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

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EXECUTIVE SUMMARY

Background

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

Study Goal

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

Design and Methodology

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

CLINICAL PRACTICE GAPS AND RECOMMENTATIONS

Narrative Summary

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

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

Clinical Practice Gaps and Education Need

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

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

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

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

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

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

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

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

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

Key Recommendations

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

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

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

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

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

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

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

Study Design

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

Qualitative Phase

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

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

Analysis

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

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

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

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

Quantitative Phase

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

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

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

Recruitment

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

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

FINDINGS

Participant Characteristics

Demographic Characteristics of Participants

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

Table 1. Demographic Characteristics of Participants

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

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

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

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

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

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

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

Gestalt Assessment

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

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

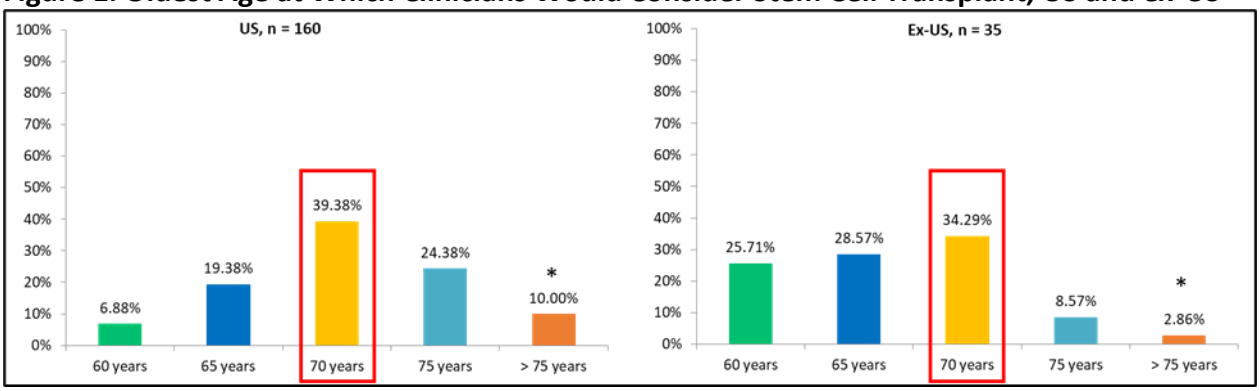
A small group of clinicians (n=5) in either academic or large health systems had access to a colleague (e.g., health psychologist) or training in administering a comprehensive geriatric assessment such as the CCI or Get Up and Go. They viewed formal assessment as crucial for determining whether the patient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

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

Transplant Evaluation for Medically Fit Patients with High-Risk MDS

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

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



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

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

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

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

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

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

Barriers to Transplant and Intensive Chemotherapy

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

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

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

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

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

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

Therapy Selection in Specific Clinical Scenarios

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

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

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

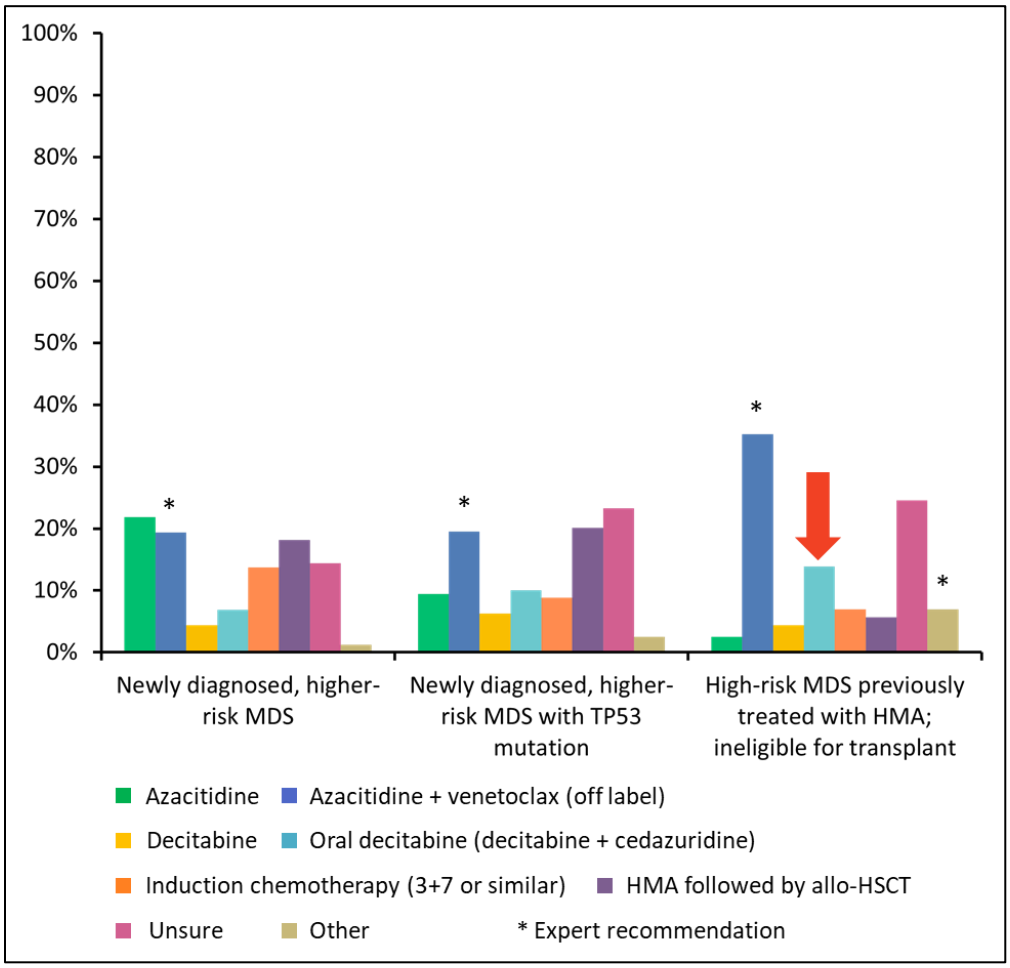
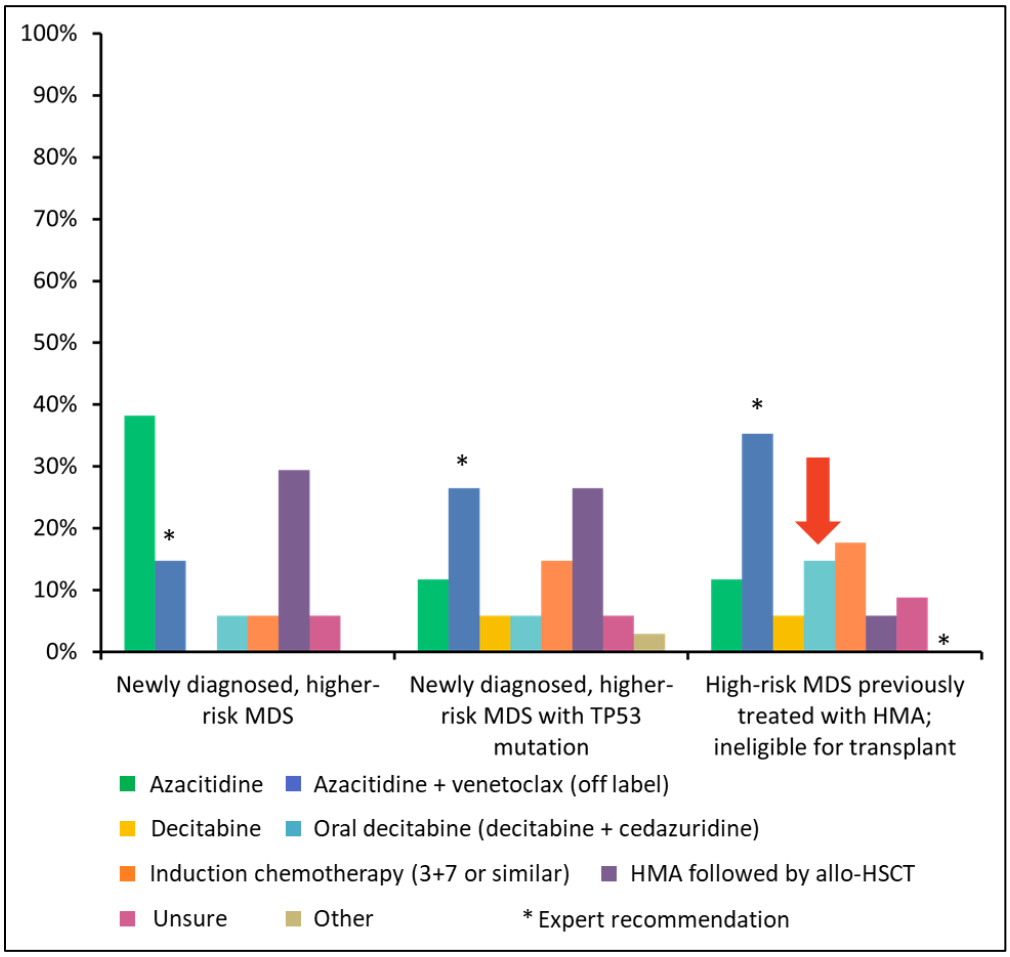


Figure 3. Primary Preferred Standard Treatment Recommendation for Clinical Scenarios of Patients with MDS, ex-US (n = 34)



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

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

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

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

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

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

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

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

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

Newly Diagnosed Low-Risk MDS

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

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

Targetable Mutations

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

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

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

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

Assessment of Response in MDS

Most interviewed clinicians consider evidence of blast count recovery as "an important metric," "easy to do," and a "simple" method for assessing response to HMA treatment. Most clinicians said they would repeat bone marrow biopsy in the presence of cytopenias or changes in circulating blast counts, "after several courses of hypomethylating agent therapy," "after about 2 to 3 cycles" of HMA therapy, or after "a couple cycles of treatment." One third of interviewed clinicians considered patient reported outcomes and reduction in transfusion burden as important, if not more important, than clinical parameters (**Appendix Table 5**).

> *If we had a positive response, I would just follow the counts. I would not repeat a bone marrow biopsy unless I saw something going, you know, the wrong way, such as a cytopenia that's getting much worse. [Physician, Hospital/Health System]*

That they have palliation of their symptoms. That's success. [Physician, Hospital/Health System]

Supportive Therapy/Care

In MDS, clinicians described supportive care or therapy in two main ways.

Symptom Management

Supportive care included therapies to manage symptoms associated with MDS in ways that are consistent with current guidance, including transfusions, erythropoiesis stimulating agents, and antibiotic therapy for infection prophylaxis. Over half of surveyed US-based clinicians (n=160) reported not using growth factors in patients with either standard induction chemotherapy or venetoclax plus HMA therapy. These findings were reflected in interviews. Some clinicians were using luspatercept, which was FDA approved in 2020 for treating anemia in patients with very low to intermediate-risk MDS with ring sideroblasts who require RBC transfusions (*If you have ring sideroblasts, then you know that luspatercept is an option*). Other clinicians felt that growth factors were controversial in the high-risk MDS setting and did not routinely provide G-CSF support.

Palliative Care

One third of interviewed clinicians also included palliative care in their definition of supportive care or therapy. They described consulting the palliative care service, palliative social workers, nurse practitioners, nurse navigators or psychologists to ask for help in supportive care, supportive care with transfusions, or hospice care and "just being comfortable."

Supportive care is a very important component of any malignancy treatment, more so in these folks because they tend to be sicker, and they tend to be more transfusion dependent. Supportive care is something that I start or attempt to start the day 1 of my clinic visit with them. I involve oncology social work. I involve financial assistance if needed. There is so much that goes on that is to be done from a supportive care standpoint. We have already talked about some of those things. It could be just transfusions. There could be pain management. There could be oxygen treatments.[Physician, Hospital/Health System]

Some clinicians debated the benefit of transfusions as part of the supportive therapy rubric, viewing them as overused in myeloid malignancies, especially at the end-of-life. They pointed to the side effects and inconvenience associated with transfusion as a rationale for reducing use in the palliative setting and viewed transfusion are largely symbolic, as two academic physicians noted:

That's just basically our physicians' defensive mechanism. You can't treat the patient, there is no cure, and you don't want to go to hospice, at least not yet. Then you're basically just providing transfusion as a symbol. A symbol of supportive care and a

symbol of our physicians' things we can offer to the patient. [Physician, Academic Setting]

Usually you can do like azacitidine or decitabine plus or minus venetoclax. So I would say those are kind of like our recommendations. So I would say a hypomethylating agent plus or minus venetoclax is kind of our go-to. Certainly a hypomethylating agent for sure. You look and see what is kind of their quality of life. I always kind of do it…if they're requiring frequent transfusions and their numbers are really low, then that would tip me off. Because any of the agents that you're doing in MDS, you're really trying to help…you're not going to cure them. So you're really just trying to help them from a palliative perspective. So if they have like high transfusion needs, then I try to give an agent to just try to spare them…like their frequent transfusions. [Physician, Academic Setting]

These clinicians described palliative care as supportive therapy for patients who no longer responded to therapy and many shared stories about particular patients who requested—implicitly or explicitly—supportive care.

I have one patient that has end-stage congestive heart failure, who is 86, and the family is very burdened by so many things that he has. So transfusing him is very difficult because every time you transfused him, he tilted into acute heart failure exacerbation. So it's very difficult. The transfusion has to be almost six hours, one bottle of cells. We tried to give him EPO, but with the EPO, it ended up increasing his blood pressure, because that's the EPO analogs increase the blood pressure. So ***it's such a tough situation that the patient and the family decided just to hold up on anything****. They didn't want to do anything subcutaneous. They didn't want to come into the inpatient centers, especially because with HMA, you can have more cytopenias in the beginning before they get better. [Physician, Hospital/Health System]*

I have a lot of little old ladies that are at the end of their lives, and half their kids are dead already, and all their friends are dead, and they've been without a husband for 40 years. And they wake up and their backs are sore, and their knees are sore, and they've got cataracts, and they can't hear. And they're the ones who are like let's treat this if it makes me feel better, but ***I don't want to be sick with chemo to get an extra 6 months or an extra year. Or can we just do supportive care?*** *They gave me a transfusion, and I felt so much better. Can't we just do that again? [Physician, Physician-Owned/Private Practice]*

Practice Gap #3: Therapy Selection in Patients with Newly Diagnosed Patients with AML

It remains challenging to plan optimal therapeutic strategies for patients who have a poor prognosis, who are older or ineligible for intensive chemotherapy, or who have secondary AML. A surprising number of healthcare professionals offer intensive therapy to newly diagnosed patients with AML with poor performance status. They also vary in their adoption of venetoclax plus HMA.

Eligible for Intensive Induction Chemotherapy

Remission induction chemotherapy (e.g., 7 + 3, CPX-351) is considered the standard therapeutic option for medically-fit patients diagnosed with AML. The emergence of newer treatment options for patients with newly diagnosed AML now requires that clinicians determine whether intensive induction chemotherapy is the optimal option for these patients, and, if so, if they are sufficiently "fit" to withstand this treatment approach.

Interviewed clinicians were mostly using 7+3 as their chemotherapy approach for medically fit patients. Clinicians described using either low-dose cytarabine or daunorubicin and cytarabine for patients with low-risk AML, secondary AML, or as consolidation. Some clinicians expressed reservations about using CPX-351 (liposomal daunorubicin and cytarabine) for patients eligible for intensive induction therapy ("*I know there's some data, but it's not quite prime time yet in terms of using the Vyxeos"*) (**Appendix Table 6**). Again, chronological age factored into decisions about fitness.

Ineligible for Intensive Induction Chemotherapy

Inappropriate Selection of Intensive Therapy

FDA-approved options for patients with newly-diagnosed AML who are medically-unfit, but not frail include venetoclax in combination with azacytidine, decitabine, or low-dose cytarabine and for newly diagnosed patients with an *IDH1* mutation, ivosidenib. Midostaurin in combination with cytarabine plus daunorubicin is approved for newly diagnosed patients with *FLT3* mutations. One of our case scenarios was a patient newly diagnosed with *FLT3*-mutated AML and an ECOG PS of 2. Expert faculty noted among those surveyed (**Figure 4a, 4b, red arrow**) that a relatively large number of clinicians, especially non-US clinicians, inappropriately selected intensive chemotherapy plus midostaurin in this scenario (US=26%; ex-US=60%). In the case of the 77-year-old patient with newly diagnosed AML and an *IDH1* mutation our experts selected venetoclax plus HMA therapy over targeted therapy with ivosidenib. Among the survey population, a similar proportion of clinicians are using single agent ivosidenib versus the

preferred approach of venetoclax plus HMA therapy (blue arrow, US=22.64% versus 20.75%; ex-US 20.59% versus 17.65%). Of note, among ex-US clinicians there appears to be confusion between ivosidenib which targeted *IDH1* and enasidenib which targets *IDH2*.

Figure 4a. Primary Preferred Treatment Recommendations for Newly Diagnosed AML Clinical Scenarios, US (n, range 159-162)

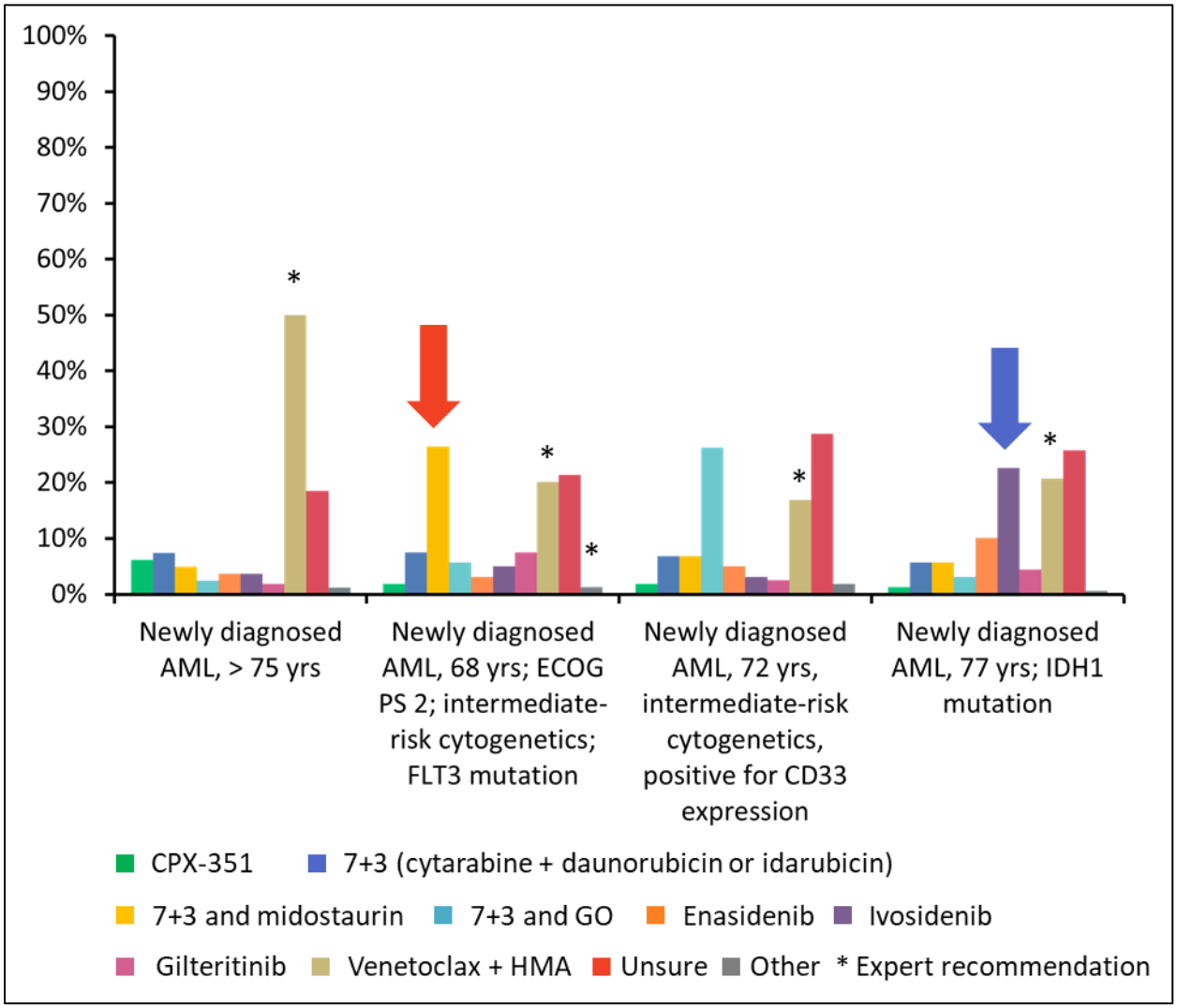
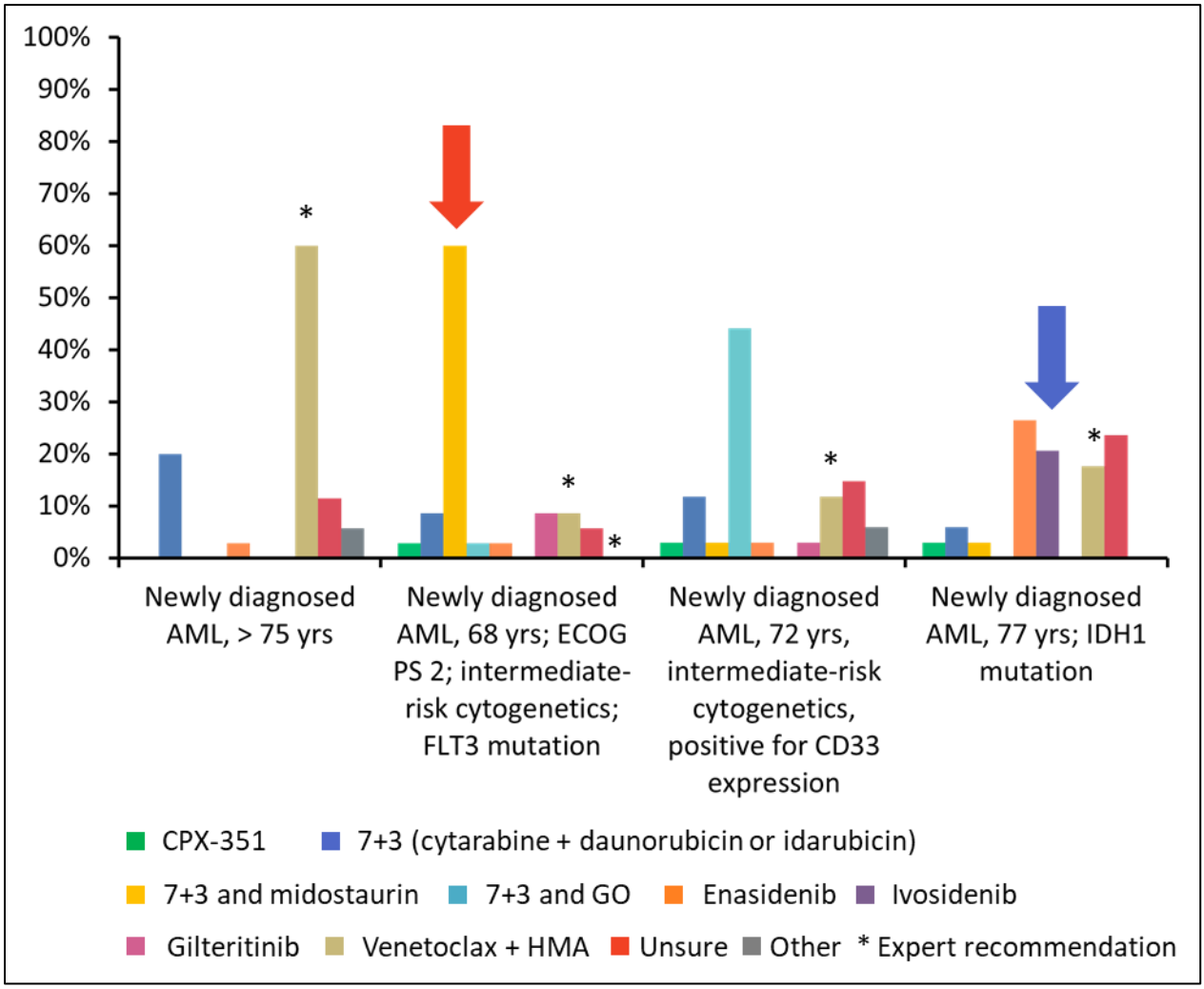


Figure 4b. Primary Preferred Treatment Recommendations for Newly Diagnosed AML Clinical Scenarios, ex-US (n, range 34-35)



Factors Influencing Therapy in Newly Diagnosed AML

Clinicians identified favorable cytogenetics, age, fitness, performance status, comorbidities, the presence of *IDH* or *FLT3* mutations, ease of administration, efficacy, and patient preference or willingness to receive or comply with treatment as key factors that influence their treatment recommendations for newly diagnosed AML. Many clinicians described fitness as the key decision point in terms of whether a patient is eligible for venetoclax plus azacitidine versus 7+3 or CPX-351; gave examples of what they defined as fitness; and emphasized the importance of testing for *IDH* and *FLT3* mutations as factors in selecting therapy. Clinicians typically referred to a similar range of characteristics, including chronological age, that they felt differentiated patients at extreme ends of the fitness spectrum (**Appendix Table 7**).

Age

And a lot of the people that I treat if they're close to 68, close to 70, they're not going to be really candidates for…not only are they not a candidate for a transplant, but they're not a candidate for intense treatment options. So then I already know that that's not a great option for them. So I start to steer to the more lower intensity right away. ***So I use age as another factor, too, pretty big factor****. [Physician, Academic Setting]*

Efficacy

The nice thing about venetoclax plus, let's say aza, is that ***it's effective for any patient with AML. So it doesn't make a difference what their baseline findings are****. They are likely to respond. The categorization may imply how long they're likely to respond more so than whether they will respond. So that's the good news. [Physician, Physician-Owned/Private Practice]*

Variations in the Adoption of HMA plus Venetoclax

As expected, there was very little signal concerning use of 7+3 for patients ineligible for intensive therapy in the interview data; however, there was variation in the adoption of HMA plus venetoclax. Over half of interviewed clinicians described either clinical trial, if available, or azacytidine plus venetoclax as their current standard of care for "older patients," patients over 75 years, or for medically unfit patients. These clinicians are also looking for mutations to treat (*IDH1, IDH2, FLT3*). The remaining clinicians were slowly moving toward adoption of HMA plus venetoclax and away from other options or using existing therapies on occasion (e.g., low-dose cytarabine). Hesitancy about adopting HMA plus venetoclax was linked to the challenge of myelosuppression or cytopenia management, formulary availability, some attachment to 7+3, and questions about whether venetoclax combined with an HMA is less intense than chemotherapy (**Appendix Tables 8 and 9**).

Standard of Care

If they are truly an AML without any actionable mutation, no IDH, and no FLT3 mutation, our standard here is venetoclax with decitabine or venetoclax with azacitidine. If they have one of the targetable mutations like a FLT3 mutation, then that's something you can add to therapy. If they have IDH1 or 2 mutations, there are drugs that are approved for that. [Physician, Academic Setting]

7+3

My only choice here is can I give the patient 7 + 3 or not. That's my first decision. ***If I can get this patient through 7 + 3, that is my go-to drug****. Of course, even if I find a mutation in a patient who is getting 7 + 3, because the molecular studies will take two more weeks to come back, and I cannot wait that long sometimes. [Physician, Hospital/Health System]*

Venetoclax Schedule and Dosing

Toxicities (clinicians noted cytopenias, neutropenia, gastrointestinal toxicity, tumor lysis syndrome), disease progression, or drug-drug interaction between venetoclax and antifungal medications were the most common reasons that clinicians reported for interrupting venetoclax when treating patients with AML. Not all clinicians had seen toxicities with venetoclax and an HMA agent; clinicians who had seen toxicities stopped the venetoclax dose and continued the HMA or lowered the dose of the HMA and maintained the venetoclax. Clinicians noted that side effects from both agents overlapped, making it difficult to identify a toxicity mitigation strategy. They also felt that the administration and dosing schedule described in venetoclax trials were not optimal in clinical practice and often opted for other schedules (**Appendix Table 10**).

Clinicians held a variety of viewpoints on the synergy between venetoclax and HMA therapy, including the following:

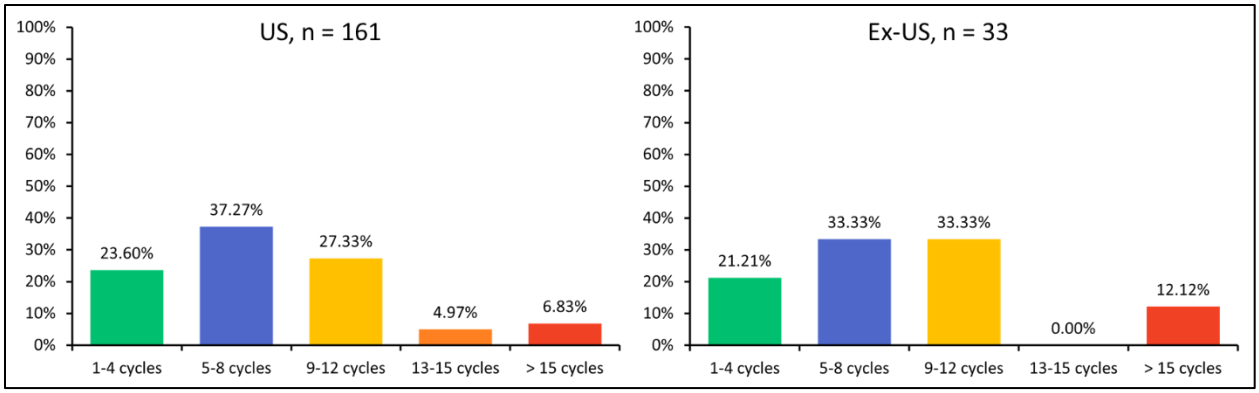
- The efficacy data was stronger for HMAs than venetoclax
- HMAs, either by themselves or in combination, require an extended period of administration to get the full benefit
- Most of the side effects from both agents overlap; therefore, they might stop both agents in the presence of toxicities
- Clinicians questioned continuous dosing and noted that in practice their preference was often to stop venetoclax at day 15 or 21
- Many simply felt uncertain about best practice when using venetoclax and an HMA.

Assessing Treatment Response with Venetoclax

Clinicians vary in therapy duration following complete remission for patients treated with venetoclax plus HMA and are not uniformly using bone marrow biopsy to assess response to treatment with venetoclax-based therapies.

Experts vary in the number of cycles they recommend for patients after achieving complete remission (9-12 or >15 cycles) (**Figure 5**). Similarly, surveyed clinicians also reported variable durations with most recommending fewer cycles than our expert faculty.

Figure 5. Duration of Therapy Following Complete Remission for Patients Treated with Venetoclax Plus HMA Therapy, US and ex-US



Venetoclax-based therapies are associated with rapid responses. Assessment for response is recommended after the first cycle of therapy (around day 28). Venetoclax is associated with significant myelosuppression; therefore, end of cycle bone marrow assessment is important to assess disease status and guide duration of therapy, dose modifications and future cycles.[15] For venetoclax in combination with either low-dose cytarabine (LDAC) or HMA, a bone marrow assessment after the first cycle of treatment is critical to determine dosing and timing of subsequent cycles because most patients will achieve their best response after 1 cycle.

Clinicians were assessing response on a monthly basis using decreasing blast percentages, hematopoiesis improvement, CBC, LDH levels, and coagulation studies. Clinicians who were using bone marrow assessment typically did so after the first cycle and repeated bone marrow biopsy after the third or fourth cycle. Some argued for bone marrow assessment after 2 cycles of treatment. Not all clinicians were using bone marrow for assessment (**Appendix Table 11**).

After 1 Cycle

AML disease is pretty aggressive and much faster growing. You're ready to perform a bone marrow biopsy after induction or after 1 cycle of treatment just to see where the response is. The quality of life is important. Untreated AML will give you very poor quality of life in a very short period of time. It is not just related to the anemia and the thrombocytopenia. It's mostly also related to the infections and other things. [Physician, Academic Setting]

After 2-3 Cycles

I usually see them weekly with a CBC. So, you know, that's a treatment assessment already. And if things are going well, I'll wait probably a month or two for a bone marrow. [Physician, Hospital/Health System]

No Rush to do Bone Marrow Biopsy

The longer you can wait, the better. There's no rush in doing so. It's just if cell counts are good, reasonable, and/or the patient's doing well, no urgency to do a bone marrow evaluation just to see if they're in CR or not. If they're not a transplant candidate, then there's no urgency in getting an evaluation. So you can wait months and months. There's no rush. [Physician, Physician-Owned/Private Practice]

Practice Gap #4: Relapsing or Recurring AML

Clinicians view relapsing or recurring disease as one of the biggest unmet needs in AML management and vary in their approaches.

Relapsing or recurring disease represents a significant unmet need in AML management. Overall, approximately 28% of surveyed US clinicians and 19% of non-US clinicians were "unsure" about their preferred treatment recommendations for patients with relapsed or recurring AML (**Figure 6a, 6b).** Secondary AML is particularly difficult to treat. Both faculty experts indicated they would use CPX-351 in our case scenario. Many survey respondents also chose CPX-351 (US n=22.01%; ex-US n=31.43%) but venetoclax plus HMA (US n=20.75%; ex-US n=22.86%) was also highly selected.

Figure 6a. Primary Preferred Treatment Recommendations for R/R AML Multiple Clinical Scenarios, US (n, range 159-160)

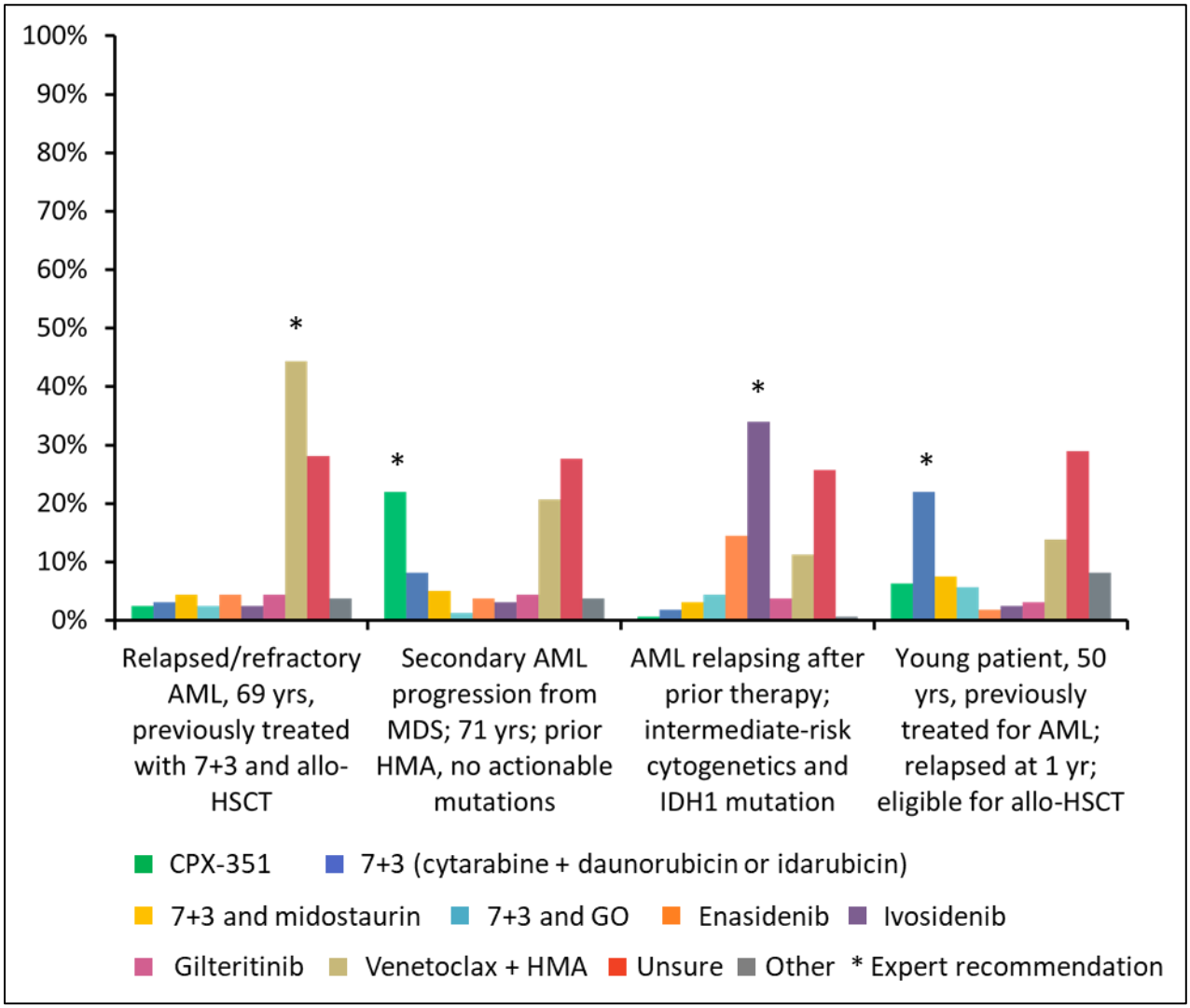
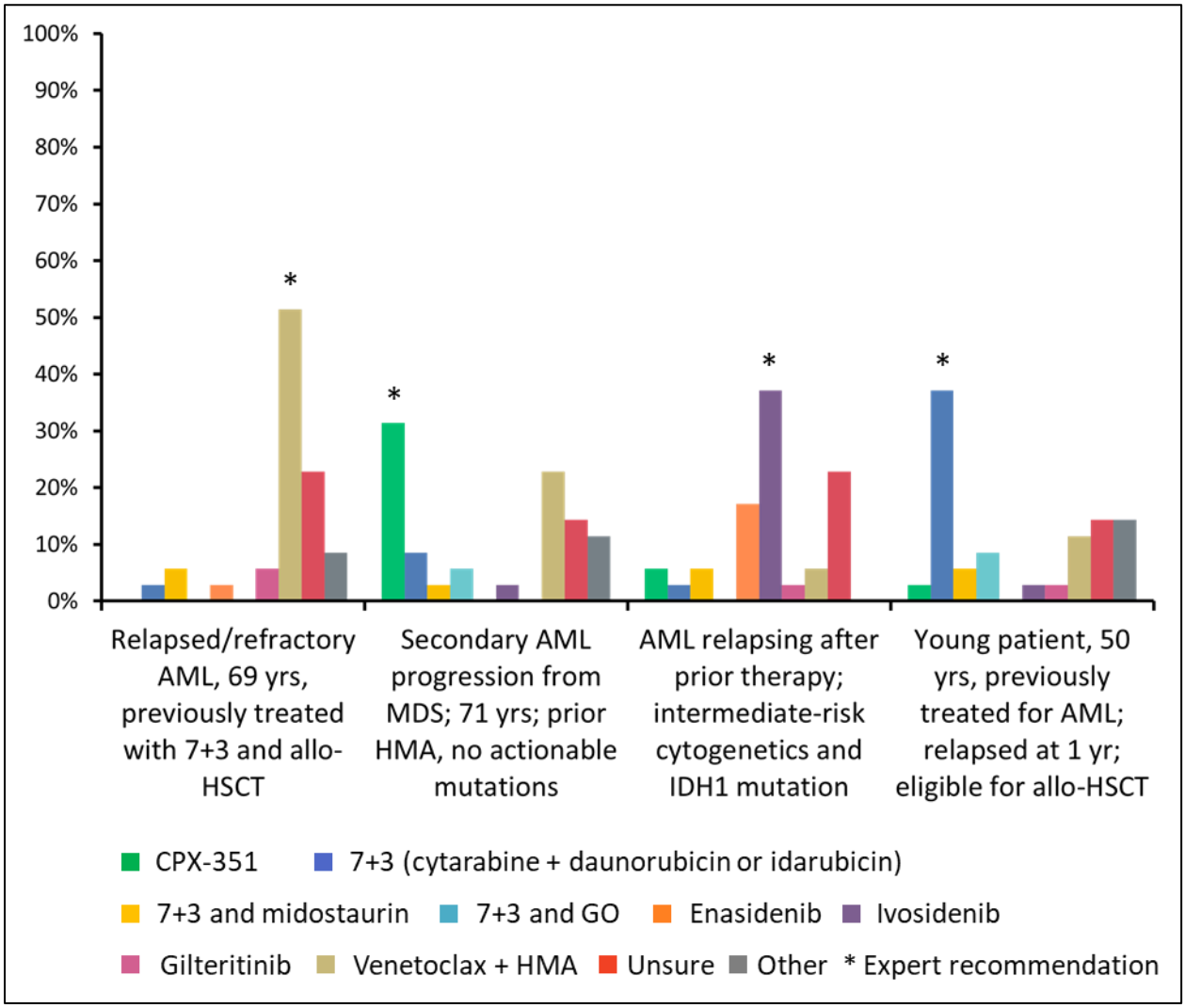


Figure 6b. Primary Preferred Treatment Recommendations for R/R AML Multiple Clinical Scenarios, ex-US (n = 35)



Interviewed clinicians viewed management options were "similar to frail patients" with "no good outcomes" in which patients were often unlikely to make it to the next line of treatment. Said one physician, "*It's a nightmare. So it's not easy*."

Cytogenetics and mutations featured prominently in decision-making with *IDH1/2* inhibitors either as single agents or in combination with HMA or gilteritinib for patients with *FLT3* mutations most frequently mentioned. Otherwise, clinicians were trying whichever options were available in their practice setting with the goal of transplant if patients were eligible and, if not eligible for transplant, then best supportive care. The following comments illustrate the depth of challenges that clinicians face in relapsed or refractory settings.

*And **really talking to the patient in detail about how this is really bad,** and if we're not making improvements soon and we can't get you to a transplant if they're transplant eligible or some other kind of clinical trial protocol, really **talking to them about getting their affairs in order** and we really need to think about palliative care and hospice. [Physician, Hospital/Health System]*

*You kind of look at their cytogenetics and see if there's something that you can maybe target. If you cannot target it, then you just try another induction chemotherapy and pray. **Pray it works**. There's a lot of papers out there that say you can do one versus the other, but in all of my time – even when I was a fellow **– there's no rhythm or reason why one works versus another. So everybody has a style, but nobody really knows**. [Physician, Academic Setting]*

*We would get them to transplant if they're eligible for transplant. If they're not eligible for transplant, then it could become that **we just do best supportive care**. [NP, Physician-Owned/Private Practice]*

The following strategies were noted for treating patients with relapsing or recurring disease. **Table 2**).

Table 2. Reported Strategies for Treating Patients with Relapsing or Recurring AML

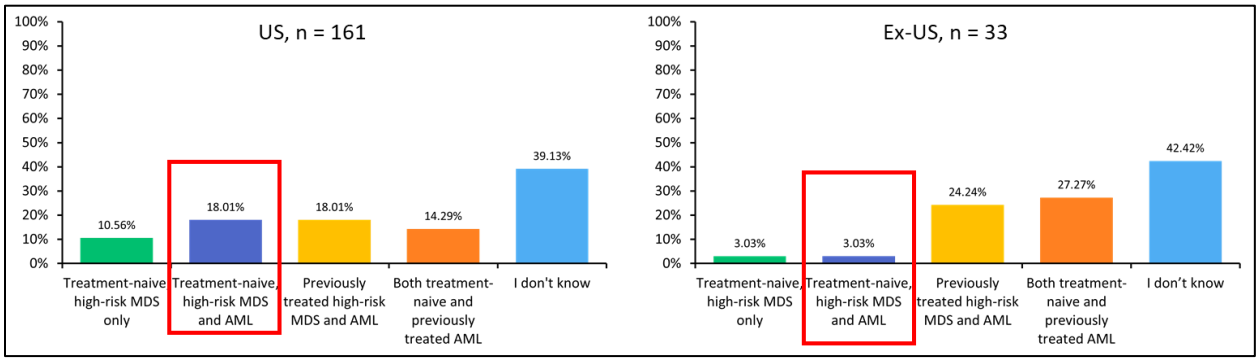
Clinical trials (experimental agents, CAR T-cell)	HMA (decitabine or azacitidine) with venetoclax
Re-induction for primary refractory patients who had never responded to induction regardless of their cytogenetic-risk profile	Reinduction with 5+2, 7+3, low-dose Ara-C, high-dose Ara-C, FLAG-Ida
Second-line therapy like cytarabine or FLAG for transplant-naïve patients who are eligible at relapse to get them to transplant.	Salvage chemotherapy with a different agent (e.g. MEC, FLAG, CLAG-M) to put patients into second remission and try for transplant
Oral azacitidine for patients who have achieved at least remission after the first induction	Off-label glasdegib Gilterinib, enasidenib, ivosidenib, gemtuzumab ozogamicin, high dose lenalidomide

Practice Gap #5: *TP53*-Mutated MDS and AML

***TP53*-mutated MDS and AML represent a clear unmet medical need. Clinicians expressed considerable uncertainty on how best to approach therapy for a patient with *TP53*-mutated AML and were very divided in their approaches.**

TP53-mutated AML is a chemoresistant disease subtype that reduces the effectiveness of intensive chemotherapy such as 7 + 3.[16] Patients with the *TP53* mutation are also frequently older, less fit with more comorbidities, and experience a higher risk of treatment-related adverse events and treatment-related mortality.[17,18] Venetoclax/HMA or decitabine monotherapy are considered less toxic options for these patients than intensive induction chemotherapy.[19] Two novel agents have recently shown some efficacy in patients with *TP53*-mutant disease. Eprenetapopt (APR-246) is a P53-stabilizing agent that in combination with azacitidine numerically, but not significantly, improved complete response rate in a phase III trial for TP53-mutant MDS.[20] In early phase trials, the anti-CD47 antibody magrolimab plus azacitidine demonstrated durable responses in both MDS and AML and especially in TP53-mutant disease.[21,22] A phase III trial of magrolimab plus azacitidine vs placebo plus azacitidine for MDS is currently enrolling (NCT04313881). Despite these favorable results with magrolimab, the majority of survey respondents were unfamiliar with this recent evidence. (**Figure 7**)

Figure 7. Clinician Awareness of Magrolimab Activity in Select Patient Populations, US and ex-US

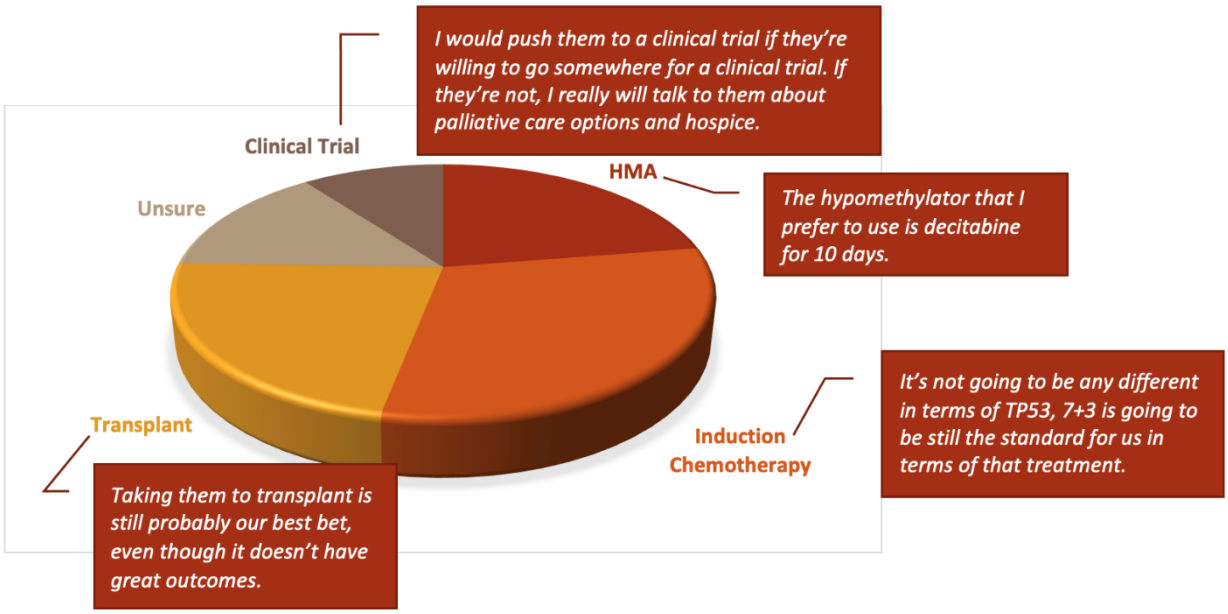


Some interviewed clinicians had not treated patients with high-risk MDS and *TP53* mutations but most of those with some experience of managing these patients said that the presence of *TP53* mutations would not change their overall approach. Most experts believe venetoclax adds little, if any, benefit to patients with *TP53*-mutated MDS. Clinicians described *TP53* mutations as "the worst of the worst" and used a similar, or "more aggressive" strategy as for high-risk MDS patients without *TP53* mutations, including transplant eligibility evaluation depending on the *TP53* mutation burden, clinical trial availability, or hypomethylating agents with or without venetoclax based on data in the AML setting (**Appendix Table 12**). Decitabine was the preferred HMA for some clinicians for patients with *TP53* mutations. Echoing the survey results, few clinicians were aware of the activity of magrolimab in particular patient populations. Clinicians aware of this agent (all in academic settings) were impressed with what they knew of the

available clinical data. These findings highlight the dire unmet need for new effective agents to treat patients with *TP53*-mutated MDS.

Clinicians expressed considerable uncertainty on how best to approach therapy for a patient with TP53-mutated AML and were very divided in their approaches (**Figure 8**).

Figure 8. Reported Therapeutic Approaches for Patients with *TP53*-mutated AML



They felt nothing works in this setting and many viewed transplant as the main goal. A small handful said that clinical trial would be their first consideration (only two specifically mentioned investigational agent magrolimab in this setting), and if unavailable, an HMA with venetoclax, which just over one third overall said they would likely choose. Almost one half said they would opt for induction chemotherapy (with or without transplant) noting 7+3, CFAR (fludarabine, alemtuzumab, rituximab), gemtuzumab, and CLAG (cladribine, mitoxantrone, and cytarabine). Age and fitness were key factors in determining therapeutic direction. Many said they would add midostaurin for patients with *FLT3* mutations or an IDH inhibitor in the setting of an IDH mutation to whichever regimen the patient was receiving (**Appendix Table 13**).

Practice Gap #6: Clinical Trial Referral

Clinicians vary in the timing of clinical trial discussion and the estimated percentage of patients that clinicians said they were able to refer for clinical trials is low. Clinicians themselves view access to clinical trials as a major challenge in the management of patients with MDS or AML. In addition, clinicians lack knowledge of therapeutic agents currently in clinical trials.

In MDS and AML, often there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Participation in clinical trials is encouraged by clinical practice guidelines and experts in an effort to optimize outcomes for patients with MDS and AML and to promote discovery of new therapies. Yet discussion of clinical trials with patients was highly variable. Among US-based clinicians 12% report they "Never" discussing clinical trials and among non-US based clinicians approximately 31% responded "Never" (**Figures 9a and 9b**).

Figure 9a. Frequency of Discussing Clinical Trials in Newly Diagnosed MDS/AML, US and ex-US

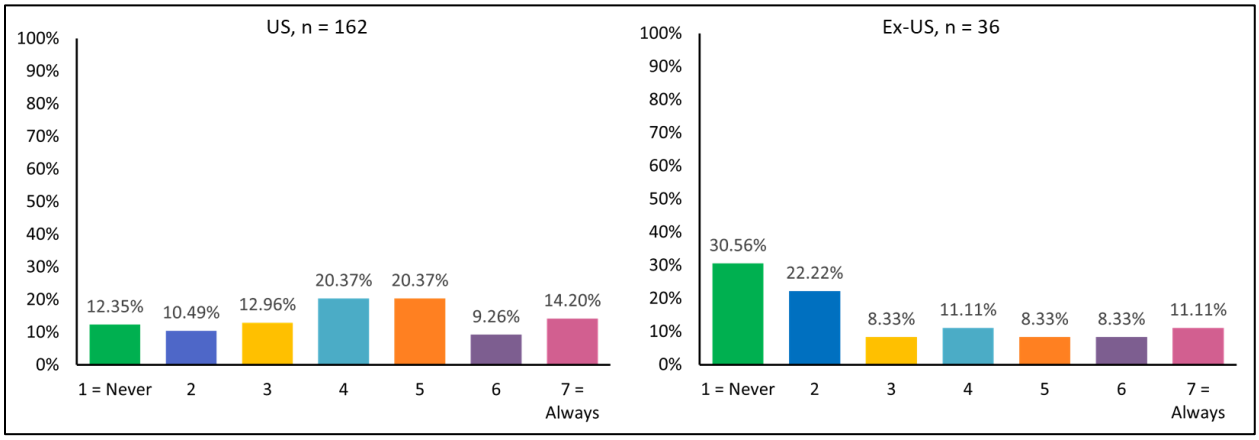
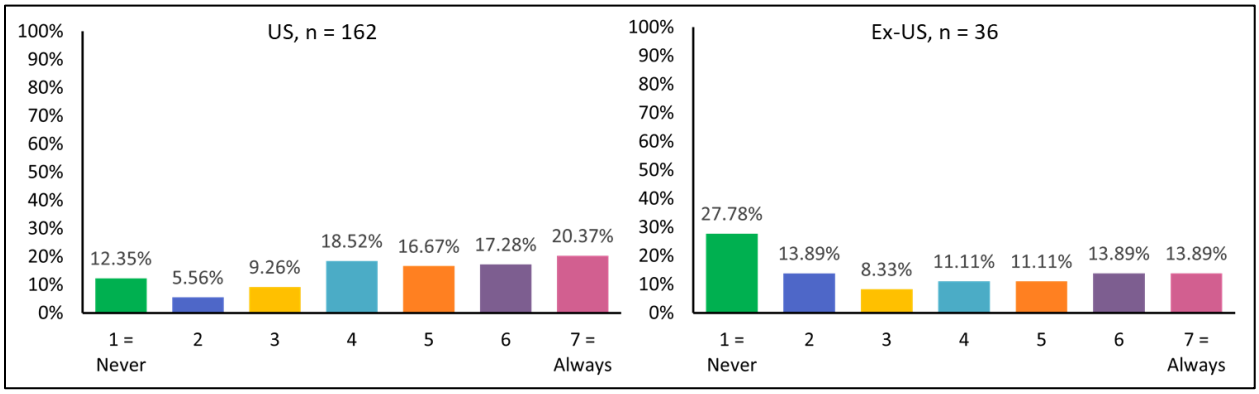


Figure 9b. Frequency of Discussing Clinical Trials in Relapsed/Refractory MDS/AML, US and ex-US



Many clinicians are also unfamiliar with the activity or mechanism of action of agents in clinical trials (**Appendix Figures 5 and 6**). In particular, just 35% of US and non-US respondents were

able to correctly identify the target of magrolimab as CD47. This lack of awareness of mechanism of action is not limited to unapproved agents. Ivosidenib which targets IDH1 and enasidenib which targets IDH2 were often confused and only correctly identified 36-45% of the time.

The picture from interviews of how and at what point in the disease process that clinicians discuss clinical trials varied across healthcare setting.

At Diagnosis and Beyond

Just under half of clinicians in academic or hospital/health system settings said they discussed clinical trials as an option for patients at diagnosis of MDS or AML and beyond. These findings align with the responses this group of clinicians gave to survey questions about how often they discussed clinical trials with patients (i.e., at diagnosis and in the relapsed/refractory setting). These clinicians described having good access to clinical trials at their own institutions and the ability to talk with colleagues about potentially open trials.

At Relapse or Refractory Disease

Approximately 25% of interviewed clinicians reserved discussion about clinical trials as an option for patients with relapsed or refractory disease. Although they too, felt they had good access to clinical trials at other institutions, distance from the clinical trial was a frequently noted barrier to patient interest in participating in a clinical trial. The remaining clinicians—all in physician owned/private practice settings—felt they had considerably less access to clinical trials as an option for their MDS and AML patients or felt that their patients would be reluctant to participate in a trial, again, as a result, in the clinicians' eyes, of distance from the trial center or lack of social and material support (**Appendix Table 14**).

> *Unfortunately, with me being in a very rural setting away from civilization sort of, and patient are in a low socioeconomic status, especially when they have AML, they are really, really reluctant to go anywhere. The only thing I can convince them is to go for a transplant. But to talk about clinical trial will be hard. [Physician, Physician-Owned/Private Practice]*

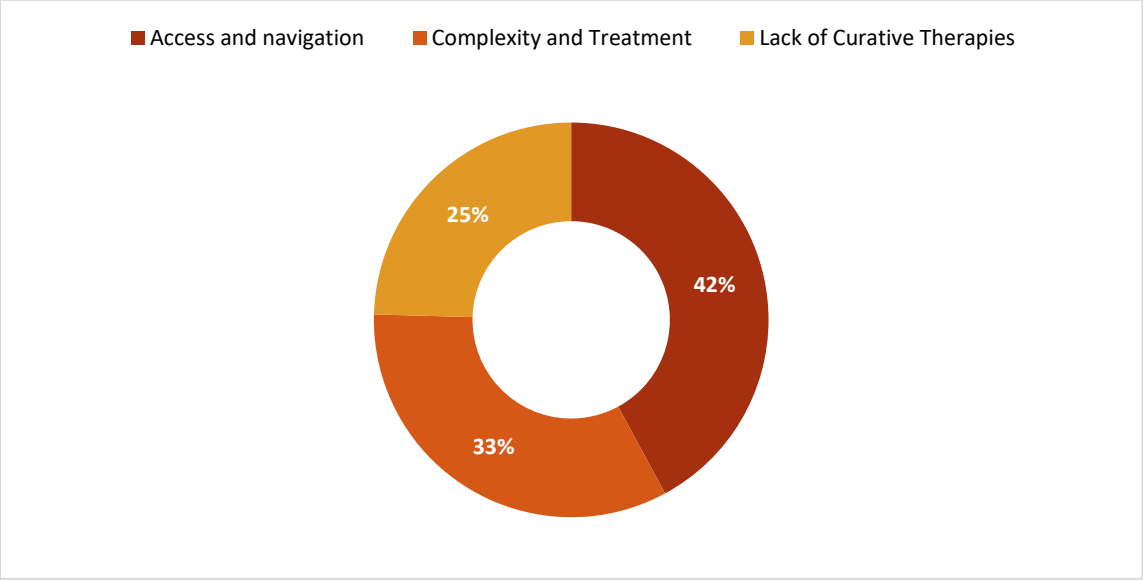
> *In certain situations we may consider induction chemotherapy, but a lot of patients don't want to be admitted to the hospital to get induction chemotherapy, or don't want that intensive therapy in a non-transplant setting in a non-curative setting for MDS. I will highly involve the patient in letting them know these are a couple of the different options that you can use, what would you like us to try. [Physician, Hospital/Health System]*

However, even clinicians who felt they had good access to clinical trials in their own or other institutions, or had a clinical trial coordinator, identified clinical trial access as a major challenge in the management of patients with MDS or AML.

Main Clinical Challenges in the Optimal Treatment of Patients with MDS or AML

The top 3 clinical challenges that interview participants identified as barriers to optimal treatment and patient management were access and navigation to therapies; the complexity of treatment; and the lack of effective therapies (**Figure 10**). Clinicians across different practice settings shared these challenges.

Figure 10. Top 3 Reported Clinical Challenges



APPENDIX

MDS/AML Survey

1. Do you currently treat patients with either MDS or AML?
   A. Yes
   B. No [If selected send directly to “thank you” screen]

2. Which of the following most accurately identifies your role on the healthcare team?
   A. Physician
   B. Nurse practitioner
   C. Nurse navigator
   D. Physician assistant
   E. Pharmacist
   F. Allied health professional
   G. Other (please specify)

3. For how many years have you been practicing medicine?
   A. < 5
   B. 5-10
   C. 11-15
   D. 16-20
   E. > 20

4. Please indicate where you currently practice medicine.
   A. United States
   B. Outside the United States

5. Approximately how many patients with MDS or AML do you provide care for in a typical month (including newly diagnosed, actively managed, and follow-up patients)?
   A. < 5
   B. 5-10
   C. 11-15
   D. 16-20
   E. > 20

6. Which of the following best describes your primary practice setting?
   A. Academic
   B. Hospital/health system owned

C. Physician owned/private practice
D. Other (please specify)

7. Which of the following best describes your specialty?
   A. Medical oncology
   B. Hematology/oncology
   C. Radiation oncology
   D. Primary care
   E. Nursing
   F. Pharmacy

8. How often do you discuss clinical trial participation with your patients with newly diagnosed MDS or AML?

   (Never to Always 7-point Likert scale)

9. How often do you discuss clinical trial participation with your patients with relapsed/refractory MDS or AML?

   (Never to Always 7-point Likert scale)

10. From memory, try to match the following agents to their target or mechanism of action (please do not look it up)

Agent	Bcl-2	Bispecific antibody to CD123 and CD3	CD123	CD33	CD47	FLT3	Hedgehog Pathway inhibitor	IDH1	IDH2	NEDD8-activating enzyme	p53	TIM-3	Unsure
Enasidenib *(IDHIFA)*													
Eprenetapopt (APR-246)													
Flotetuzumab													
Gemtuzumab ozogamicin *(MYLOTARG)*													
Gilteritinib *(XOSPATA)*													
Glasdegib *(DAURISMO)*													
IMGN632													
Ivosidenib *(TIBSOVO)*													
Magrolimab													
Midostaurin *(RYDAPT)*													
Pevonedistat													
Sabatolimab (MBG 453)													
Venetoclax *(VENCLEXTA)*													

11. Magrolimab has shown encouraging activity in which of the following patient population(s)?
    A. Treatment naïve high-risk MDS only
    B. Treatment naïve high-risk MDS and AML
    C. Previously treated high-risk MDS and AML
    D. Both treatment naïve and previously treated AML patients

12. At what stage do you consider there to be sufficient evidence for you to be comfortable using a new/novel agent to treat your newly diagnosed patients with MDS or AML?
    A. Regulatory approval based on phase III data and expert recommendation
    B. Regulatory approval based on phase III data
    C. Regulatory approval based on phase II or premature phase III data
    D. No regulatory approval but inclusion in treatment guidelines based on clinical data
    E. No regulatory approval but phase III data demonstrating a survival advantage and expert recommendation
    F. Other (please specify)

13. Are you sufficiently familiar with the investigational agent magrolimab to use it in your practice if approved by your regional regulatory agency (FDA, EMA, etc)?
    A. Yes
    B. No

14. How confident are you in your ability to appropriately use the recently approved oral decitabine (decitabine + cedazuridine) for patients with MDS? (*7 pt Likert scale*)

15. For each of the following clinical scenarios of patients with MDS please indicate your primary preferred standard treatment recommendation in your practice.

(Use matching question format; answers may be used more than once; each case can only have 1 answer)

Clinical Characteristics at Presentation	**Azacitidine**	**Azacitidine + Venetoclax** (*off label*)	**Decitabine**	**Oral decitabine** (decitabine + cedazuridine)	**Induction chemotherapy (3+7 or similar)**	**HMA followed by allo-HSCT**	**Unsure**	**Other**
Newly diagnosed, higher-risk MDS								
Newly diagnosed, higher-risk MDS with TP53 mutation								
High-risk MDS previously treated with HMA; ineligible for transplant								

16. For each of the following clinical scenarios of patients with AML please indicate your primary preferred standard treatment recommendation in your practice.

(Use matching question format; answers may be used more than once; each case can only have 1 answer)

Clinical Characteristics at Presentation	CPX-351	7 + 3 (cytarabine + daunorubicin or idarubicin)	7+3 and midostaurin	7+3 and GO	Enasidenib	Ivosidenib	Gilteritinib	Venetoclax + HMA	Unsure	Other
Newly diagnosed AML, > 75 yr										
Newly diagnosed AML, 68 yr; ECOG PS 2; intermediate risk cytogenetics; *FLT3* mutation										
Newly diagnosed AML, 72 yr, intermediate risk cytogenetics, positive for CD33 expression										
Newly diagnosed AML, 77 yr; IDH1 mutation										
Relapsed/refractory AML, 69 yr, previously treated with 7 + 3 and allo SCT										
Secondary AML progression from MDS; 71										

17. In your practice, for patients treated with venetoclax plus HMA therapy who achieve a complete remission, how long do they routinely stay on the combination regimen after reaching a CR?
    A. 1-4 cycles
    B. 5-8 cycles
    C. 9-12 cycles
    D. 13-15 cycles
    E. More than 15 cycles

18. Do you routinely use growth factors with standard induction chemotherapy?
    A. Yes
    B. No

19. Do you routinely use growth factors with venetoclax plus HMA therapy?
    A. Yes
    B. No

20. What is the oldest age of a patient you would consider for stem cell transplant?
    A. ≤ 60
    B. ≤ 65
    C. ≤ 70
    D. ≤ 75
    E. > 75

21. What educational method or approach do you prefer when learning about managing your patients with MDS or AML? (*multiple selections allowed*)
    A. Live meeting/webinar
    B. On-demand webcast
    C. Online short video
    D. Online text
    E. Downloadable slides
    F. Podcast
    G. Live Q&A with an expert
    H. Other (please specify)

22. If you would like to participate in a 45-minute qualitative survey, please enter your email address. (Only for US-based clinicians)

TABLES

Table 1. Cytogenetics, Mutation Profiles, and Patient Preferences in MDS and AML

Bone Marrow Biopsy for Unexplained Cytopenias
If you see a cytopenia that you cannot explain, I'm very trigger happy with bone marrow biopsies. [Physician, Hospital/Health System]
If they have MDS, their erythropoietin level is high most of the time. Essentially, they require bone marrow biopsy. That's a gold standard for diagnosis of MDS. [Physician, Physician-Owned/Private Practice]
MDS is one of the somewhat rare hematologic conditions where you really can't make a diagnosis without a bone marrow biopsy. [Physician, Academic Setting]
It's almost expected that you will have a bone marrow evaluation. It'd be very unusual not to do bone marrow evaluation. It's obviously not a difficult procedure to undergo. It's not too difficult to convince a patient that they need it. Bone marrow evaluation for diagnostic purposes is essentially a must, as far as I'm concerned. [Physician, Physician-Owned/Private Practice]
Ultimately, we would need to do a bone marrow biopsy if the patient didn't have any obvious explanations for their abnormal blood counts. So if they had unexplained cytopenias, I often will simultaneously do a genetic test, where we look for mutations that are associated with MDS. And, in fact, in some patients we often get that information back before we even do the biopsy. [Physician, Academic Setting]
***We do bone marrow biopsies at diagnosis. Only for the very older patients, you'd not**. But for almost everybody it's a bone marrow biopsy to calculate the blasts percentage. Very, very rarely in a very older patient, but almost everybody gets it. [Physician, Academic Setting]*
Cytogenetics, Mutational profile, and Patient Preferences
I'm looking to see if a patient has any mutations for targetable therapy. If a patient has IDH mutations, that would be one thing. And also, if the patient's fit enough to do an allogeneic transplant. [Pharmacist, Hospital/Health System]
We do screen for p53 mutations. There are certain cytogenetic abnormalities, like loss of chromosome 5 and 7, that correlate with p53 mutation, which primarily fits into a higher risk or high-risk category. [Physician, Academic]
We'll do a bone marrow biopsy, and from there we'll send off both conventional studies – FISH, cytogenetics, and also next-gen sequencing for both prognosis and treatment decisions.[*Physican, Academic Setting*
In AML, we've had so many new therapies, just flooded in terms of lots more options. So kind of looking first to determine patient's risk status, the cytogenetics and molecular abnormalities that we're looking at to determine if they're favorable risk status, or if they're poor versus intermediate. And that's one thing to look at. And also, we want to see the targets. Does the patient have a FLT3 mutation? Does the patient have an IDH mutation? And lastly, also looking at the patient's fitness level as well, to help kind of determine which route to go. [Pharmacist, Hospital/Health System]
All these patients would receive bone marrow biopsy, including next-generation sequencing and cytogenetics, and these patients would be risk stratified based on their cytogenetics and molecular makeup into favorable, intermediate, or high-risk patients. [Physician, Academic Setting]
Once you assess all the performance status, they usually get a bone marrow biopsy. And in the bone marrow biopsy, you can see is it just MDS, is it MDS almost about to convert to leukemia? We can send cytogenetic markers to see is there a 5q deletion where you can maybe use lenalidomide or Revlimid; if not, they have complex cytogenetics, or do they have an IDH1 mutation? You can see,

based on the cytogenetics, what are potential treatment options for them. [Physician, Academic Setting]
If I have somebody who's younger, who's fit, who I think might benefit from a transplant who may have MDS, then I will actually proceed with the bone marrow biopsy initially, check cytogenetics, check all of the next-generation sequencing for all of the mutations. And then get them up to a consultation at one of our transplant centers, and then make decisions based on therapy based on whether somebody thinks that they're going to transplant them early, or if we're just going to wait it out and see how things go. [Physician, Hospital/Health System]
Patient Willingness to Receive Transplant
*I have a lot of little old ladies that are at the end of their lives, and half their kids are dead already, and all their friends are dead, and they've been without a husband for 40 years. And they wake up and their backs are sore, and their knees are sore, and they've got cataracts, and they can't hear. And **they're the ones who are like let's treat this if it makes me feel better, but I don't want to be sick with chemo to get an extra 6 months or an extra year. Or can we just do supportive care**? They gave me a transfusion, and I felt so much better. Can't we just do that again? [Physician, Physician-Owned/Private Practice]*
*We also want the patients to be very, very involved in their care. The patients and the caregivers and their families. We want this to be a team approach, not just the physician and the staff telling the patients what we're going to do. Sometimes we can make an offering of several options and let the patients kind of decide what they want to do. Sometimes we learn things from them that we hadn't thought of **and the patients would say, look, I would rather live less time and have a happier, productive life rather than living longer and I'm totally dependent on someone**. We let that all be a part of that conversation that we are having with the team and the patients, as well as their caregivers. [Physician, Academic Setting]*
*I will tell you that for both acute myeloid leukemia and MDS, I will have patients who I feel are medically fit for potential induction chemotherapy or a transplant evaluation, or both, and **sometimes patients will just say I don't want to travel the 2 hours to go to Kansas City to have my treatment done, so do whatever you can locally, and that's all that I want done**. And some of those patients we'll give induction chemo to but knowing that might only buy them some extra time. But patients sometimes trump what we want to do for them. [Physician, Hospital/Health System]*

Table 2. Definitions and Approaches to Assessing Fitness

Gestalt Approach
Even from when you start to look at them, you can really get the impression, as well, whether these patients would require oxygen supplementation or not, and how much muscle mass they have. ***When you look at these patients you can get also a fair estimate on them****. [Physician, Academic Setting]*
Once you see the patient ***you get the gist****. [Physician, Hospital/Health System]*
Usually we define fitness as whether or not we think a patient is likely to be able to tolerate intensive chemotherapy. ***We have kind of a binary system for deciding whether a person is fit or is not fit.*** *[Physician, Academic Setting]*
There are scoring systems, but I think I have learned to rely on my clinical acumen to get a better and more comprehensive understanding of the patient's history than just the score. [Physician, Hospital/Health System]
Trust in Tacit Knowledge
After being in the business for 30 years, many times you don't necessarily need an official scale system. ***You can make up your mind just looking at a patient****. [Physician, Physician-Owned/Private Practice]*
*Most of the time****, this is physician judgement*** *whether this patient is fit or not according to the age. [Physician, Academic Setting]*
I know there are tools to do that, scoring systems, but we have not done that. We are looking at ECOG functional status. We work closely with pulmonary and cardiology and endocrinology, and these are the most common comorbidities that the patients have. Again, not a formal process. ***It becomes like a judgment call quite often****. You have to decide whether your patient is essentially, not in MDS but at least in leukemia, you have to make this call whether your patient is going to be handling intensive chemotherapy or not.* ***Oftentimes, it's to start off, an eyeball test****. I think we probably err on the side of caution. [Physician, Hospital/Health System]*
We all try to look for the ECOG performance status, and that's what we use at least for just assessing if the patient will be eligible for high chemotherapy like 7+3, even Vyxeos. So ***ECOG performance status but there's also a subjective level to it****. Even if someone has a good performance status but is the eyeball test like you sometimes see. [Physician, Hospital/Health System]*
Age and Its Gray Areas
So, a patient who is on the younger end of 65 – so maybe they're 50 and completely fit – or the patient who's 90 and is bedbound and debilitated, those are fairly easy to assess for most people. ***It's the people in the gray areas in between who are maybe 70 and have, you know, one or two comorbidities****. And you have to make a more informed decision based on how functional they are, how, you know, fit they are, what other medical conditions they have, and what their life expectancy is. And so, I think that's more of a Gestalt. [Physician, Academic Setting]*
Most MDS patients are older patients, so they will benefit from those assessments, even without MDS. It's always good to get a sense of how an older person is doing and not just their medical comorbidities, but also their geriatric vulnerabilities, which are factors that affect their tolerability to treatment, affect their quality of life, and also affect their independence to live in the community and live at home. There will also be patients who are vulnerable even before they were diagnosed with MDS or AML. Those are the patients then obviously you would consider whether there is a way you can optimize or improve their function or remedy their vulnerabilities. **It is this group of patients who are the most tricky when it comes to the medical decision-making by the physicians**. [Physician, Academic Setting]

Table 3. Factors Determining Eligibility for Intensive Therapy in High-Risk MDS

Age
I know age is a factor, also performance status. *So typically, if it's someone who is older, if they have a higher risk, if they have certain mutations that we can possibly target, then that might be something that we would treat here, start on a hypomethylating agent. If we can do some of the orals like Bcl-2 inhibitors, or again, they have those mutations and the IDH mutations, then we can target those. [Pharmacist, Academic]*
It's depending on the age. *They may be slotted in for the high risk, either like a hypomethylating agent and then adding like other…depending on what the mutations are, like venetoclax with it, or there's the other drug called…that's fairly new, though. So depending on what their age, if they are younger, of course, and then going into transplant from after that if they're high risk. [NP, Academic Setting]*
If they're over 70 – is kind of my cut-off point, 70 or 75 *– and they have a lot of other comorbidities going on, then you certainly can't be more intense than really a hypomethylating agent or maybe danazol. [Physician, Academic Setting]*
If a patient has higher-risk MDS, doesn't have very many comorbidities, ***we do have a little bit of an age cut-off there. It's roughly around age 75****. So, it's very similar to what we would think about if the other patients are fit for chemotherapy. [Physician, Academic Setting]*
The main factor at the end of the day, like I said, would be ***whether somebody's fit or not fit which in reality comes along with age. So that is the main factor****. Well, of course, there are other factors. Let's say we know that somebody's not fit, we decide whether somebody is going to be compliant or noncompliant. A patient might want to say I really want very little treatment-wise, I mean I agree for the treatment, but I don't want it to be too aggressive, I want you to be aware of it. So individual patient's wishes, and there is no specific format how they express it, would matter. [Physician, Hospital/Health System]*
Fitness
For ***high-risk patients who have mild alterations in their blood counts but high-risk genetics, I think that is more of a gray area****, in terms of whether they should be treated like a high-risk patient and put on the trajectory for stem cell transplant, if they're eligible, versus a high-risk patient who has an elevated blast count and/or, you know, substantial cytopenias – a hemoglobin less than 10, a neutrophil count that's reduced, or thrombocytopenia with a platelet count less than 100 – to the point where they're kind of getting into that danger zone that they're going to develop symptoms. For those patients, again, we kind of stratify them by their age, eligibility, down the road for an allogeneic stem cell transplant, which is really the only curative therapy. [Physician, Academic Setting]*
Age and the performance status – these are the two major factors*. You can add comorbidities like someone has maybe advanced, very complicated diabetes or someone has rheumatoid arthritis or very uncontrolled other or renal failure. So even if their performance status might be good, but that kind of push them to the unfit patients. [Physician, Academic Setting]*
ECOG 2 and above would be considered unfit *and those would not be offered usually a definitive treatment with a transplant. [Physician, Academic Setting]*
A lot of it is just clinical gestalt *and just looking at their comorbidities, and looking at their performance status, and looking at if they're willing to travel to as well, but I'm really using like can they walk, can they walk up a flight of stairs, can they walk more than a half a mile? Do they have any major heart disease, lung disease, liver disease that's going to exclude them from a transplant? Are they willing to travel? Those are the main ones. [Physician, Hospital/Health System]*

Right off the bat, you have to decide is this a good performance status, so we look at the ECOG immediately. That way you do intensive therapy or just hypomethylating agent, venetoclax. [Physician, Hospital/Health System]
*Using ECOG classification and a little bit of age, too, you know. We used to focus a lot on biological age more than just the chronological, but **we'll be very careful with somebody who was above 70**. [Physician, Hospital/Health System]*
***That is a more subjective measure.** And in part it has to do with their comorbidities, any other organ dysfunctions they might have. It has to do with their functional ability. I think patients who spend greater than 50% of their day in bed or in a chair and you have poor performance status, do worse, are patients that I would be concerned about being able to tolerate intensive chemotherapy. [Physician, Academic]*
Tolerance for Therapy
***There's an assessment of their tolerance of intensive therapy**. I look at hypomethylating agents as kind of intermediate between kind of low-dose therapy and intensive therapy. At the standard dose of decitabine and azacitidine, they clearly are acting as cytotoxic agents. [Physician, Academic]*
We are trying to look at the comorbidities the patients may already be experiencing because of the age group. It's usually diagnosed with 70 and up. We're looking at how they may tolerate these different regimens of medications. Also we're looking at their risk stratifications, as well as their quality versus quantity of life. [NP, Physician-Owned/Private Practice]
*Once the patient begins their treatment, then obviously depending on what kind of treatment and where the patient is, with MDS and AML, as you well know, we have options. We can admit the patient to the hospital and give them very intensive chemotherapy. If they're frail we can give them a less intense chemotherapy, still in the hospital. If they are healthy, we can treat them outpatient. A lot of those things are determined by several factors. One is frailty of the patient. **Are they going to be able to withstand the treatment**. That's the first, if you will, the decision point. What intensity can they tolerate.* [Pharmacist, Physician-Owned/Private Practice]
Age, comorbidities, performance status, **how much he or she can take**….If he is more on the elderly side and not really as excited to do an allotransplantation, then the next best thing is what's available to us. In this case, still HMA alone is the standard therapy with or without growth factor support if they are anemic or neutropenic. After assessing the disease, **then you look at the patient and see what he or she can take**. So in an MDS world where hypomethylating agents are the drug of choice, that's kind of our baseline.[*Physician, Physician-Owned/Private Practice]*
Patient Preference/Quality of Life
You look at the patient's comorbidities and whether the patient wants to be aggressive with the therapy, or whether they're, for whatever reason, that they're inclined not to. They're trying to avoid being in a hospital. They understand what their situation is. They accept it in some fashion, and therefore you don't have to necessarily try to be as aggressive. [Physician, Physician-Owned/Private Practice]
*We want this to be a team approach, not just the physician and the staff telling the patients what we're going to do. Sometimes we can make an offering of several options and **let the patients kind of decide what they want to do**. Sometimes we learn things from them that we hadn't thought of and **the patients would say, look, I would rather live less time and have a happier, productive life rather than living longer** and I'm totally dependent on someone. We let that all be a part of that conversation that we are having with the team and the patients, as well as their caregivers.* [Physician, Academic Setting]
Let's say we know that somebody's not fit, we decide whether somebody is going to be compliant or noncompliant. A patient might want to say I really want very little treatment-wise, I mean I agree for

the treatment, but I don't want it to be too aggressive, I want you to be aware of it. So individual patient's wishes, and there is no specific format how they express it, would matter. [Physician, Hospital/Health System]
Patients' wishes also come into play. There are people who are much more motivated if they have a good support system, then we know that things will fall through the cracks. These folks will require multiple trips to the clinic, multiple labs, infusions. Sometimes insurance can bet in the way also, particularly for targeted therapies. The copay costs can be excessive. One of the targeted drugs for IDH1 and IDH2, each drug is probably $1000 a pill. Even the copay cost, even if it is 10% to 20%, that becomes unaffordable. [Physician, Hospital/Health System]
We have a lot of patients that don't want to be admitted to the hospital for treatment. Anything you can do for me, as an outpatient, I'll do. I don't want to be admitted is a very common theme we hear, especially in the older patient population and especially with COVID. [NP, Academic Setting]
If we do MDS, say the treatment they planning to do that as outpatient, and they have limitations for transportation, that's not going to work. So before they start the treatment, I'm involved in there. So we talk about it, what's going to work for them or not, like they're going to need transfusion support and things like that, transportation and all that, so we can work out the best plan that's going to be workable and patient can be compliant with it. Insurance, also. So I look at the aspect of the insurance, as well, as anything that could be…before the decision is made to let's just treat with this, just kind of making sure that everything is going to be…and not like in the midst of treatment we're going have problems. [NP, Academic Setting]
I've got people that are in their seventies, and they're exercising, and they've got a trip planned to Europe, and they want whatever they can do as aggressive. They've got a daughter's wedding up, or they've got a grandbaby coming or even a great grandbaby coming that they want to make it to. They want to be aggressive. And ***you've got to talk to your patients, and you've got to get a feel****. [Physician, Physician-Owned/Private Practice]*

Table 4. Newly Diagnosed High-Risk MDS

Goals of Care
In general, those patients who don't get a transplant, they will be provided these supportive care measures. We also have drugs like what they call hypomethylating agents. Those are the azacitidine, the Vidaza, the Inqovi and Onureg. Those are the four commercially available drugs that you can give them to allow for the marrow to try to reconstitute and be as close to normal as possible with the goal of preventing or reducing the number of transfusions they will require. Sometimes our measure is how frequently are we having to transfuse this patient. That alone is considered a benefit of giving these drugs such as the ones I mentioned. [Physician, Physician-Owned/Private Practice]
If they're not a transplant candidate and they're high-risk MDS, then mostly the overall treatment approach is palliative. The standard treatment hasn't shown to really prolong survival while maintaining quality of life that much better. If they're not curative, then you also want to pay attention to their quality of life. You don't want to have a treatment approach which might extend their life expectancy by a few months but in the process basically making them hospital bound most of the time. That's what I think about it. [Physician, Academic Setting]
Evaluation for Transplant/Intensive Therapy
7 + 3, right. If we're talking about induction chemotherapy that's a fairly easy call on us. If we see somebody with bad kidneys, heart failure, bad neuropathy, in general a poor protoplasm, a patient with an ECOG 2. ***You would hesitate to pull the trigger****. You have to tread lightly.* ***Oftentimes it is just a gut feeling.*** *You see the patient, they are moving around, active. There are people who have been runners all their life, you know they're in good condition, it's just unfortunately they got diagnosed.* ***There you could be more aggressive. I don't have a good answer. It's a clinical judgment at that point of time.*** *There could be people that you might look at, 72,* ***anybody who is older than 70 we hesitate****. Then there are people who are older, and we have treated them aggressively. [Physician, Hospital/Health System]*
Some of those patients who are maybe very fit, we may also refer them for an allogeneic bone marrow transplant as well. I will probably say maybe ***9 out of 10 patients that I do see with high-grade MDS in my center are probably not fit for a bone marrow transplant*** *right away. [Pharmacist, Hospital/Health System]*
If we know they're high risk, the first thing is to evaluate whether they are a candidate for allogeneic transplantation*. That's obviously considered the only curative approach for patients with high-risk MDS. For transplant to work, you also have to consider social support system, psychiatric stability, and the availability of caregivers.* ***Those are not medical, but they are important for the success of a person to go through intensive treatment****. [Physician, Academic Setting]*
The group that I work with, who they are going to look at for a transplant based on, a lot of times, age. So, under age 75. And it's kind of been a moving target, but probably close to that. ***If you have a really healthy 75 or younger, you can still be transplant eligible, but for the most part, I have not had them think that someone above that age is going to be eligible.*** *So how frail they are, what their geriatric scores or comorbidity scores are, and then age does come into a factor of deciding transplant eligible and ineligible. [Physician, Hospital/Health System]*
Not everybody needs a transplant and ***not everybody qualifies for a transplant. Some of the barriers to receiving a transplant would be frailty****. Not necessarily age, but just physical performance status and so on. It's a rough course. If you have, say a 72-year-old that has diabetes and COPD, they are not good candidates for a transplant. Age alone is not a factor.* [Pharmacist, Academic]
Bridging Therapy

*The rare case where we might use something more intensive, is a patient that we want to take directly to transplant and **where we want to be able to cytoreduce them significantly before we do so**. In those cases we do consider more intensive therapy. [Physician, Academic Setting]*
*Because HMA alone has been challenged in its effectiveness. But I would say, certainly, there is modest improvement – so not everybody responds – and if they respond, their response can be short lived. So **you need to use it as a bridge to see what else you want to do**. [Physician, Physician-Owned/Private Practice]*
*If the patient is a candidate for it, then obviously you have to evaluate whether the patient can go straight to the transplant if they have an available donor, what the timeframe will be, and whether their disease can withstand this time period of securing a donor. **If not, then it's appropriate to give them some additional treatment before going to transplant**. [Physician, Academic Setting]*
*If they have a very high blast percentage, sometimes you begin intensive chemotherapy for especially those with very, very high, about 15%, 20% or so of blasts percentage. Others, **you would try to get them hypomethylating agents plus venetoclax, and then eventually think about transplant**. It all really depends on the performance status and age of the patient. [Physician, Academic Setting]*
*I have sent people straight to transplant also. More often than not, **the whole transplant process takes time. They would need some therapy**, usually azacitidine. [Physician, Hospital/Health System]*

Table 5. Response Assessment in MDS

Bone Marrow Timing
I usually will obviously look at their blood counts and see if they are getting better, or if they have any other symptoms like fatigue or night sweats or anything else which are pretty rare in MDS but can happen, I will use symptoms as an agent, mainly cytopenias. And then usually after about 2 to 3 cycles of whatever we're going to give if it's not an induction chemotherapy, I will assess with a repeat bone marrow biopsy to see what's going on. [Physician, Hospital/Health System]
After first month, second month, after 2 cycles or 3 cycles, I will do the bone marrow biopsy, and then we will reevaluate how the patient is doing [Physician, Academic Setting]
PROs/Transfusion Burden
At the end of the day the goal here would be to stabilize blood counts; that means if somebody receives transfusion-independence, whether this is for red cells or platelets, that is one of the parameters. Of course, you always ask a patient how he or she is doing. We also recognize that at the end of the day this is multifactorial, which means that other factors might play a role, and it is quite uncommon that you'll hear a direct answer. [Physician, Hospital/Health System]
The easiest way to do it is just like do their transfusion needs decline, are they able to come in like a little bit less often? Are their blood numbers starting to improve a little bit? Are they feeling a little bit better? Like if they were short of breath, tired, or fatigued, are those symptoms getting a little bit better? So I look at all of that. Like quality of life symptoms, transfusion needs, and whether the blood numbers are improving. Those are all factors that kind of play a role. Maybe somebody who needed a transfusion every week, maybe now they need it every 2 weeks. Maybe if you had to give 2 units of blood every week, now you are doing 1 unit of blood, and that makes a big difference. [Physician, Academic Setting]
The goals of treatment are going to be symptom relief, alleviation of any symptoms that are being caused from the disease itself. If a patient, for example, is anemic and needing transfusions, 1 assessment of response would be, are they now no longer anemic. Do they now no longer need blood transfusion? Are they able to maintain hemoglobin on their own? That's an example of what I would look for in a response.[Physician, Hospital/Health System]
If the patient's initially symptomatic, so if their counts are improved, their symptoms are improving, are they still needing transfusions, are some of the things that we look at. Patient-reported outcomes, how they're feeling. The counts is the biggest thing, so in terms of if they're needing transfusions, depending on what their main cytopenia was and how that's been responding.

Table 6. Newly Diagnosed Patients with AML—Eligible for Induction Chemotherapy

7+3 as Standard
Newly diagnosed AML, depending on their risk factors, they will be…and if they are young, tolerate it. Even if the elderly unable to tolerate, if the performance score is higher then they will be slotted in for like 7+3, the standard. And then they may add, depending on if they have FLT3 or any of the IDH mutations, then they may add another oral pill like venetoclax or ivosedinib and things like that. So, depending on what their mutations are. [NP, Academic Setting]
A person who is under 70 years of age, we would talk about doing induction chemotherapy with either idarubicin or daunorubicin, along with Ara-C, we do 7+3. And if the patient is FLT3 positive, then we obviously will talk about adding Rydapt into that regimen. [NP, Physician-Owned/Private Practice]
If you can do it with agents like that in APL, we've been looking for that, I think in AML. Right now, 7+3 is really the kind of chemotherapy that we use for AML. That is very effective; 70%, 80% of patients that are under the age of 60 can get in remission. Depending on their chromosome risk, they might be cured with intensive therapy alone and a little bit of maintenance at inv(16), or they've got bad chromosomes and you have to transplant right away. [Physician, Academic Setting]
Daunorubicin and Cytarabine
Most patients will get 7+3 induction, which has been the standard for decades. I think the improvements that have been made are adding a targeted agent to that induction. And so, the most notable one would be targeting FLT3 mutations in combination with 7+3 induction. Oh, right, I was thinking of Vyxeos, which is like 7+3, in a way, for treatment-related secondary AML. So, you know, that might be different for those patients. But most fit patients who are transplant-eligible will get 7+3 plus or minus, you know, a FLT3 inhibitor, if they have the mutation. [Physician, Academic Setting]
We would consider using a hypomethylating agent or low-dose cytarabine. And that's if the patient would be able to tolerate that. [Physician, Hospital/Health System]
Most patients are getting that combination [azacytidine and venetoclax]. There are some patients who have what looks like to be secondary disease or therapy-related disease. Those patients, if they are not totally unfit, might be able to receive something like Vyxeos, which is a liposomal chemotherapy formulation. [Physician, Academic Setting]
If they have suspected secondary AML, which about 10% of patients in the United States with AML have with Vyxeos [Physician, Academic]
If they have low risk, usually I do consultation and treatment with HiDAC (high-dose cytarabine), if they are intermediate or high risk it will be allogeneic bone marrow transplant. [Physician, Academic Setting]
If the patient is an elderly patient that had MDS that transformed into AML, if you do Vyxeos, which is the liposomal 7+3, followed by a transplant, they have a higher overall survival over patients that receive 7+3 and a transplant. So it's an overall survival benefit. It's very expensive. Hospitals don't like to do it inpatient. We do it outpatient now. [Physician, Hospital/Health System]
Consolidation
If they're going to transplant, we would have already typed them up. We would have their siblings set up to get typed, and the transplant process starts working. I may still need to give them 1 cycle of consolidation, and I just use cytarabine consolidation. If the patient does not need a transplant, then I would finish off four cycles of consolidation. If they need a transplant, then I send them to transplant right away. I still might have to admit them again for cytarabine, for which I will do. [Physician, Hospital/Health System]
If they are of good risk and have achieved remission, they don't need transplantation, the next option would then be to consolidate them with high-dose chemotherapy. Typically, there are many agents

you could use, but high-dose cytarabine is what we use for a good risk AML that does not need to get transplant as achieved with CR1. [Physician, Hospital/Health System]
For poor-risk patients, multiple factors go into consideration. First of all, is this MDS-related or treatment-related AML? Then I would put them on Vyxeos for induction and then take them to transplant. And if they have FLT3 mutation, I would add midostaurin upfront with induction and then take them to transplant. If they have none of these above, I might still use 7+3 and HiDAC co-consolidation and take them to transplant. [Physician, Hospital/Health System]

Table 7. Factors Influencing Therapy Selection in Newly Diagnosed AML

Fitness
It's relatively easy to identify the patients who are clearly not fit for any therapy: Someone who's, you know, bedbound, wheelchair bound, you know, advanced dementia, things that where their life expectancy before the leukemia diagnosis was probably less than a year. And so, treating them with induction is probably going to shorten their life expectancy anyway, and so those patients would probably benefit more from palliative and end-of-life care. Whereas patients who, let's say they're 80 but maybe have some diabetes, hypertension, but still fit enough, and they're fully functional – you know, they spend time with their family, their grandkids, you know – those patients probably are not fit enough for stem cell transplant, but still, you could treat them with, you know, a hypomethylating agent and maybe venetoclax, as well. [Physician, Academic Setting]
It really is not a decision between hypomethylating agent therapy versus hypomethylating agent therapy plus venetoclax – ***it's whether the patient is eligible for venetoclax plus azacitidine versus 7+3 or Vyxeos****. [Physician, Academic]*
Cytogenetics
Their risk, I think, plays into that. I think a patient, for example, that has favorable-risk cytogenetics with no other concerning factors, we maybe can't treat as intensively as you could, you're still shooting for cure, so you're going to treat, maybe perhaps with intermediate-level intensity or lower-intensity chemotherapy as opposed to doing something like a hypomethylating agent, which we think is unlikely to be curative.[Physician, Academic Setting]
Age
I think age is definitely important. As much as oncology is heading away from solely relying on age as a factor for deciding on therapy, I do think it's still important, because most patients, unless they have favorable, you know, cytogenetic risk, most patients will probably not be cured without an allogeneic stem cell transplant…and cytogenetics, because now we have targeted therapies that are being looked at in the first-line or are already approved in the first-line treatment. [Physician, Academic Setting]
The main thing, ***transplant eligibility versus ineligibility is really important****. So, we'll start with that. For transplant-eligible patients who are really usually younger than age 70, I often will start with more intensive regimens, and that often is 7+3****. If they're older than 70, if they're still transplant eligible but I think they're not going to be necessarily a good candidate for intensive induction****, I'll use a hypomethylator agent plus venetoclax.* [Physician, Hospital/Health Care Setting]
Patient Preference/Willingness/Social Support
What I look for is just the same factors – what does the patient want, what is their motivation, what's their social support, what is their comorbidities, what is their physical strength, and can they handle it? [Physician, Academic Setting]
Their willingness to take treatment or not*, and also because some patients might live far away and they feel like coming for these IV infusion might be troublesome. Or they have many other comorbidities also could be dictating their longevity which is not very common but it could happen. I've had patients who have severe pulmonary issues or cardiac issues and AML, given all these issues*

together patients opted out not to receive any treatment for AML. ***One other scenario would be patients, as I said, who don't have much social support.*** *In first line if they are not candidate for intensive treatment, my go-to for almost all patients if they are agreeable is a combination of HMA and venetoclax, but in second line I would do more of a targeted approach based on patient's molecular makeup. If they have FLT3 I do Xospata, if they have IDH1 or 2 I use Idhifa or Tibsovo. [Physician, Academic Setting]*

Table 8. Newly Diagnosed Patients with AML—Ineligible for Induction Chemotherapy

Standard of Care
The standard of care now has changed. I think in the past we had several different options we could have considered, but with the addition of venetoclax and fairly high response rates in that patient population, I think that would be the way to go. [Physician, Academic Setting]
Now we have really good data, and I forget the name of the trial, things like VIALE-A trial shows an overall survival benefit. So in those patients, I like to combine most likely the HMA, like decitabine or azacitidine with venetoclax is what's commonly done in patients that are not candidates for intensive therapy.
My one size fits all, I told you, is venetoclax plus aza. Right now this is one size fits all. But I talked about the future that if you know he has FLT3, or you know he has IDH mutation on top, you have room for improvement. But right now, the go back to regimen is the combination of 5-azacitadine plus venetoclax. [Physician, Physician-Owned/Private Practice]
If you determine the patient is ineligible for intensive induction therapy, then there are multiple other treatment options available. The most exciting and the most new of which has been the addition of venetoclax to a hypomethylating agent. This has sort of become the new standard for these patients. [Physician, Hospital/Health System]
I would say overarchingly our probably preferred treatment option is going to be azacytidine plus venetoclax, based on the results of the VIALE-A trial which show an overall response benefit.
Slower Adopters
We are looking at, I think, a little bit more supportive care, so we are also using some of our newer agents on formulary, such as the luspatercept, so one is just maintaining quality of life and trying to reduce transfusion need. So by working from that angle as well as, again, ***our normal hypomethylating agents or possible oral agents that are available for Bcl-2****, or the specific mutations that could be present. [Pharmacist, Academic]*
And if they cannot tolerate or don't accept intensive therapy, then there are a variety of approaches. ***We might offer them a hypomethylating agent plus venetoclax****, which again it's hard to know whether to call that intensive or not. But it tends to be very myelosuppressive; with dose adjustments, one can mitigate some of the myelosuppression of that therapy. And* ***that might be what's offered to patients who are older and unfit in lieu of intensive therapy****. [Physician, Academic Setting]*
7+3 or Vyxeos
I look a little bit at what the cytogenetics or FISH are, but I think you can do azacitidine plus venetoclax for everybody, so that's easy. ***The intense therapy you can do also for everybody, the 7+3****. [Physician, Academic Setting]*
The other group (nonfavorable AML), which fall into the intermediate or high risk, those are the ones we worry about because we know chemotherapy alone does not cure it. ***It works very well, but it's not going to cure them****. [Physician, Physician-Owned/Private Practice]*

Table 9. How HMA Agents are Being Used in MDS

Current Standard
For the vast majority of patients, ***even if they are fit, we don't consider intensive chemotherapy as the best option for these individuals****. While it can put people into remission, it is quite toxic, and those remissions are often very short lived. So, we typically go with hypomethylating agents even in those individuals.* [Physician, Academic Setting]
Like almost everyone else, *when deciding if they need some sort of chemotherapy and high risk,* ***hypomethylating agents are the first things that I start with****. [Physician, Hospital/Health System]*
For somebody with high-risk by a revised IPSS score MDS ***it's a pretty straightforward for our institution. It's going to be single agent azacytidine, as is per the NCCN guidelines****.*
Higher-risk MDS, we would do probably venetoclax and Dacoge*n, depending again on their performance status, and then we would try to keep everything as an outpatient so the patient can, obviously, be at home.* [NP, Physician-Owned/Private Practice]
For those who are high risk and not transplant eligible, ***the most common thing is hypomethylating agents. I almost never use intensive induction therapy for those people, because the goals really for them are mostly palliative****.* [Pharmacist, Academic Setting]
Then would be the azacitidine regimen*. The purpose of that is to delay progression or to extend life. It can be used at any age. It has a good performance status, and with the absence of any major comorbidities for the patient. Of course, we're always looking for a cure, but it's been known to have excellent performance status in patients who are 60 to 75 years old.* ***These are for patients where the stem cell transplant has not, at that time, yet been considered****.* [Physician, Academic Setting]
For those who are high risk and not transplant eligible, the most common thing is hypomethylating agents. ***I almost never use intensive induction therapy for those people, because the goals really for them are mostly palliative****, and clinical trial are kind of for both, but definitely more for – we have a non-transplant eligible patient who would like to go for a clinical trial, oftentimes, I'll try to get them on that. And if they don't, a hypomethylating agent.* [Pharmacist, Academic Setting]
Interchangeability of HMAs
If they have some cytopenias, either their neutropenic or they're needing blood products or platelets, we usually will start with one of the hypomethylating agents like Vidaza. We also use oral Dacogen. We use that quite a bit lately with our patients over 80 because they seem to tolerate that better. I've used venetoclax with patients that have gone from MDS to AML with Vidaza. That has worked very well too. [NP, Academic Setting]
Another one is called azacitidine or decitabine. Those are the most common that we use. These are in the National Cancer Registry. This regimen of medication is used throughout the AML/MDS system. Everyone, every cancer center probably in the United States is basically using this same regimen of medications, along with the same prognostic scoring system. [Physician, Academic Setting]
In general most people prefer azacitidine. I have looked at the literature to see if there is anything strongly supporting either one. The literature supports both drugs. It's a matter of personal preference. [Pharmacist, Physician-Owned/Private Practice]
When it comes to hypomethylating agents, the two most commonly used are decitabine and azacitidine. And ***for the most part, they're used interchangeably****…except there's data for patients who have higher-risk cytogenetics with a P53 mutation that they may do better with decitabine.* ***I tend to give more azacitidine because of the survival data*** *in a general cohort of patients and* ***because of its sort of synergy with other agents like venetoclax*** *in leukemia.* [Physician, Academic Setting]
Drug Availability/Institutional Preference and Pathways

*Azacitidine is most commonly used, that's the most commonly used drug we have. I think **it's just a matter of habit. Both drugs [decitabine] are good**. [Physician, Physician-Owned/Private Practice]*
*One was the drug availability. I think when we're using an HMA, Vidaza was the formulary drug locally…basically, **our go-to drug was Vidaza, and that was because of what we had available**. [Physician, Hospital/Health System]*
I will look to the NCCN guidelines and our internal pathways to help me guide what I should use therapy-wise, and really patient preference as well. [Physician, Hospital/Health System]
Preference for One HMA Over Another
[Azacytidine] is really only 5 days in a 28-day cycle, so that's something that is doable. Often in combination with venetoclax if they are agreeable. [Physician, Academic Setting]
Aza is easy because it's oral therapy. So you can take the oral therapy for about 3 weeks, and then you take the 7 days subcutaneous. You don't have to give IV; you can do subQ 5-azacitidine. [Physician, Physician-Owned/Private Practice]
You can do the decitabine subQ as well, but we traditionally use more of the decitabine, the five-day regimen. And in patients that don't have good IV access, we have utilized the subQ azacitidine in those patients. But one of the things we always have issues with is all these multiple injections that the patients get due to the volume of the azacitidine. [Pharmacist, Hospital/Health System]
Higher-risk MDS, we would do probably venetoclax and Dacogen, depending again on their performance status. [NP, Physician-Owned/Private Practice]
Combination
I would say overarchingly our probably preferred treatment option is going to be azacytidine plus venetoclax, based on the results of the VIALE-A trial which show an overall response benefit. [Physician, Hospital/Health System]
*Increasingly, if patients don't respond or respond ineffectively, we increasingly are using venetoclax, which we're using also for unfit elderly AML patients. But **there's fairly compelling data that the addition of oral venetoclax benefits patients with high-risk MDS/higher-risk MDS**. So we will then sometimes add that. In some cases, the decitabine is changed to azacitidine because the combination is generally…we **generally use venetoclax plus azacitidine**. Certainly, if the patient has very high risk or what looks like evolving AML, then the combination therapy is usually instituted.*[Physician, Academic]
I tend to add the venetoclax when they're kind of close to being the leukemia. If they're just purely MDS, you can do like…the difference is really just a hypomethylating agent. *[Physician, Academic Setting]*
If I feel like they have higher-risk MDS I will put them on a treatment; in today's world most of the time azacitidine and venetoclax. if the patient is requiring a lot of transfusions, is having a lot of infections or is neutropenic, then I will talk to them about initiating treatment usually with azacitidine and venetoclax. [Physician, Hospital/Health System]
Different Dosing Regimens
There are different regimens. We've done dose reductions. Or for like the azacitidine, we've done the seven-day treatment. We've done like a five-day treatment of the azacitidine instead of the seven and lower dose. [Pharmacist, Hospital/Health System]
I do the dose escalation those first 3 days. I'll dose reduce patients down to 70 mg once a day of venetoclax per the package insert. I know we've definitely had some discussion as to if we should be doing 70 or if we should be doing 50. The 50 is what they did in the VIALE-A trial. I remember the old package insert said you could do 100, which is a little bit easier to kind of manipulate those tablets. It's always a little bit of a discussion. I will say probably the past 10 patients I've done I've just strictly followed the package insert for that dosing. [Pharmacist, Hospital/Health System]

You could always still use the hypomethylating agent but lower doses of it. [Physician, Physician-Owned/Private Practice]

Table 10. Administration and Dosing Schedules for Venetoclax

Dose Reduction
The thing with the venetoclax is you can dose reduce it, you can go all the way up to 400, but maybe you just drop it to 100. Like I had somebody who couldn't tolerate 200, so I went down to 100, and they were fine. [Physician, Academic Setting]
These treatments are not meant to be discontinued, but they can be modified. You can stretch the intervals. You can dose-adjust. [Physician, Physician Owned/Private Practice]
Stopping Venetoclax or Both Agents
If I had to stop one, I'd probably stop the venetoclax. Or actually the HMA, too. It depends on what the side effects were. But most of the side effects for both are really overlapping, in terms of, you know, the effects on their hematological, you know, adverse events. So, it may be hard to tease that out. [Physician, Academic Setting]
We do stop venetoclax often, holding it because of blood count issues. It's pretty clear, I think, from the data that venetoclax does very little on its own to AML. It's really not a very good drug. Its benefit is only when it is added. The key is to continue on with the HMA. [Physician, Academic Setting]
This is a tough group to figure out whether the cytopenias are from the hypomethylating agent, from the disease itself, or from the venetoclax. If they're having nausea, vomiting, feeling super fatigued, I will interrupt their venetoclax to see if their symptoms get better off the therapy, and if they do then we will either talk about dose reductions or we will talk about stopping that part of the therapy completely. [Physician, Hospital/Health System]
Usually with any toxicity I would stop both in general. [Physician, Academic Setting]
I have typically stopped both, because I think it's almost impossible to ascertain what is causing what, unless it's a very specific side effect. [Physician, Hospital/Health System]
I would first stop venetoclax and keep the azacitidine going. I think that's probably because we are much more comfortable with azacitidine. I don't have a good answer for that. I am not sure what is the right thing to do? [Physician, Hospital/Health System]
I know in the label they say give it continuously, but most of the time we are giving 2 to 3 weeks and stopping based on cytopenias. If there's significant cytopenias with a white count less than 1 and persistent, usually we will stop at around day 20 and repeat the marrow and see where we are. Even experts I've talked to they would stop some at day 15, some at day 21. [Physician, Physician-Owned/Private Practice]
We do opt for 28 days consecutively, unless they experience really febrile neutropenia with complications, which I feel like I often see some around the day 21 or so mark. Then we might kind of hold off and then proceed forward with our bone marrow biopsy to assess any sort of response. We'll do Vidaza for days 1 through 7, the venetoclax 1 through 28. I try my hardest to finish that 28 days. I depends on the hypomethylating agent they had as well. I know with Dacogen there is some data that says maybe you could do at day 21. [Pharmacist, Hospital/Health System]

Table 11. Assessing Treatment Response with Venetoclax

After 1 Cycle
AML disease is pretty aggressive and much faster growing. You're ready to perform a bone marrow biopsy after induction or after 1 cycle of treatment just to see where the response is. The quality of life is important. Untreated AML will give you very poor quality of life in a very short period of time. It is not just related to the anemia and the thrombocytopenia. It's mostly also related to the infections and other things. [Physician, Academic Setting]
You are doing your bone marrow at day 28 usually to see what percentage of blasts is the usual AML assessment after cycle 1 of intensive chemo. You're looking at their blast percentage, and you can do your flow cytometry to be accurate, and then cytogenetics, did we clear the clone, you know? How much did we do with one cycle? [Physician, Physician-Owned/Private Practice]
I've almost had to do four to six-weekly marrows on the one patient I had because I didn't know if the cytopenias were coming from venetoclax or because they were not responding to the treatment and the AML was progressing. So it's a case-by-case basis. I don't know if there's a protocol for that. [Physician, Academic Setting*]*
it's a lot different than just giving a single agent hypomethylating agent, where you could easily just treat through the counts and repeat the bone marrow biopsy in 6 months and assess response at that point. We know that with this new combination it's a way different thing that needs to be treated much differently. We would really try to treat it like it's induction with a cycle 1 bone marrow biopsy. I think that once the VIALE-A trial came out and we got more experience with it, we were really trying to follow exactly what the trial did as far as response. If they don't have response how we retreat into cycle 2 as well. [Pharmacist, Hospital/Health System]
After 2-3 Cycles
They do get CBCs very frequency initially, twice a week. Then we space it out to once a week. So I would expect response in about two to three months. You should expect to see start improvement in about one or two months. And then, once they are sustained ANC over 1,000 and platelet over 100, and you've seen what looks like a complete morphologic response, you're going to follow it up with a bone marrow biopsy.[Physician, Academic Setting]
But most of the time, what our practice is that we should not do the bone marrow before 2 cycles. most of the time what we do is just the peripheral blood counts. We just follow them, we are getting the peripheral blood count, we are supporting them, and then we do it. After first cycle, no. [Physician, Academic Setting]
No Rush to do Bone Marrow Biopsy
I'd be more likely to, at some point in the first year, to repeat a bone marrow biopsy to really determine whether a patient is in a complete remission. [Physician, Academic Setting]
We typically don't do the bone marrow. Basically, if hematologically they are doing better. That's how it goes. [Physician, Physician-Owned/Private Practice]

Table 12. TP53-Mutations in MDS

High-Intensity/Aggressive Therapy or Clinical Trial
I don't quite understand fully what I'm going to do in the non-transplant setting for a TP53 mutation that's different. I know that clinical trial is preferred in this setting, but again it's very hard for our patients to travel for these clinical trials, and we don't offer that many MDS clinical trials at our institution. [Physician, Hospital/Health System]
TP53 is the adverse prognostic marker. We all know that. I would just be more alert and watchful and perhaps treat them or see them more closely. No, my treatment would not change. [Physician, Hospital/Health System]
Courtney DiNardo has published that the patients that have p53 and receive HMA plus venetoclax they're actually very good, even better than the historical controls of the regular just hypomethylating agent by themself. So that's what I try to do. [Physician, Hospital/Health System]
Decitabine Preferred
There's data for patients who have higher-risk cytogenetics with a P53 mutation that they may do better with decitabine. There was a New England Journal paper that showed that patients had a better prognosis. Patients did better when they were treated with decitabine, but it wasn't necessarily a head-to-head comparison to azacitidine. [Physician, Academic Setting]
I know there's some literature suggestive that Dacogen might be better in these cases as compared to azacitidine. I would try my best to get them to a transplant, but those are the only few things that I can think of. [Physician, Hospital/Health System]
Investigational Therapies
We have had clinical trials open with, to me, a very important drug, APR-246, which had had some good results with p53-mutant MDS. I'm persuaded by the results in MDS that APR-246 has benefits. So those patients are generally referred for that trial. If they don't have p53 mutation but they are in the higher-risk category, they're generally started with a hypomethylating agent. [Physician, Academic]
We have this proteosome and the CD47 and some targeted agents that are now looking at p53 and may be able to improve on that specifically. I can't remember the name of the agent because it's not approved yet, kind of a proteasome inhibitor. [Physician, Academic Setting]
That drug [magrolimab] has shown interesting results in TP53 mutations with MDS and with really high response rates, including CR rates. [Physician, Academic Setting]
There are a couple of things with p53 that are very interesting. It's called the APR-246, I believe, it unfolds the p53. I think they have it on Moffitt. We haven't been able to get those clinical trial, but if I have a patient that is p53, sometimes I ask for to send a couple other places. And we are going to start getting magrolimab, a clinical trial of magrolimab. It's an antibody that makes the macrophages eat the blasts, the cancer cells. And those respond very well to p53. I have a couple of patients lined up for the clinical trial. [Physician, Hospital/Health System]
These patients don't do as well. There are trials using the specific anti-p53 agent. So if there is something around a trial of that nature, you may consider sending that patient on that trial. But otherwise, we just try to treat them aggressively because we know they have usually bad disease. [Physician, Physician-Owned/Private Practice]

Table 13. Reported Therapeutic Approaches for Patients with TP53-Mutated AML

Transplant
I mentioned there is so-called intermediate and so-called poor risk. Among the poor risk are the TP53, chromosome 5 deletion, 7 deletion, complex karyotype – all of these are under the bad group. 11q minus is sort of intermediate to poor, but it's more in the intermediate, and they don't do well you need a transplant for this as well. [Physician, Physician-Owned/Private Practice]
If they have a TP53 mutation, that is a high-risk thing, and usually until that time we have involved the transplant team because there's a very high risk of relapse. We have not added yet to any of our patient venetoclax during the induction or consolidation, intensive induction or consolidation of venetoclax we will send them for the transplant. And if they are transplant eligible, they will go straight away for transplant. [Physician, Academic Setting]
Chemotherapy is not terribly effective in that population, so they may be better off with a less-intensive regimen approach, and consider definitely transplant if that's a possibility. [Physician, Physician-Owned/Private Practice]
If we can do something like, for example, that gets them to a very low TP53 mutant allele burden state, then taking them to transplant is still probably our best bet, even though it doesn't have great outcomes. I think for most patients, maintenance HMA is the bare minimum of what we can do. Most patients will tolerate that. [Physician, Academic Setting]
If they're eligible or they're able to, he's going to elect to do a transplant. I'm talking older. Younger, full dose chemotherapy, Rydapt in between, transplant as soon as we can. [NP, Academic Setting]
Clinical Trial
But there are emerging data, that was presented at ASH, of a P53 inhibitor, but I think the latest update is not necessarily positive, in terms of the findings. So, you know, I think you try to get them on a clinical trial. And if not, I think we don't necessarily have any particular targeted agents for that subgroup to treat them any differently. They just would mandate that they proceed to stem cell transplant, if possible. [Physician, Academic Setting]
First of all, there's distinction that needs to be made whether somebody is a candidate for aggressive treatment or not. If somebody is a candidate for aggressive treatment, in all likelihood this patient will not be with me, but my desire and my recommendation to the patient and the family would be that they seriously consider a clinical trial. Now, if it is a patient who is not a candidate for aggressive treatment, then it's going to be something along the lines of hypomethylating agents and venetoclax. Well, of course, I will take patients' individual considerations as well. [Physician, Hospital/Health System]
Well, that's again, a problem. I would say they're good for a study. So find a study is their best possibility. Chemotherapy is not terribly effective in that population, so they may be better off with a less-intensive regimen approach, and consider definitely transplant if that's a possibility. Because they're not, again, going to do well. But the right answer probably is a study somewhere. [Physician, Physician-Owned/Private Practice]
That's pretty much the same as MDS patients, maybe even worse. Even with transplantation, those are very poor outcomes. Our general approach for those patients we don't even provide them with 7 + 3 or intensive induction chemotherapy. We really go to HMA plus venetoclax, because those patients are relatively resistant to traditional chemotherapy. Then, obviously, a clinical trial will be the first consideration. [Physician, Academic Setting]
That's terrible. Those patients don't do well, and we have nothing good that works. So I would push them to a clinical trial if they're willing to go somewhere for a clinical trial. If they're not, I really will talk to them about palliative care options and hospice. If they really want to try something I will try a

hypomethylating agent and venetoclax to see if it will do something for them, knowing that more than likely nothing is going to work. [Physician, Hospital/Health System]
HMA with Venetoclax
There is a regimen called CLAG, which is a regimen that was initially published in Poland. We have seen some good benefits, especially in this MDS AML population using that regimen. The other option is to use something like a hypomethylating agent which they have not seen before, add the venetoclax to it and give them that option. Even maintenance with one of the oral agents to see if that can help. [Pharmacist, Physician-Owned/Private Practice]
I think right now our typical approach for an older patient with TP53-mutated AML is probably still going to be HMA venetoclax. I think we do let them know probably up front that this is a very poor prognostic feature. There are not really any really strong, good treatment options that can be much more directed towards that. I know there is some data that maybe says decitabine might be a little bit better for p53 mutated AML or we may ought to try that along with venetoclax. It's one of those really difficult situations I think in AML for older patients right now. [Pharmacist, Hospital/Health System]
p53 itself makes itself high-risk AML. And if they're not candidates for intensive chemotherapy, then the decitabine I mentioned, along with venetoclax, is an excellent regimen for these patients. The decitabine has high response rates in this setting. If you're not doing intensive chemotherapy, decitabine would be our drug of choice. [Physician, Academic Setting]
the one group I'd consider more using hypomethylator plus venetoclax in these transplant-eligible patients would be the p53 patients because of how poorly they do. And for those, the hypomethylator that I prefer to use is decitabine for 10 days. [Physician, Hospital/Health System]
Induction Chemotherapy
My preference would be to give intensive chemotherapy. That's a very high-risk patient, and those patients it's more difficult to get them into remission and also keep them in remission. In looking at the data with venetoclax plus hypomethylating agent, there was a fair bit of activity in p53-mutant AML and also in secondary AML. But I think the best results are obtained with intensive chemotherapy. I would also try to get that patient to transplant, although I think there's some data that suggests that TP53 mutations even affect the outcome after transplant. But I would try to treat that patient as intensively as I could. [Physician, Academic]
*That's challenging. I do the 7+3. **If it is young patient, I do 7+3. If it's elderly, I think about HMA**. Adam Goldberg at MSK did a retrospective analysis on patients that received Vyxeos but had a p53 mutation. And they did terrible, like terrible, terrible, terrible. So on those patients, sometimes I'm inclined to put them on a hypomethylating agent plus venetoclax. [Physician, Hospital/Health System]*
The induction part would all be the same. They would get induced. We are hoping they will achieve remission, patient continues to have adverse risk factor, that automatically puts patients in the poor risk category. These are the patients that will need evaluation for bone marrow transplant so I would send them that way. [Physician, Hospital/Health System]
We've used typical induction therapy. We've used Dacogen for 10 days. We've used the midostaurin, Rydapt. We've used that typically for those patients. [NP, Academic Setting]
Those patients they will be on high risk depending on the type of whether they're able to tolerate, then they'll go for the 7+3 and an oral agent and then also go into, once they in remission, transplant. [NP, Academic Setting]
I probably would use more intensive treatments such as 7+3. For those who were not transplant eligible, I may use something like cytarabine and venetoclax, which is another option. But for the people who are transplant eligible, I would want something such as 7+3. [Physician, Hospital/Health System]

It's not going to be any different in terms of the, 7+3 is going to be still the standard for us in terms of that treatment. So I think if a patient's not fit to get it, it's just their prognosis is not going to be as good. But I think there's near targets, where we may be able to utilize something else. But I think at this point it's still going to be if the patient has a FLT3 mutation, we're going to add on the midostaurin in those patients. But otherwise, 7+3 is kind of still the standard. [Pharmacist, Hospital/Health System]

Table 14. Access to Clinical Trials for Patients with Newly Diagnosed MDS/AML

At Diagnosis and Beyond
We will discuss right at the beginning and kind of…you know, being on a community center, we're always having a discussion and offer for patients to go immediately after induction, right, if the patient…as soon as the patient would be discharged from the hospital, that's when we will tell, look, this is your chance to go to the academic centers if there's any additional, you know, therapy or clinical trials that would be open. And we would encourage patients to do that. [Physician, Hospital/Health System]
At the beginning, when they make that initial visit to us, we have a clinical research coordinator who is going to come in and just let them know of the availability of the clinical trials. [Physician, Academic Setting]
We discuss it at diagnosis when we have all the information. You wait until the bone marrow comes back and until the results come back. You discuss the treatment plan with them. You give them the option of a clinical trial, and if we feel that clinical trial is the best option then obviously, we're going to promote that. [NP, Academic Setting]
At Relapse
Relapsed/refractory, there are more options. Not only that, those who cannot go through intense chemotherapy as you asked me. There may be more likelihood of having a clinical trial. Relapsed/refractory, not fit for intense chemotherapy up front. That's where it is. [Physician, Physician-Owned/Private Practice]
For the acute myeloid leukemia, usually we induce with the 7+3 and then at the time of relapse or if the patient relapses later on and down the road then we usually use the trials. [Physician, Academic Setting]
In order to be a clinical trial candidate, they have to have good labs, good social support. The trials aren't going to take somebody who's supportive care, so you've got to be cognisant of that. So step one is you have to assess and make sure they're a candidate. So if they're a candidate based on all of those factors, that's step one. Step two is, I think, after they've failed one line of therapy. You give it one shot, and you can mention hey, there's a clinical trial. [Physician, Academic Setting]

FIGURES

Figure 1. Bone Marrow Biopsy in Evaluation of Patients with Suspected MDS or AML

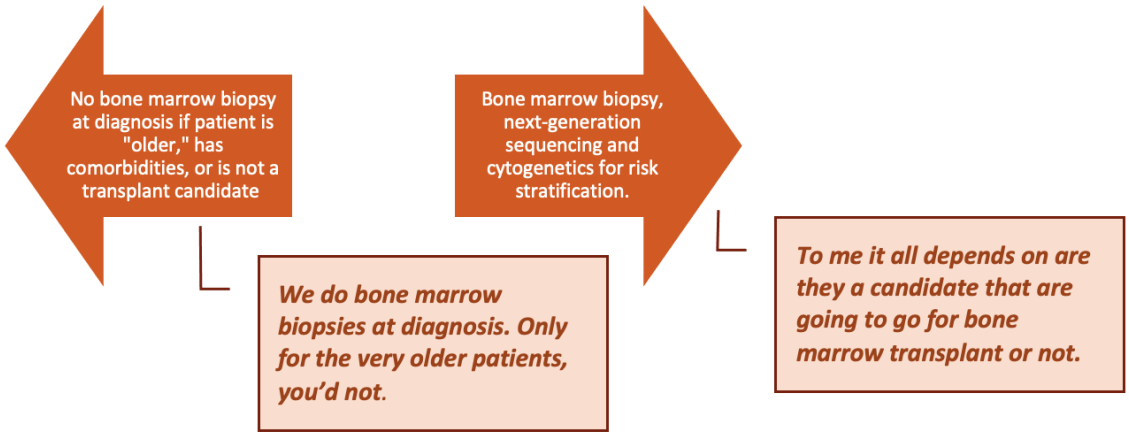


Figure 2. Clinician Reasoning on Fitness Determination

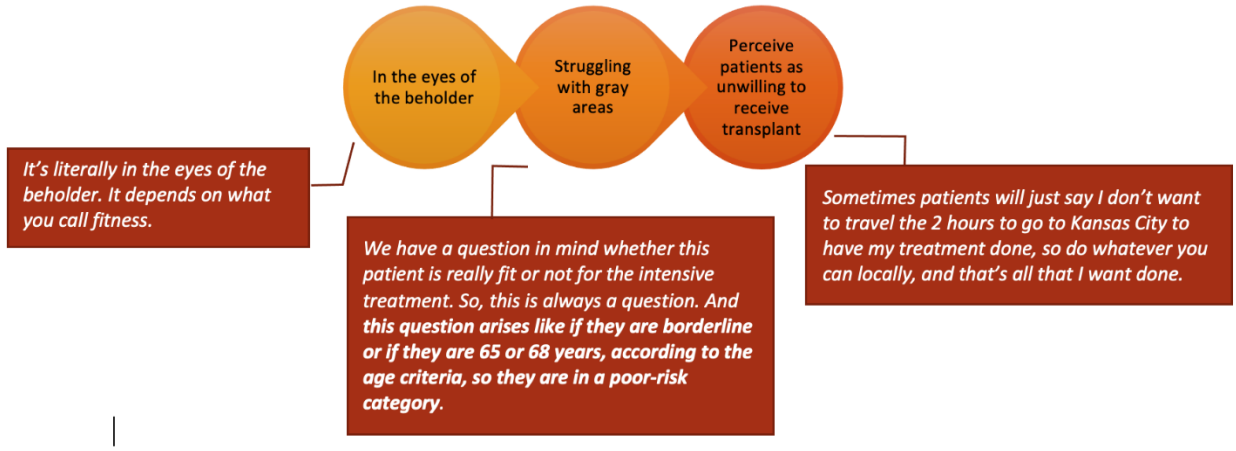


Figure 3. Primary Preferred Standard Treatment for Clinical Scenarios in MDS, US

US-based Clinicians Case Scenario, n, (%)	Azacitidine	Azacitidine + venetoclax (off label)	Decitabine	Oral decitabine (decitabine + cedazuridine)	Induction chemotherapy (3+7 or similar)	HMA followed by allo-HSCT	Unsure	Other	N
Newly diagnosed, higher-risk MDS	35 (21.88)	31 (19.38)	7 (4.38)	11 (6.88)	22 (13.75)	29 (18.13)	23 (14.37)	2 (1.25)	160
Newly diagnosed, higher-risk MDS with TP53 mutation	15 (9.43)	31 (19.50)	10 (6.29)	16 (10.06)	14 (8.81)	32 (20.13)	37 (23.27)	4 (2.52)	159
High-risk MDS previously treated with HMA; ineligible for transplant	4 (2.52)	56 (35.22)	7 (4.40)	22 (13.84)	11 (6.92)	9 (5.66)	39 (24.53)	11 (6.92)	159

Figure 4. Primary Preferred Standard Treatment for Clinical Scenarios in MDS, ex-US

Ex-US Clinicians Case Scenario, n, (%)	Azacitidine	Azacitidine + venetoclax (off label)	Decitabine	Oral decitabine (decitabine + cedazuridine)	Induction chemotherapy (3+7 or similar)	HMA followed by allo-HSCT	Unsure	Other	N
Newly diagnosed, higher-risk MDS	13 (38.24)	5 (14.71)	0 (0)	2 (5.88)	2 (5.88)	10 (29.41)	2 (5.88)	0 (0)	34
Newly diagnosed, higher-risk MDS with TP53 mutation	4 (11.76)	9 (26.47)	2 (5.88)	2 (5.88)	5 (14.71)	9 (26.47)	2 (5.88)	1 (2.94)	34
High-risk MDS previously treated with HMA; ineligible for transplant	4 (11.76)	12 (35.29)	2 (5.88)	5 (14.71)	6 (17.65)	2 (5.88)	3 (8.82)	0 (0)	34

Figure 5. Agents Matched from Memory to their Target or Mechanism of Action, US (n=163)

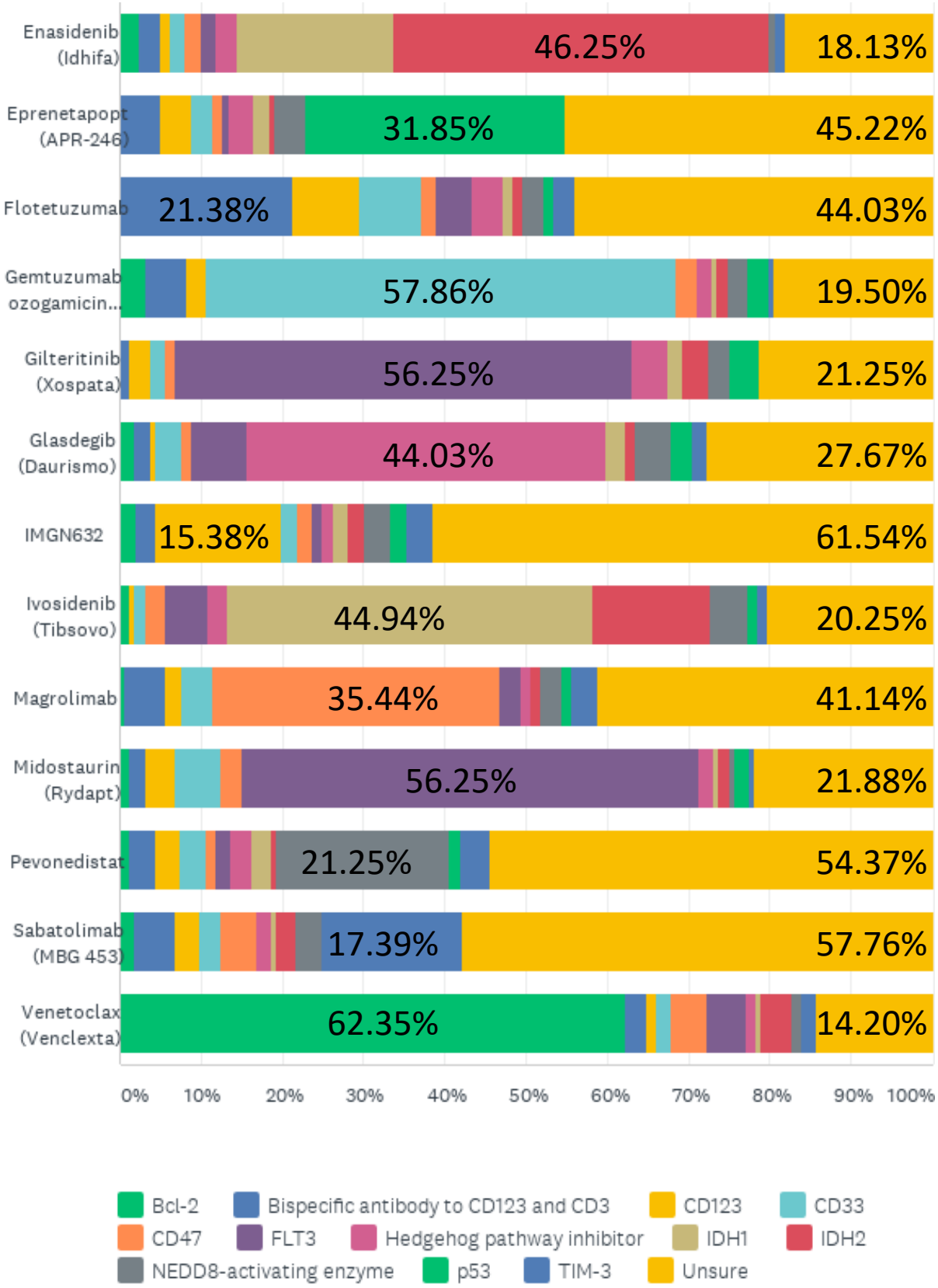
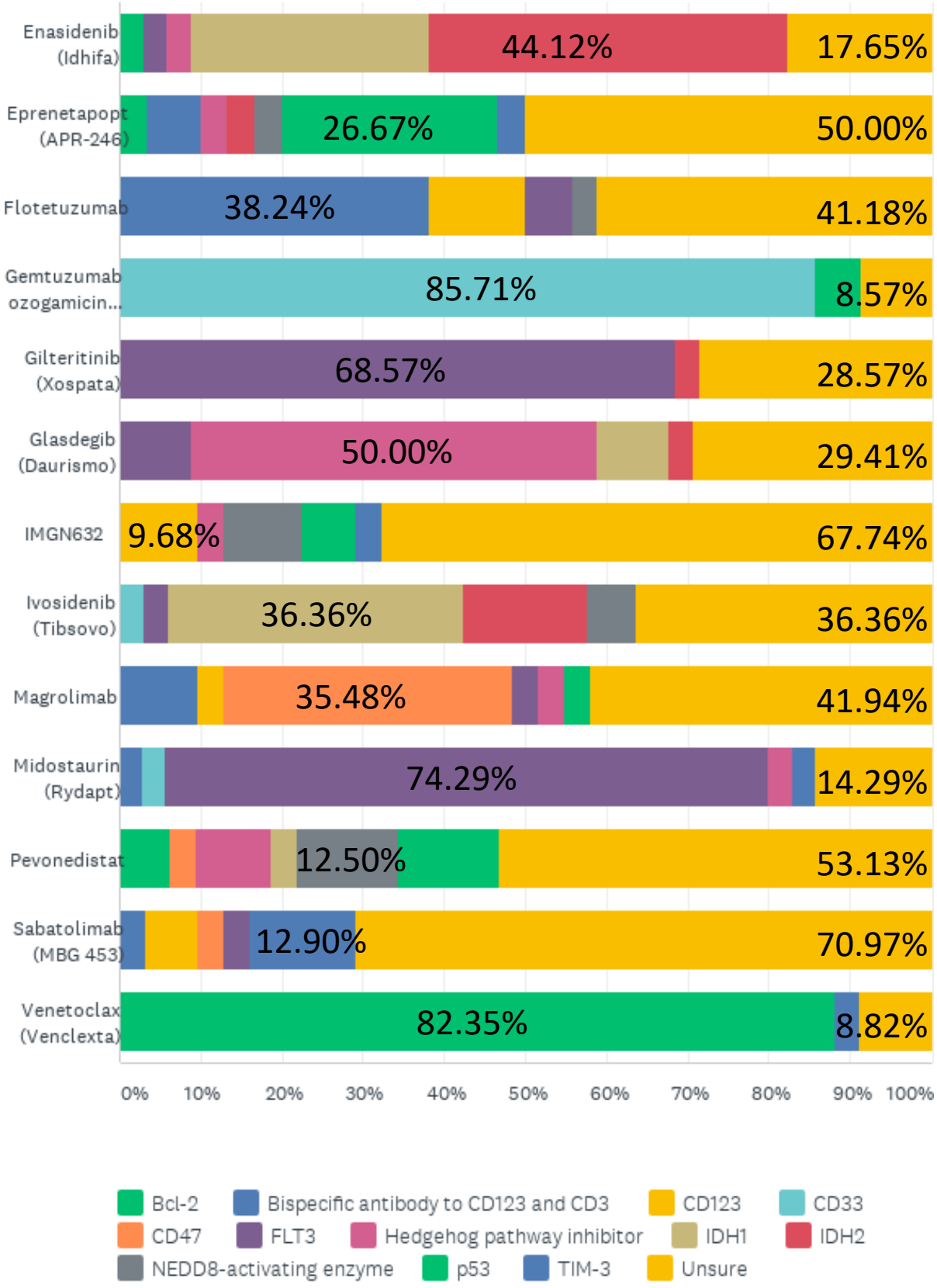


Figure 6. Agents Matched from Memory to their Target or Mechanism of Action, ex-US (n=35)



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