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

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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.

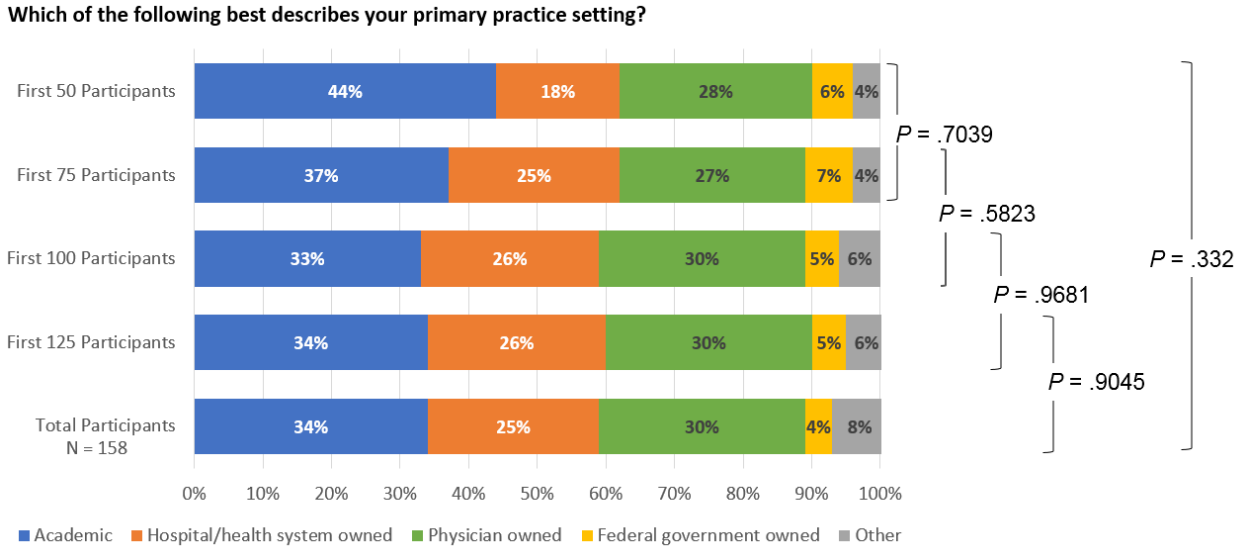
Recruitment

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).

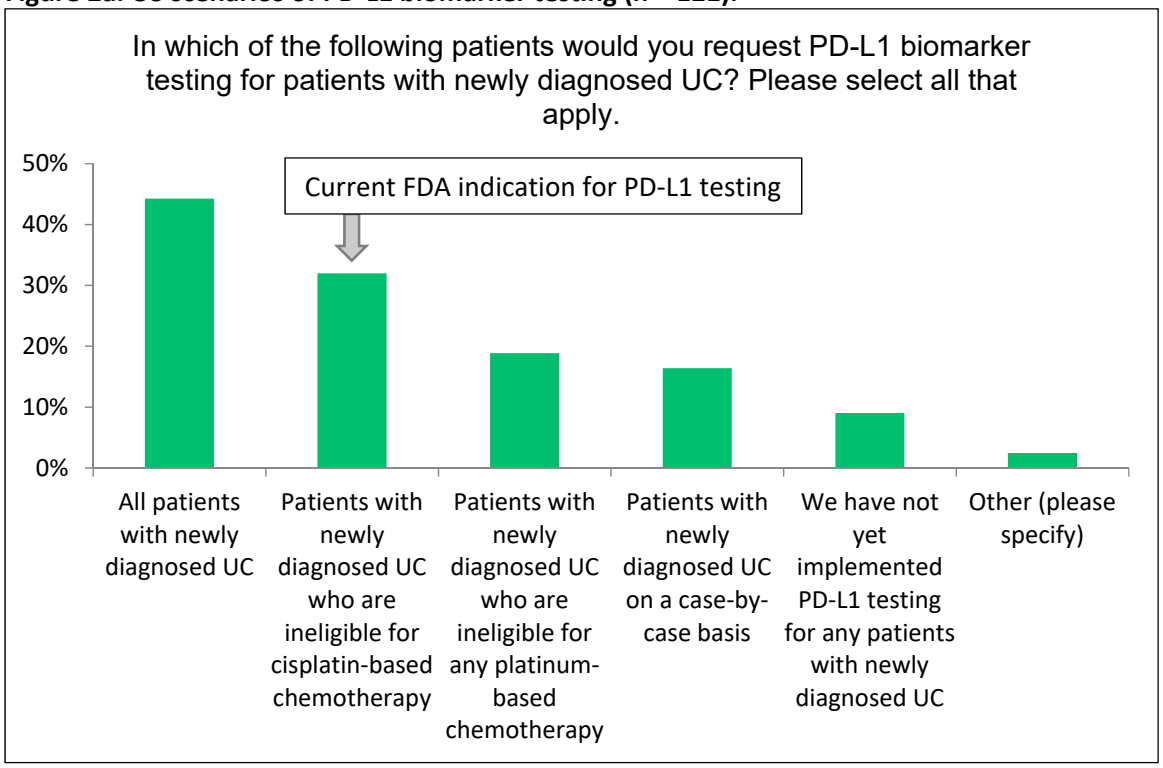
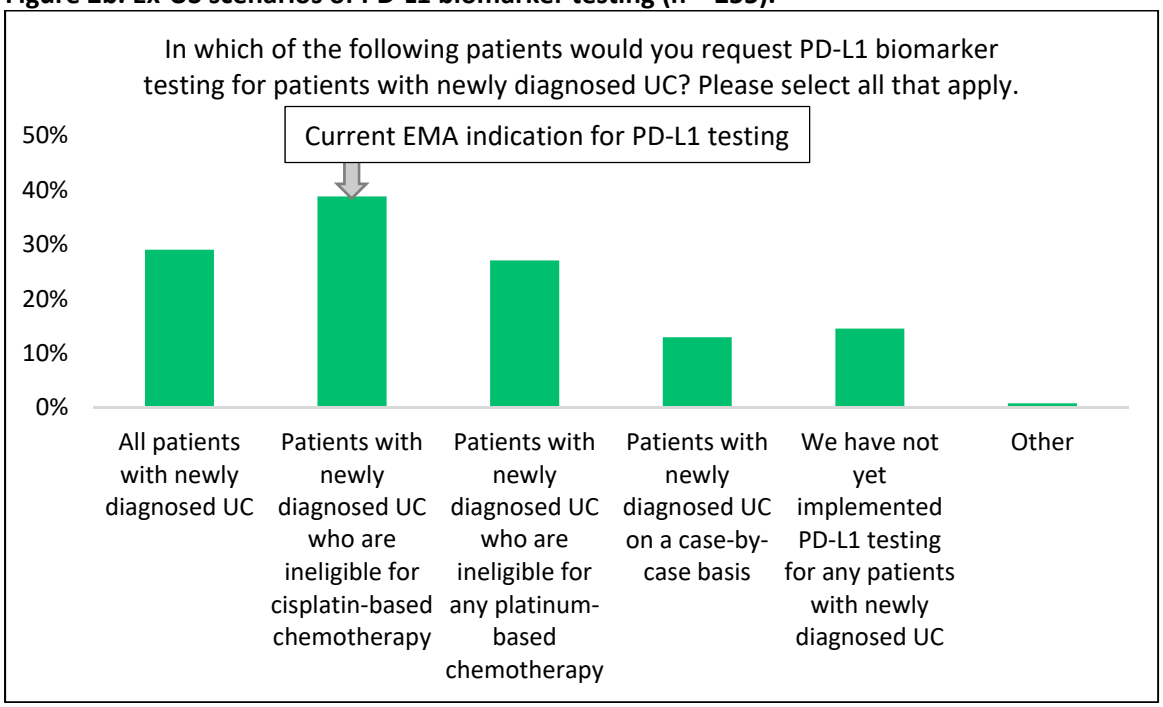


Figure 2b. Ex-US scenarios of PD-L1 biomarker testing (n = 255).



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).

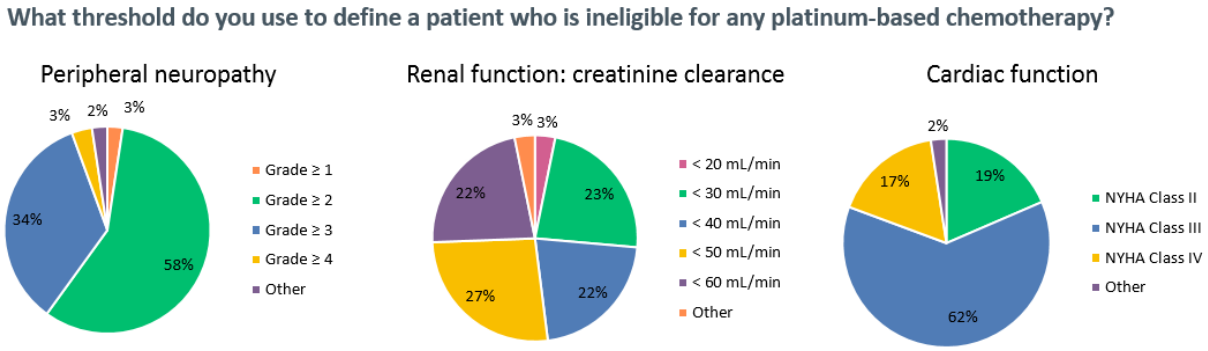
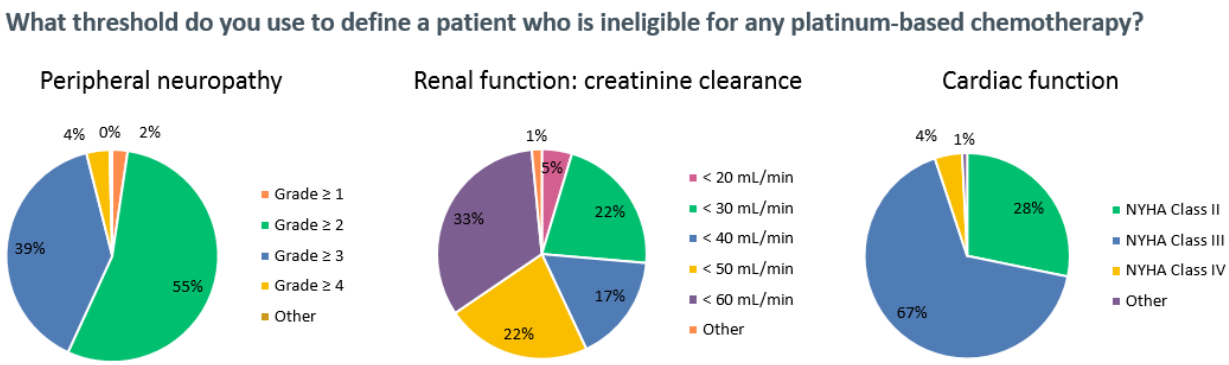


Figure 3b. Criteria for determining chemotherapy eligibility reported by ex-US clinicians (n = 255).



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).

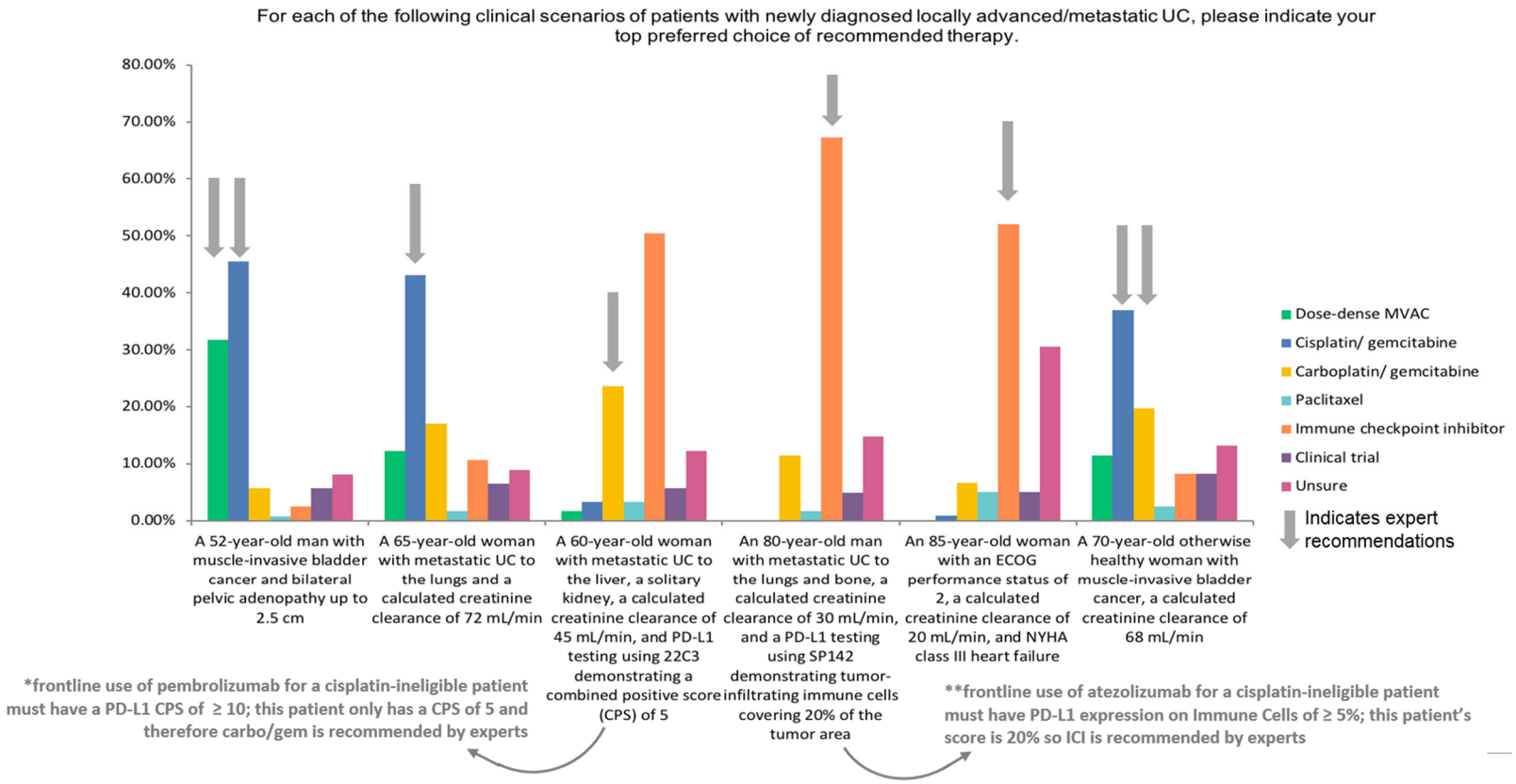
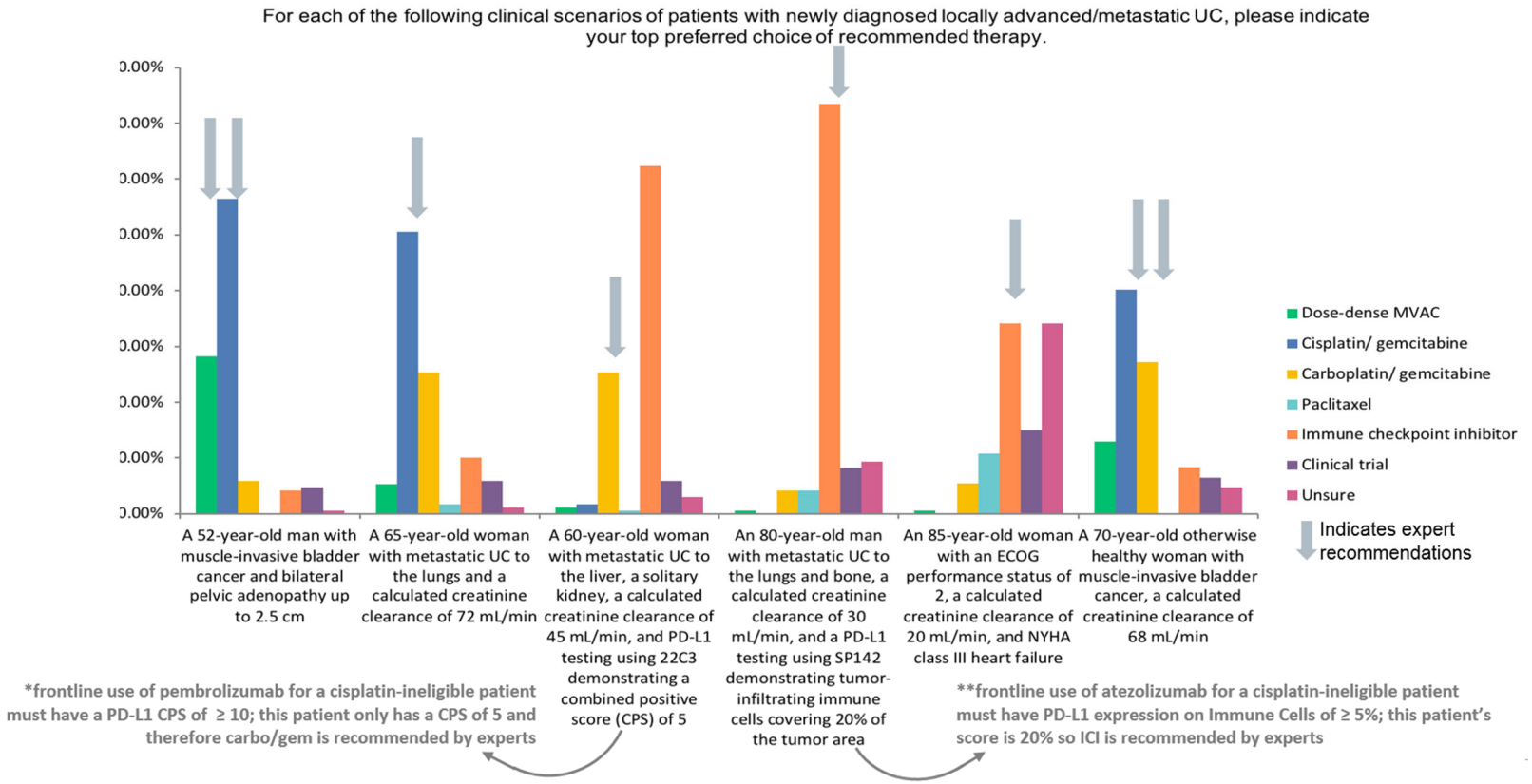


Figure 4b. Ex-US clinicians preferred options for newly diagnosed locally advanced/metastatic UC (n = 257).



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).

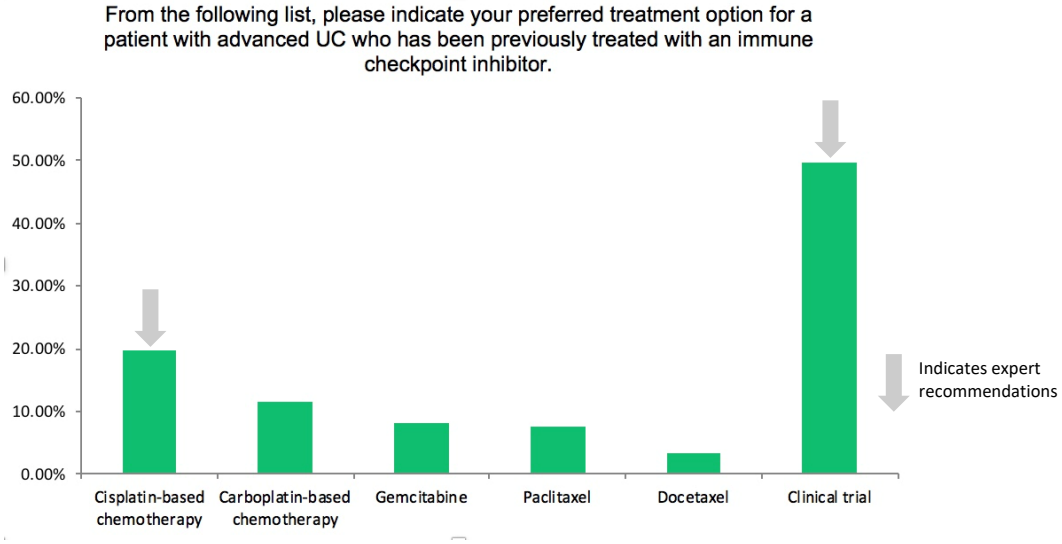
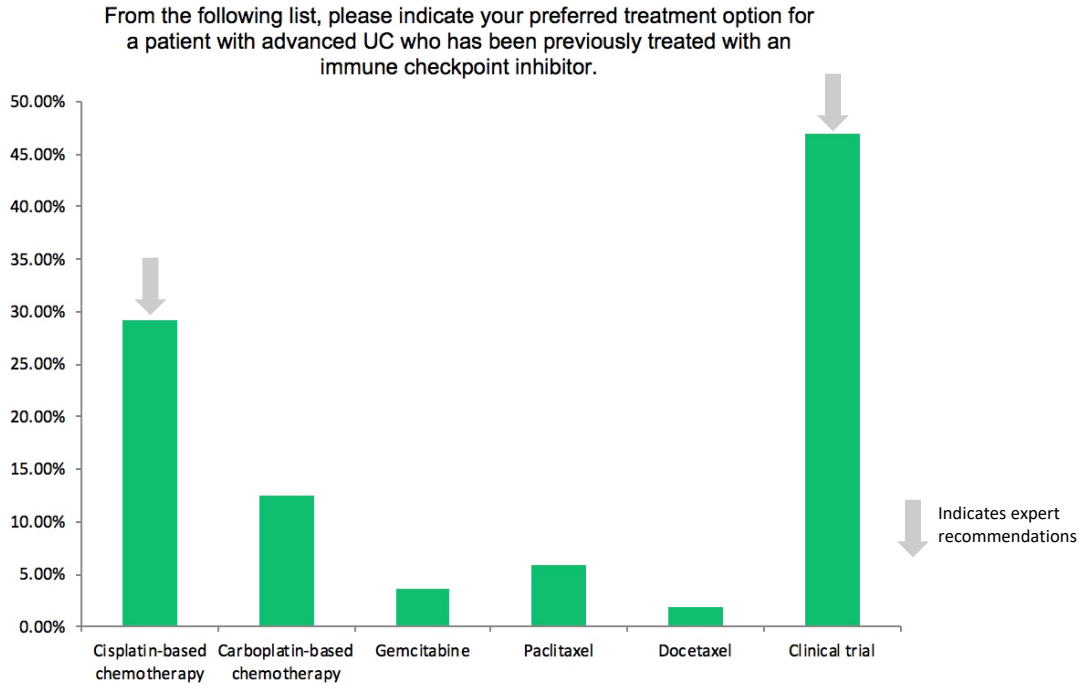


Figure 5b. Ex-US–based preferences for patients previously treated with immunotherapy (n = 254).



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).

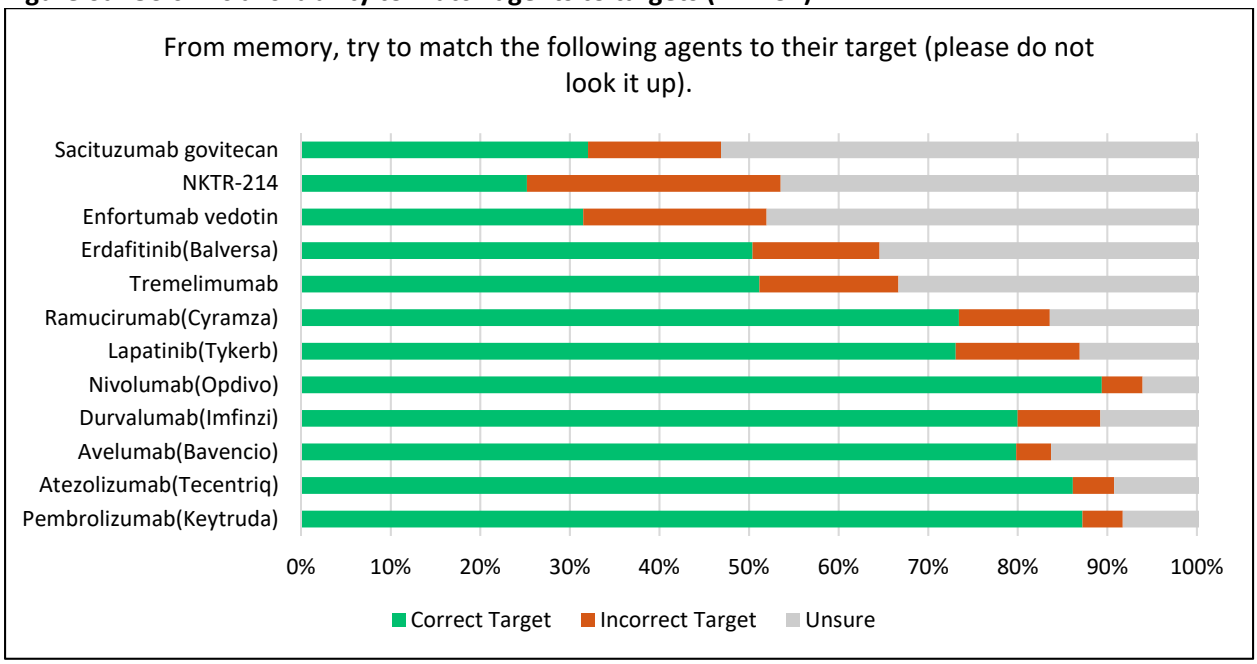
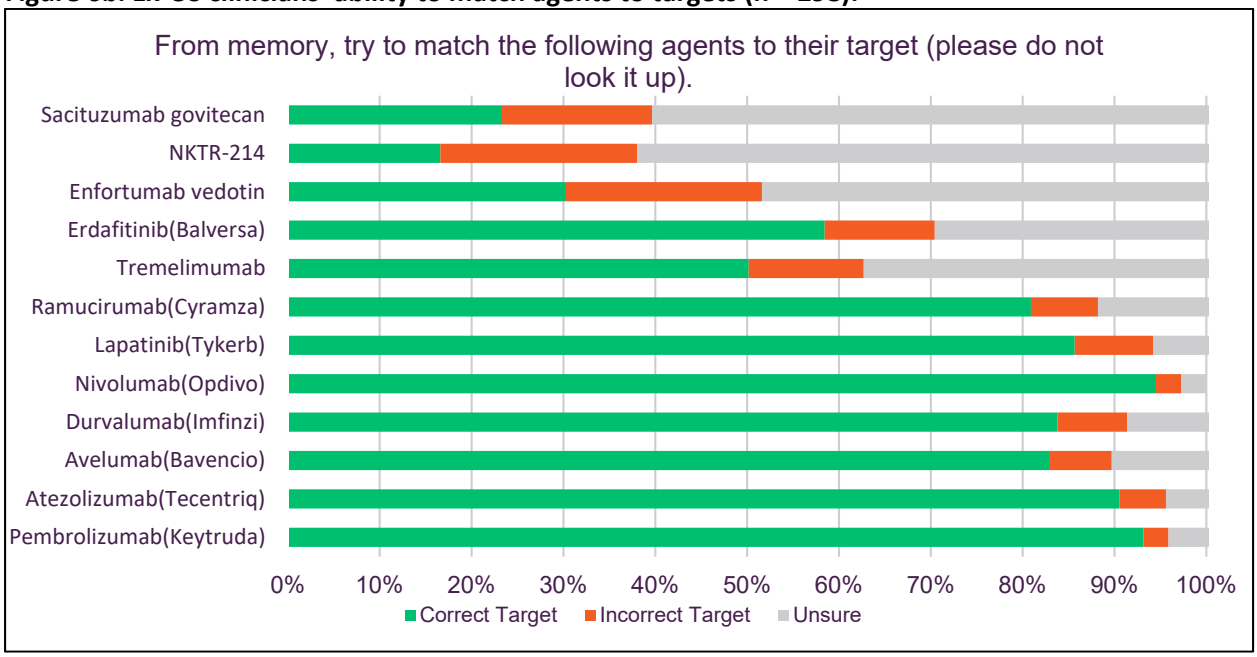


Figure 6b. Ex-US clinicians' ability to match agents to targets (n = 298).



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).

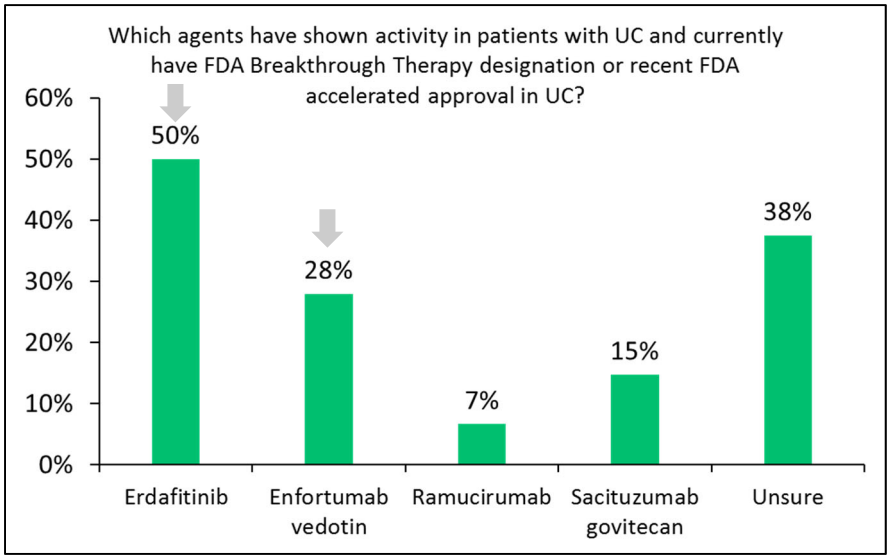
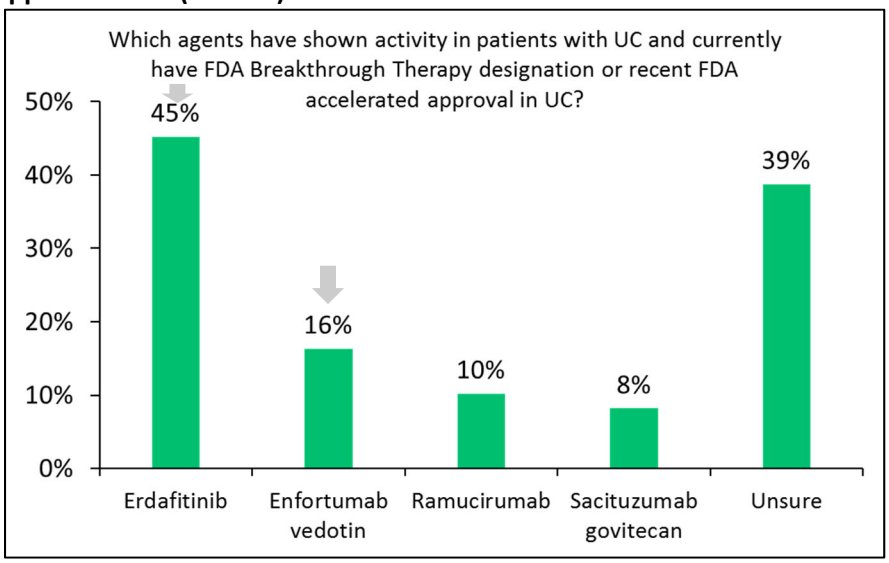


Figure 7b. Ex-US clinicians' ability to identify therapies with either Breakthrough Therapy designation or recent FDA approval in UC (n = 294).



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).

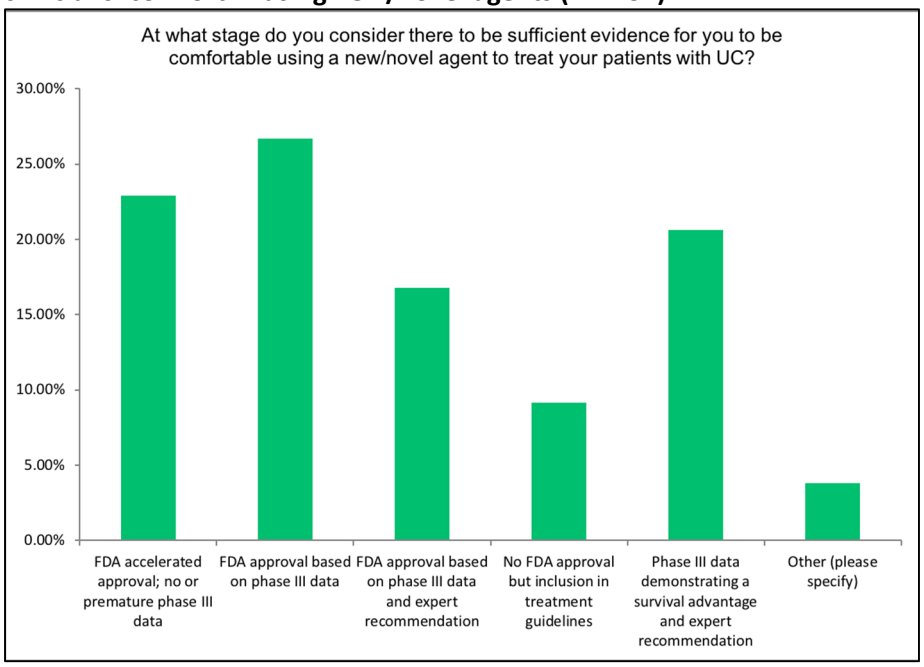
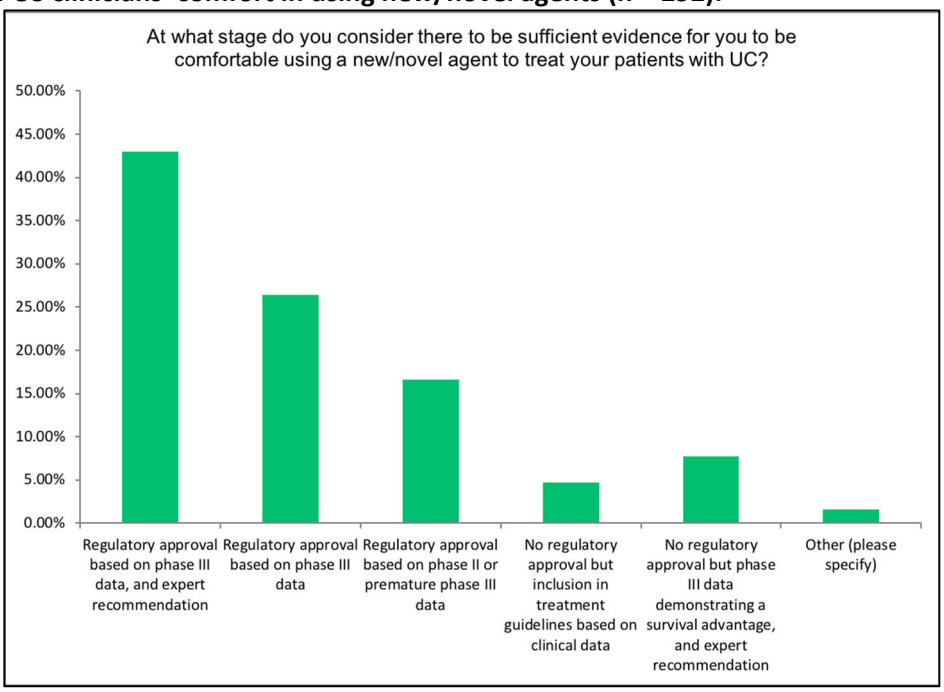


Figure 8b. Ex-US clinicians' comfort in using new/novel agents (n = 292).



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.

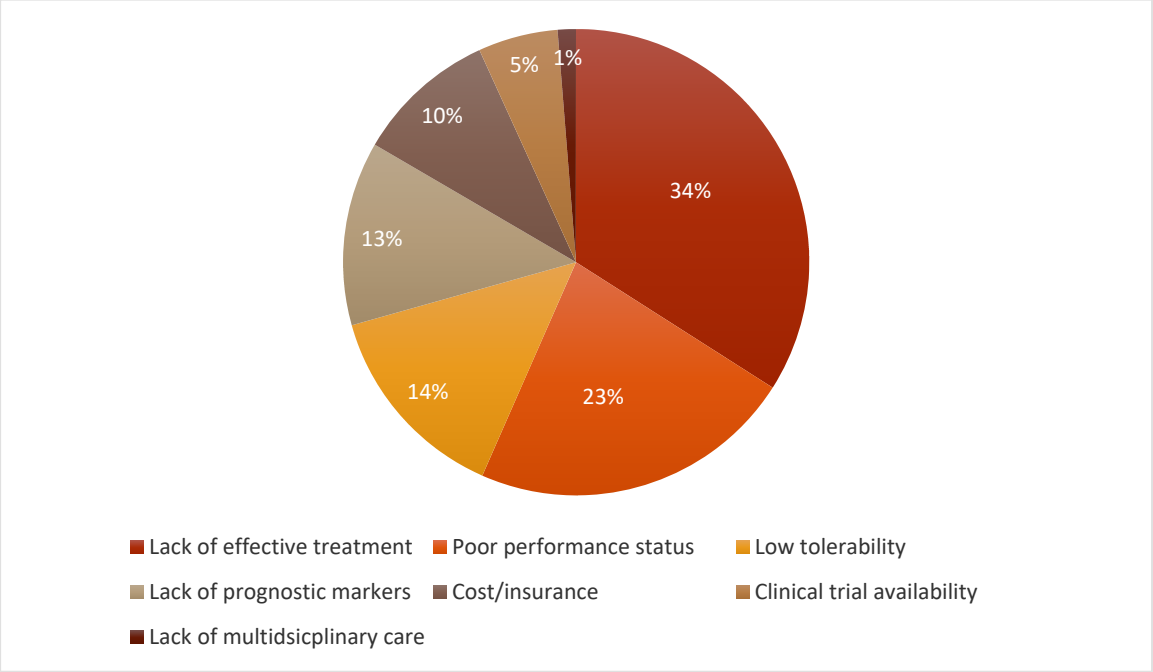


Table 12 summarizes how participants described these challenges.

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

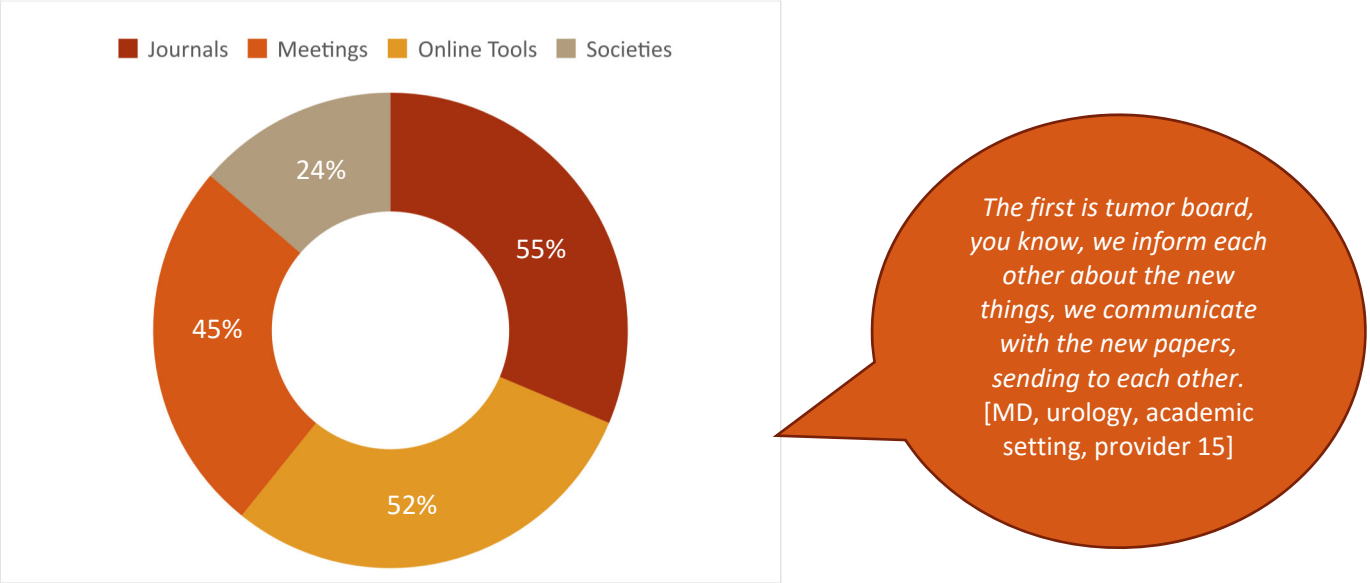
Participants consistently commented that patient age, performance status, smoking, obesity, and other comorbidities limit the efficacy of any treatment in the first-line setting. Time and again participants emphasized that patients with UC are "older" and "very sick" patients for whom it was challenging 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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