- Perceptions related to pre-exposure prophylaxis
- Updates on newer regimens for HIV
- ASCO abstract updates/comments
- Upcoming conferences and local meetings
- New clinical guidelines
- Potentially better treatments based on clinical experience
- Treatment options that may be useful for palliation
- Upcoming new drug approvals
- Treatment of a rare side effect

Twitter, Medical Conferences, and Journal Clubs

Physician advocates of Twitter say the platform, which is based on the sharing of brief "tweets" limited to 140 characters, is ideal for networking and education.[12] One of the most significant developments in social media–driven physician learning is the use of Twitter to rapidly and broadly disseminate the results of key studies and other developments that occur at medical conferences. The short, rapid-fire nature of the tweet makes it ideally suited to conference updates from attendees and CME providers alike.

Tweet volume during conferences has increased in recent years. For example, tweet volume surged 83% from the 2011 to 2012 American Society of Clinical Oncology (ASCO) meeting.[13] Moreover, the demographics of those tweeting about meetings have shifted: In 2012, biotech analysts were the primary tweeters at the American Urological Association, but by 2013, urologists themselves had taken over the top spot.[14]

Twitter use in the CCO survey of physicians skewed toward the mid-career physicians (aged 45-54 years), of whom 87% reported using it for personal or professional reasons compared with 50% of those aged 25-34 years. When asked whether they follow major medical conferences via Twitter, 52% of the 45-54 year olds said they followed tweets and/or tweeted themselves compared with 37% overall. These data suggest that approximately one third of physicians use Twitter as a means of keeping abreast with medical conference updates.

Twitter has also made waves for its use as a vehicle for virtual journal clubs,[15] allowing for dramatically expanded participation compared with a traditional journal club, longer time to dissect and discuss a paper in depth, and insights from a wide variety of international participants and even the authors themselves. However, such usage still seems experimental and, in some cases, has not produced the hoped-for results. For example, our physicians said:

- *"Once a year, we have a Twitter chat to disseminate information but find that it does not reach enough [people] or the right people."*
- *"I've tried to have a 'professional' Twitter and Instagram to share thoughts and articles, but it's slow going. Mostly because it takes not an insignificant amount of time to curate meaningful things to post, and I am still very busy with training. It's most useful to follow at conferences."*

Barriers: Physician Concerns and Institutional Barriers

Resistance to social media is tied to specific barriers related to professional and patient issues. The most commonly cited reasons why physicians do not use social media platforms are concerns about personal privacy (48%) and concerns about patient confidentiality (47%), although some said they did not have enough time, did not think it was appropriate, or simply were not interested. Institutional barriers are an additional consideration; one physician stated that the hospital does not allow use of social media, whereas another reported only using a confidential university system to respond to patients' questions and to provide lab results.

Some respondents were vocal about the reasons they have stayed away from social media, citing:

- Privacy (" . . . that patients will learn about my private life, request to 'friend you,' etc")
- Time constraints (" . . . takes up too much time")
- Lack of awareness and opportunity ("I am interested in participating in CME using social media, but I just have never had a chance")
- Institutional barriers ("I wish our conservative academic health center allowed us to use more social media, but I believe HIPAA concerns and encryption concerns have not yet been addressed legally")
- The desire to maintain boundaries ("Social media is for socializing. Prefer not to mix up")

Red Alert: Social Media Notifications Are Great—for Some MDs

Clearly, one of the key uses of social media in the CME space is to disseminate information about newly available educational activities. The survey results suggest the message is getting through but only to some. More than one half (57%) of physicians said they had received a notification from some outlet, but only approximately 1 out of 10 physicians said they received such notifications through Facebook, and numbers for Twitter and LinkedIn were also in that range, whereas a fair number reported getting such notifications through QuantiaMD (34%) and Doximity (28%).

When physicians were asked if they recalled the specific notifications for any CME activities that they have received, their replies included:

- Advances in the diagnosis of pulmonary carcinoma
- Treatment options in type 2 diabetes
- Reducing cardiovascular risk in dyslipidemia
- Hepatitis C virus treatment
- HIV and infectious disease cases
- Irritable bowel syndrome
- Immunotherapy
- Targeted therapy for lung cancer
- Iron overload
- Management of multiple myeloma
- HIV pre-exposure prophylaxis
- Treatment of bacterial infections (Gram negative rods)
- New treatment options for psoriatic arthritis and ankylosing spondylitis

Patient Communication

Although email and patient portals are not social media, strictly speaking, the survey also explored how physician learners are interacting with, educating, and sharing content with patients through these platforms. Overall, 43% of learners said they do use email to communicate with patients. Notably, 55- to 64-year-old respondents of the survey seemed somewhat more likely than other age groups to use email in this manner (53%), and men were slightly more likely to report they had emailed patients vs women (46% vs 38%, respectively).

Midwestern physicians in the sample were less likely to email patients (29%), and of interest, there was a clear linear trend in email use favoring urban doctors (46% reported emailing patients vs 39% for suburban and 27% for rural). However, it is worth noting that most of the respondents were urban and suburban, with fewer rural physicians represented, so this subset analysis should be viewed as exploratory and hypothesis-generating.

Will Social Media Growth Continue?

Many physicians seem to have made up their mind about social media for education and/or other professional uses. Either they use it or they have a clear reason why they do not, such as privacy or time constraints. On the other hand, 29% of physicians stated there was "no particular reason . . . just have not used it."

Could these physicians be social media converts, given the chance? There is indeed some evidence to suggest that physicians not accustomed to using social media for learning may start to favor it after being exposed to it in an educational context.

When program planners at Johns Hopkins Bayview Medical Center launched the residency-specific Twitter page @TEACHbayview, they found there was a significant increase in the use and frequency of Twitter for medical education over the ensuing 6 months.[16] Like most residents today, the Bayview trainees were already heavy social media users, although only a minority used Twitter for medical education. Yet, after the launching and raising awareness of the Twitter page, the number of residents using Twitter for medical education weekly increased from 11% to 60%. The residents also developed more favorable attitudes toward social media–based medical education as a result of the intervention.

The missing link here is outcomes: Did this intervention have an appreciable impact on learning for these internal medicine residents? The authors did not measure it, and it remains an open question. Likewise, in a recent meta-analysis of 10 studies looking at how medical students use social networking sites for learning, none explored the impact of social media on academic performance.[17]

Moreover, the data suggest that email use with patients may be specialty specific. For example, reported rates were 41% among infectious disease specialists and 52% among oncology specialists but only 29% among primary care physicians. However, the diversity of specialties represented in the survey makes it difficult to make cross-specialty comparisons with a large degree of confidence.

Patient portals are a similar story—at least on the surface. Overall, 44% of learners said they used portals to communicate with patients, almost identical to the proportion who use email. However, this time, the 55-64 year olds were much less likely to use portals for patient communication (34%), as were men (41% vs 49% for women). And in a reversal of the urban-to-rural trend seen in email, portal use was less frequently reported for urban physicians (40% vs 53% for suburban and 64% for rural).

It is also important to note that the survey did not evaluate the potential relationships among use of email for patient communication and clinicians' use of electronic medical records with patient portals or use of bidirectional apps such as WellDoc and others.

Limitations and Caveats

It is hard to study social media in a vacuum. In order to reach survey participants, an email was sent out to site members who have elected to receive emails from CCO. Because they are email users and they have opted in to these messages, the participants in this survey may represent established technology adopters who may be more inclined than others to be active online and, in particular, with social media. That said, email is very widespread today; moreover, there is no particular reason to think that the social media behaviors of physicians who have opted out of our survey emails would be different from those of physicians who have opted in to receive emails.

Although we believe the results of this survey are a reasonable surrogate for the attitudes and opinions of US physicians regarding social media, caution is warranted that the survey-taking population is not a general sample of US physicians but a sample of US physicians who are members of CCO. Finally, some of the demographic breakouts and other subsets described are by design based on smaller numbers of learners, and thus, should be viewed as hypothesis-generating rather than conclusive.

Recommendations

Based on current demographic trends and the results of this study, we recommend that CME planners, providers, and stakeholders seek out practical ways to incorporate proven social media tools and strategies into their educational programs to drive engagement, while considering new ways to evolve education through experimentation and innovation.

In particular, our recommendations are:

Think young. Thanks to high levels of social media adoption, younger physicians (such as residents and fellows) will more likely be the beneficiaries of CME-based social media initiatives. Mayo Clinic researchers found that younger CME course participants had more favorable attitudes toward social media, and as a result, they recommended course directors guide their efforts toward the "more youthful, technology-savvy CME participant"[18]—keeping in mind that such strategies will only become more relevant as more Millennials enter the healthcare workforce.

Leverage and innovate. What is being done now that potentially could be done better or differently by using social media? Can a Facebook group be used to obtain a deeper assessment of educational needs? Is there an opportunity for obtaining postactivity follow-ups on Twitter? Social media experiments are a high-risk, but potentially high-reward, venture that could yield new insights on how to reach physicians, educate them, and measure the impact of education.

Content is key. We found that when our physician learners use social media, they are mainly seeking to absorb news and information and learn about new CME activities. That is in line with a broader survey of physicians showing that at work they used social media to keep up with healthcare news (40%), whereas there was somewhat less interest in discussion with peers (33%) and progressively less interest in using it for practice marketing (20%) and connecting with patients (7%).[19] With that in mind, CME providers can meet the needs of physicians by making new activities and educational content readily accessible via social media feeds.

Allow for interaction. Content consumption dominates social media, but that does not diminish the social aspect. Remember that our study and others show that a sizeable chunk of social media–savvy physicians (at least one third) value the discussion opportunities that social media provides. Make it easy to share the content on social media. Consider taking it one step further and allow for discussion opportunities, such as CCO's ClinicalThought™ platform, where we have made it easy for physicians to interact and discuss the latest data—with each other and with the experts themselves who are making news and helping put that news in clinical context.

Keep it relevant. A cardiologist is not necessarily going to be interested in best practices for treating psychiatric disorders—unless, perhaps, best practice involves drugs that may elevate the patient's cardiovascular risk. Think about the audience when choosing content for social media feeds, but look for opportunities to think outside the box and use social media to deliver relevant education that the physician may otherwise not encounter.

Make it engaging. "Social" implies a group comprising individuals who speak with each other, not at each other. Develop a social media "voice" and tone[20] that approximates conversation and is appropriate to your audience.

Rethink learning measurement. One of the biggest challenges at the intersection of social media and CME is how to analyze the formal and informal learning that takes place as a physician participates in an activity or accesses the resources and people that make up his or her personal learning network. Li and colleagues[21] have proposed a conceptual model for analyzing social media learning that has the potential to yield new insights. We are currently interested in our learners' online interactions on our ClinicalThought™ expert-driven social media platform and think an analysis of learner comments and questions may help us quantify the informal learning that is taking place online.

Redefine metrics. Speaking of engagement, consider looking beyond the traditional measures of engagement to find data that tell the whole story behind the learner's interaction with the content. How often is your CME content shared? How many learners do you reach with each social media interaction? How often are users commenting and interacting with one another?

Try social promotion. Given the demands on a physician's time and attention, it is sometimes a big challenge to get the word out to them on social media. The major platforms offer multiple ways to advertise, boost posts, and otherwise help highlight a specific message. A single promotion or small campaign could be deployed to test the waters and determine if such an approach spurs additional engagement among members of the target audience.

Social Media Tomorrow: Cautions, Caveats, and Optimism

As social media has come of age, it is not only integral to general social issues, but increasingly a part of physicians' professional lives. It is a particularly relevant tool for informal learning, for finding the CME activities most relevant to their clinical practice, and in some cases, such as CCO's ClinicalThought™ and *in*Practice® Training Program, social interaction is integral to the education itself.

But not all physicians are the same. An analysis of the attitudes and preferences of our US physician population reveals some strong opinions that we should keep in mind. Just as some physicians flock to it, some continue to be skeptical of combining structured CME activities with immersive, free-wheeling social media platforms that elicit concerns about privacy, appropriateness, patient confidentiality, and time constraints.

Therefore, we end this white paper not with an ebullient call to action that proclaims social media as the future of CME, but with a call to our CME colleagues to follow a path that walks a careful line between *practical integration and forward-thinking experimentation.* Our experience with social media, and our interactions with physicians, tell us that social media is a tool that can be judiciously used to help reach learners and enhance the learning experience.

We are excited by the promise of incorporating more social features into educational activities and making more content available via social media for those physicians who are plugged in and receptive to using Facebook, Twitter, and other platforms as adjuncts to their own "personal learning network"—that is to say, the informal web of people and resources that clinicians cultivate and access, not only through Web browsers and mobile devices, but also offline, in order to learn and provide the best patient care possible.

We are particularly excited to continue our exploration and incorporation of social features in the ClinicalThought™ expert-driven social media platform, the *in*Practice® point-of-care resource, and our *in*Practice® Training Program that offers collaborative opportunities for residents, fellows, and program directors. All the while, we are honing our social media strategy to offer more targeted content to learners who have followed us on the leading social media platforms and are planning new ways to experiment and innovate using social media to help make CME even more relevant to the practicing physician.

About Clinical Care Options

Clinical Care Options (CCO), a leader in the development of innovative, interactive, online, and live CME-certified CME programs and proprietary medical education technologies for healthcare professionals, creates and publishes original CME and information resources that are designed specifically for healthcare providers. CCO's educational programs are developed not only to provide the latest scientific information, but also to support the understanding, confidence, application, and competence of healthcare professional learners. In addition to the latest point-of-care resource, *in*Practice®, CCO provides a spectrum of live and online educational programs and formats.

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Intelligent Virtual Assistants—Think Siri and Alexa—in Medicine and Continuing Education: Small Devices With Big Concerns and Big Potential!

March 2019

A Clinical Care Options (CCO) White Paper

The marketplace has exploded with "smart speakers" for sale, and the media is saturated with advertising for the latest Amazon Echo or Google Home. However, privacy experts have expressed concern that the same companies producing these devices are also known to harvest user data.[1] This can be especially troubling when considering their use in the healthcare setting, due to privacy laws such as Health Insurance Portability and Accountability Act of 1996 (HIPAA). From a privacy perspective, the entity we are truly concerned with is not the smart speaker itself but the cloud-based intelligent virtual assistant (IVA) loaded into these devices. Although IVAs are not yet HIPAA compliant, they have *enormous* potential for the medical field.

How Do Cloud-Based IVAs Work?

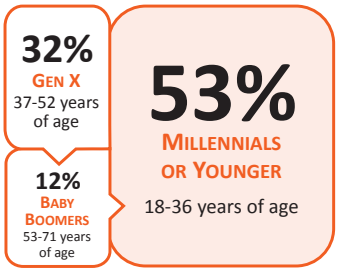
IVAs use "on-device listening" with microphones that are always "listening" unless specifically turned off; when they detect their "wake" or "hot" word such as "Okay, Google" or "Alexa," they record your input and then upload it to the cloud for processing.[1-3] Some newer smart speakers use lights to show when input is streaming to the cloud.[4] These IVAs are truly impressive, using natural language understanding (also known as natural language processing) to match speaker input to executable commands:

> "[Natural language understanding] is all about providing computers with the necessary context behind what we say and the flexibility to understand the many variations in how we might say identical things."[5]

This is *how* IVAs infer that you are asking for the local weather forecast when you say, "Alexa, what's it like outside?" Like other artificial intelligence (AI) uses such as social media platforms and facial recognition programs, IVAs continually improve using machine learning algorithms.[5] "[T]he output of a machine learning algorithm is entirely dependent on the data it is exposed to. Change the data, change the result."[5] The more data provided to the IVA, the better it can serve its purpose. Thus, whereas each cloud-based IVA has a way to delete recordings, users are warned this "may degrade" the experience since this removes data for algorithms.[4]

Who Is Using Smart Speakers Enabled With IVAs?

A good picture of the user base will provide a clear sense of whether one should incorporate smart speakers within one's engagement strategy.[6] Smart speakers are gaining adoption faster than any technology since the mobile phone.[7,8] As of December 2018, 26.2% of adult Americans had access to a smart speaker, a 40% growth rate in 2018 alone, and more than 40% of owners now have more than 1 device.[9] Initial smart speaker users were affluent, older millennial males[7]; however, these devices are quickly gaining traction with a younger demographic.[10] According to a 2017 survey of 1000 American consumers, 53% of smart speaker owners are millennials or younger (18-26 years of age), 32% are Gen X (37-52 years of age), and only 12% are Baby Boomers (53-71 years of age).[6]



Apple introduced the first cloud-based IVA, Siri, via the iPhone in April 2011,[11] but the first stand-alone device was the Amazon Echo released in November 2014.[12] Uptake has been rapid; between May 2017 and May 2018, US smart speaker ownership more than doubled.[10,13] By June 2018, 24% of US households had smart speakers,[14] and this number was expected to have risen dramatically after the 2018 holidays.[15] Tech watchers were not disappointed: 8% of people in the United States received a smart speaker for the holidays, bringing the number of smart speakers in circulation to almost 119 million![16] Healthcare industry researchers expect that by 2020, one half of all searches will be conducted by voice.[17] Smart speakers are expected to reach 55% of US households by 2022.[17] Consistent with this home use trend, the global healthcare industry's IVA market size is expected to reach $2.95 *billion* by 2025, representing an explosion of these devices into the medical field.[18] By way of illustration, the global healthcare IVA market was valued at approximately $186.3 *million* in 2017.[19]

> ...the global healthcare industry's IVA market size is expected to reach $2.95 billion by 2025...

Which IVA Could Continuing Education Developers Target?

The top 5 IVAs in the United States (with their delivery devices) currently are:

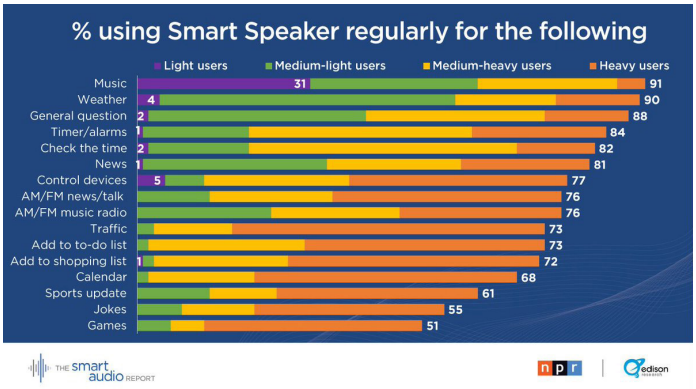
1. Alexa (Amazon Echo, many other devices)
2. Google Assistant (Google Home, Bose, Sony, many other devices)
3. Siri (Apple devices)
4. Cortana (Microsoft/Windows devices)
5. Bixby (Samsung devices)[20-22]

Amazon Alexa currently dominates mostly because it was first to market.[23] Although many cloud-based platforms do support HIPAA compliance requirements, including Amazon's secure cloud computing platform Amazon Web Services, Google Cloud, and Microsoft Azure, and can be used for content delivery,[23-25] their capabilities are not currently smart speaker–friendly. Since the groundwork is already in place for healthcare providers to use these platforms, the tech companies simply need to incorporate appropriate safeguards into their IVAs to meet the requirements of HIPAA.[23]

Cortana is expected to do well in the business space because it is already integrated into so many Microsoft devices,[26] but Google Assistant is being integrated with Chrome OS devices, such as Google Pixelbook.[27]

What Types of Content Are Users Currently Accessing via IVA?

In the pre-IVA world, speaking to a machine was awkward for both the person speaking and those listening, but smart speakers have changed this experience; 72% of smart speaker owners are now comfortable using them in front of others.[15] Indeed, with the recent leap in smart speaker usage, voice interaction is now becoming a habit.[28] Smart speaker owners use them for a multitude of tasks, including asking general questions, checking the weather, setting timers/alarms, controlling other devices, managing lists, receiving news or radio broadcasts, and hearing jokes or playing games.[15,29] However, the most frequent use—and important for continuing education—is playing and streaming audio: Users are growing accustomed to syncing data from mobile devices to their voice-based devices.[14] NPR Chief Marketing Officer Meg Goldthwaite said, "[S]mart speaker owners are turning off their TVs and closing down their laptops to spend more time listening to news, music, podcasts, and books, fueling the demand for more audio content."[30]



Source: NPR & Edison

Most owners use smart speakers in their homes, and the location of home use is trending toward the living room, bedroom, kitchen, and home office.[14,31] It is only natural that innovators have begun to think of other applications for cloud-based IVAs and are increasingly being integrated into other types of products. For example, homebuilders are integrating Alexa into entire houses, and Toyota is adding Alexa to its cars.[32]

Smart Speakers Come With Privacy and Security Issues

Using IVA-enabled smart speakers creates issues that derive from an individual's right to privacy that is part of the makeup of the laws of the United States, including HIPAA.[33] Legal analysts put it this way: It is no problem for Dr. Jones to encourage Mr. Smith during an office visit to use his own Google Assistant to remind him to take his blood pressure medication at home at a certain time. However, Dr. Jones should not ask her own Alexa to set a reminder to tell Mr. Smith at Monday's clinic to avoid salty foods due to his hypertension. This would be a HIPAA violation "synonymous with leaving a handwritten note with the same information out in your office lobby for anyone with a hint of curiosity to read."[34] However, since continuing education itself does not usually include any private patient data, it is not likely to run afoul of HIPAA.

Since IVAs are voice activated, they can misinterpret sounds as their "wake" word and record conversations not meant for them.[2] For example, an Amazon Echo recently accidentally released a couple's private conversation to a third party without their knowledge or consent.[35] This is not likely to be a problematic issue for continuing education since learners will not be disclosing sensitive patient information to their IVA while using it to participate in continuing education.

It has been shown that hackers can potentially send "hidden" audio commands directly embedded into music or spoken text undetectable to human ears but detectable to IVAs that can manipulate them into doing things without the user's knowledge, such as dial phone numbers, send messages, make purchases, open Web sites, or even transfer money.[36,37] For continuing education developers, this could translate to a potential for loss of proprietary information. To help combat this, some IVAs, including Google Assistant and Alexa, have voice recognition feature users can enable to restrict access to sensitive actions unless the device recognizes the user's voice or is given a spoken code.[37]

By using their device, most cloud-based IVA manufacturers state that the user agrees to be bound by their conditions of use and privacy policies.[38,39] An important question remains: Have others exposed to a smart speaker provided informed consent for their conversations to be recorded?[34] If smart speakers become as prevalent as smartphones, will society as a whole waive their rights to privacy? Have we done so already? The relevant law is still evolving; some legal experts believe that places once deemed private, like the inside of a home, will lose the expectation of privacy with the onset of technology.[40] Others feel smart product manufacturers are taking consumers' privacy and security concerns very seriously since they believe consumers will not buy these items if they do not trust them.[3] As part of the solution, component makers like Qualcomm, Inc (San Diego, CA) are creating processing chips that encrypt incoming and outgoing data.[3] In addition, some smart product manufacturers such as Google have internal AI ethics boards to ensure proper application of AI technologies.[41]

> If smart speakers become as prevalent as smartphones, will society as a whole waive its right to privacy?

How Are IVAs Being Used in Medicine Now?

Voice-activated content was pioneered in the field of medicine by major health systems like Mayo Clinic (Rochester, MN) and Boston Children's Hospital (BCH, Boston, MA). Mayo Clinic's Sandhya Pruthi, MD, stated that "voice-enabled experience is a new and growing channel for reaching people and delivering information they are seeking."[42] Alexa is being used in hospitals to help surgeons comply with safety checklists before procedures, and several healthcare providers including Mayo Clinic ("Mayo First Aid"), WebMD, BCH ("KidMD"), and HealthTap ("Dr. AI") created apps to deliver voice-driven self-care instructions for ordinary medical needs like cuts, fevers, and burns.[1,23,42-45] A Samsung company is releasing an IVA-based device in 2019 called ElliQ designed to encourage older adults to engage in healthy lifestyle choices.[46] Going forward, healthcare-related use of IVA technology will likely focus on medical record navigation, medical transcription, and medical information searches.[47]

> Alexa is being used in hospitals to help surgeons comply with safety checklists before procedures...

Delivering Continuing Education via Smart Speaker Is a Both a Challenge and an Opportunity

In general, consumer sentiment regarding smart speakers is highly positive: 75% of smart speaker owners want to learn to do more with their devices and would recommend them or purchase them as a gift.[14] Continuing education, however, targets a very specific audience. The prospects appear good. For instance, one survey indicated 48% of pediatricians queried would be willing to try voice-assistant technology in their practice.[17] Thus, it is likely that even more doctors would consider smart speakers for non-HIPAA–related uses. "In homes that have had smart speakers for at least a year, they are now the number one device for consuming audio," says Tom Webster, Senior VP of Edison Research.[30] To take advantage of this tidal wave, continuing education providers could consider creating modules that can easily be streamed by a smart speaker, whether it is placed in the home or the clinician's office. One continuing education provider has already begun to seize this opportunity by teaming up with the AudioEducate platform to create an accredited programs delivered via Alexa skill.[48]

Each IVA has unique building tools. For example, the Alexa Skills Kit can be used to create Alexa apps using the Alexa Voice Service, a collection of interfaces that "allow developers to voice enable connected products with a microphone and speaker."[26] User-friendly straightforward step-by-step interfaces will make it easy to create and deliver education aimed at the medical community. Google Assistant has an app developer program designed to be used by nonprogrammers.[49] To take advantage of Siri on Apple's HomePod, continuing education developers can use "SiriKit" to interface the IVA with iOS apps.[49] Microsoft's Cortana has an online editor and tutorial to create a "skill" that walks you through the entire process.[49]

Cutting-edge continuing education developers will need to consider several questions when designing modules for delivery via IVA. First, how will the educator assess whether learning has occurred? In addition to AudioEducate, educators can look to education platform Canvas by Instructure, with whom Alexa partnered to create a skill that allows learners to engage with their course materials using voice.[50] It is not a great leap to extrapolate how clinicians could interact with continuing education modules delivered via smart speaker/IVA in a similar way.

Another interesting question to consider is whether audio content alone is enough in our modern lifestyle where most education content is delivered in a multimedia fashion or live. However, audio content may still be a preferred format for some users, and audio is certainly a convenient format to consume at times when it is not possible or desirable for the user to view a screen.[51]

Furthermore, as every educator knows, reducing barriers is a key to learner success. Smart speakers with IVAs can do this in spades—language barriers are reduced since education modules can be programmed to be delivered in any language necessary.

Smart speakers have additional potential: They are easy to use, convenient, cost-effective, and appealing to the increasing numbers of "digital-native" clinicians entering the practice of medicine. They are also accessible for older clinicians or other-abled professionals who have difficulty using their hands or have poor eyesight. Another barrier reducer is the need to introduce the IVA to the education provider's mobile or Web account just once, and as such, an IVA also can reduce the time involved in logging progress in an education module.[52]

One caveat is that educators may need to frequently monitor or update modules delivered via smart speaker because technology is changing at a rapid pace.[53] Furthermore, smart speakers, like other cutting-edge technology, have been released prior to being entirely ready, leading to debugging in real time.[32]

Is audio content alone enough in our modern lifestyle where most education content is delivered in a multimedia fashion or live?

Takeaways for Continuing Education Developers

Smart speakers have enormous relevance and potential for continuing education. The privacy issue is not as simple as *not* having a smart speaker in the medical office because most smart phones already carry a cloud-based IVA that can be activated—either intentionally or accidentally—by uttering a phrase or by pushing a button while the device is in a pocket or bag. The medical industry should not be overly concerned about introducing a smart speaker into the office for fear that an IVA is listening and occasionally erroneously recording snippets of medical conversations—that has probably already happened when a practitioner's cell phone was inadvertently activated in a patient room. IVAs are simply more conspicuous when they are in a larger device sitting in a dedicated spot on the counter or desk. The key takeaway is this: For now, the medical community should make informed choices about how, when, and where we choose to use IVA-enabled devices and keep a keen eye on developing laws and security upgrades.

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