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Mastering the Complexity of AML Treatment: A Multidimensional Approach to Diagnosis, Therapy, and Side Effect Management

Announcer:
Welcome to CME on ReachMD. This activity, titled “Mastering the Complexity of AML Treatment: A Multidimensional Approach to Diagnosis, Therapy, and Side Effect Management” is jointly provided by Global Education Group and Iridium Continuing Education and is supported by independent educational grants from AbbVie Inc. and Astellas Pharma Global Development, Inc.

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Dr. Fathi:
Hello and welcome to our program titled, Mastering the Complexity of AML Treatment: A Multidimensional Approach to Diagnosis, Therapy, and Side Effect Management. My name is Dr. Amir Fathi, Director of the Leukemia Program at Massachusetts General Hospital and Associate Professor of Medicine at Harvard Medical School. I'm joined today by my esteemed colleagues, Dr. Courtney DiNardo, Professor of Medicine in the Department of Leukemia at MD Anderson Cancer Center, and Dr. Brian Jonas, Professor of Medicine at the University of California Davis.

Our disclosures are displayed on the screen.

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The learning objectives for today's program are to discuss the impact of molecular testing, risk stratification, and measurable residual disease on treatment selection and personalization in patients with AML; to utilize trial evidence and guidance-based recommendations concerning targeted therapies to manage AML case scenarios typically encountered in community settings; and to develop effective strategies to monitor for and manage treatment-related toxicities in patients with AML.

Dr. Jonas, would you walk us through an overview of AML?

Dr. Jonas:
Yeah, thanks, Amir. I'd be happy to. So AML is the most common leukemia in the U.S. We'll start with that statement. And I think the data on the that you'll be seeing will kind of demonstrate this. There's estimated 60,000 cases of leukemia in the United States, at least estimated in 2023. And there's a pie chart showing how this distributes amongst different types of leukemia. As you can see there, the AML patients represent 1/3 of the diagnoses of leukemia, and so 20,380 is the estimated number for 2023, for example, with the second most common being chronic lymphocytic leukemia, or CLL. And you can see other leukemias, CML, ALL, and then there's a bin of other leukemias that account for a small percentage.

Unfortunately, AML is also associated with a pretty high rate of mortality, and of these 20,380 cases diagnosed each year, there's also an estimate, unfortunately, of 11,310 deaths per year related to AML. And this is the estimate from 2023. AML is a disease that's more commonly encountered in older adults. So the median age of diagnosis in the United States is 69, and it's slightly more common in males. So it's definitely a disease of older patients. But that being said, there are patients who are younger who get AML, and so it's not

explicitly a disease of older patients.

So what is AML? You know, when I talk to my patients, I go through the various forms of education, and this is one of the things I discuss, what is this disease they have? And so AML is a cancer of the bone marrow, basically. It's a malignant stem cell disorder, hematopoietic stem cell disorder, and it's caused by an abnormal clonal expansion of myeloid cells. This leads to accumulation of immature cells in the bone marrow that we call blasts, and they're ineffective, and they don't function properly, and this leads to impairment of hematopoiesis.

In terms of risk factors for who gets AML, older age is the biggest risk factor, which I alluded to before, given the median age of 69. And so the biggest risk factor is aging, in fact. Other risk factors for AML include antecedent hematologic disorder like MDS, myelodysplastic syndromes, or myeloproliferative neoplasms. Other known risk factors for AML include exposure to previous chemotherapy, particularly DNA-damaging agents, and also radiation, for that matter. So other environmental exposures can be connected to development of AML, including tobacco smoke and nontherapeutic radiation. And then there's also a subset of patients who have underlying hereditary mutations that can lead to a predisposition to development of AML.

Now, what does AML look like? I always think of AML as being able to cause any symptom, right? The blood is everywhere, and anywhere where there's blasts, there could be symptoms. But some of the most common symptoms relate to the failure of the bone marrow that occurs in the setting of AML, and this can lead to things like infections, anemia from low red cells, easy bruising from low platelets. Other symptoms can include headache, fatigue, weakness, bleeding, and bone pain And so but really any symptom is theoretically possible, but I would say these are some of the most common ones.

And so when we think about the pathogenesis of AML, some really interesting work over the years has to has led to the recognition that there's a number of people that develop mutations way before they even have the onset of disease. And this has been termed CHIP, clonal hematopoiesis of indeterminate potential. And it can occur in upwards of 10% of patients who are 65 or older. And sometimes these are associated with cytopenias, and there's another entity called CCUS. And what happens is cells are mutated, and then over time, they get additional mutations, and eventually are transformed. And so, this usually happens at the level of a hematopoietic stem cell, usually not the primitive stem cell, but a subsequent progenitor cell. And then these cells will have a competitive advantage and expand in the bone marrow. And oftentimes there's an oligoclonal situation where there's multiple clones and they're each becoming more and more mutated. And eventually the disease hits a tipping point where there's enough mutations and the disease clone emerges. And this is represented in cartoon fashion on the slide. And eventually there, the patient has a diagnosis of AML. And like I said before, many times there's multiple clones present at the time of diagnosis, but usually some sort of dominant clone that's leading to the clinical phenotype.

And as I mentioned, kind of through the last couple of slides, of course, AML is a disease of mutations, and so most patients with AML are going to have an identifiable driver mutation. In fact, one estimate is 97.3% of patients will have an identifiable somatic mutation, of which 96% will have at least one driver mutation.

And so some examples of the most common mutations seen in AML are shown here in this plot. Most common is FLT3, which can be seen in around 30-35% of patients. And notably, there's two versions of FLT3; one's called FLT3-ITD, or internal tandem duplication, which is the most common one that occurs in 20-25%; and there's a FLT3-TKD, tyrosine kinase domain mutation, which it can occur in 10%.

Other mutations that are common include NPM1, which is about 30%; IDH1 and 2 which together comprise around 20%, with IDH2 being a little more common than IDH1; DNMT3A, around 20%; NRAS, about 15%; TET2, depending on which source you read, can be anywhere from 5 to 20%; p53 or TP53 is, unfortunately, very common and associated with poor outcomes that has incidents about 12%; and KIT and CEBPA around 10% each.

And so these mutations, in addition to chromosome abnormalities, which are not necessarily shown specifically on the slide, but these are very important for determining the patient's prognosis, and kind of thinking about the biology of the disease, like, what are we up against? And it also looks at – it also affects the risk of relapse. And as a result, this has kind of started to lead to an understanding of how we might approach patients based on some of these features, because certainly, these genetic features, affect response to treatment, and again, which treatment options we may want to consider for a particular patient.

I mentioned all these mutations, I think it's helpful to think about the mutations in terms of pathways that they affect, because a lot of them affect kind of common pathways. And so, there's a number of different pathways that can be involved. For example, if you look in the upper left, you see altered tyrosine kinase function mutations, and this is including things like FLT3, KIT, and RAS. And these are affecting signaling pathways in the cell. Mutations that can affect DNA and protein suppression of - sorry, DNA and proteins – tumor suppression protein stability. Sorry, that was a hard one to pronounce for some reason – And that would be where NPM1 fits in. There's

another of genes that affect DNA methylation and epigenetic modification, like IDH1/2, DNMT3, TET2, and ASXL1. Working our way around the slide at the tumor suppression pathways heavily affected by TP53. Splicing is an interesting area, and that's heavily involved in myeloid malignancies and AML, included in AML, and there's a number of mutations, SF3B1, SRSF2, U2AF1, ZRSR2, that can be involved. And then, of course, there can be mutations in transcription factors that regulate the expression of genes. And this can be involved in leukemogenesis. And some classic ones include RUNX1, for example.

So these mutations are all conspiring to lead to these diseases. AML is, of course, a heterogeneous population of diseases, and you can see this with this underlying diversity of mutations that can contribute to disease.

And so, over time, we've learned that, as was mentioned before, many of these disease mutations are prognostic, and they have an impact on how patients are going to do, how they're going to respond to treatment, and maybe what how we should approach their treatment. So for example, the NCCN and ELN have developed risk stratification systems that can predict survival, at, you know the 5 years, for example. And there's three categories: adverse risk, intermediate risk, and favorable risk, which you can see. And these can stratify patients and predict their long-term survival, such that, for example, 55% of patients with favorable mutations will be alive at 5 years. But if you fall into the intermediate-risk category, the number does decrease to 24 to 38%. And then in the adverse-risk category, 5-year survival is much more challenging, and that's in the 5 to 11% range.

And so some examples of these different risk factors, so in the adverse-risk categories there, you can see on the left there's a number of gene fusions and gene rearrangements, such as KMT2A for example, most of the KMT2A partners, for example, would lead to adverse-risk disease. And there's a number of mutations that are now recognized to impair a myelodysplasia-like biology to the disease, and they're summarized there, like ASXL1 and BCOR, and so on. And TP53 is associated with adverse risk. And then there's also abnormalities in the chromosomes, like deletions of chromosome 5, 7, and 17, or patients with complex or monosomal karyotypes will have, unfortunately, adverse-risk disease.

Now, on the favorable side, there's a couple notable examples of core-binding factor AMLs, RUNX1, RUNX1/T1 combo, and core-binding factor beta MYH11 combinations, and also NPM1 mutations without FLT3-ITD as well as CEBPA with abZIP in-frame mutation are considered favorable for risk in the new models. And then kind of things that don't fall in either category are now kind of lumped into the intermediate risk. And then the one big change from the previous classification system, risk stratification system I should say, is FLT3-ITD, which now ends up in the intermediate-risk category, regardless of the NPM1 status.

And I mentioned before too that some patients have underlying germline predisposition to AML. And this can be upwards of 4 to 10% of children and young adults. And it can be estimated at 4% or so of adults. And there's a number of mutations that have been identified, and I imagine this list is going to get longer over time as we learn more about the biology of AML and about some of these genes that might be involved in underlying risk to getting cancers. So some well-known ones include RUNX1, GATA2, CEBPA, for example, are some of the ones that have been characterized for a longer period of time. There's also emerging ones as well. And then p53 can be involved in a familial syndrome, for example.

And so I think it's important when you have a younger patient, especially where somebody who's screened and has a mutation that might be concerning for a underlying heritable disease, like, for example, in older patients, we're picking up a lot more DDX41 mutations. So when you see these things, either the underlying patient biology or age or mutations on a mutation panel, one might want to look into getting genetic testing on patients or at least a referral to genetic counseling, because this can have an impact on therapeutic decision-making, has an impact on discussions at least with the family about screening and about potentially surveillance of people that may have an underlying risk. It also could impact the choice of donors for transplant, and in some cases, some of these gene mutations can increase the toxicity associated with some of our treatments. So understanding germline mutations is a huge importance to the field and on the individual patient level.

All right, Courtney, I'd like to turn it over to you now to discuss how we can use some of this information to make personalized treatment recommendations for our patients.

Dr. DiNardo:
Sure. Happy to. So, you know, I think it's really kind of exciting how much things have changed in AML in the past, gosh, 10 years or so, with, you know, 12 new approvals for different AML patient populations. But it also kind of makes it a little bit more challenging, of course, to try to figure out what the right treatment is for the right patient at the right time.

So, you know, just thinking through, you know, the diagnosis of an AML patient, a lot of this is kind of what you had been talking about also. But you know, one of the most important things is just recognizing that we want to get the information back about the patient's leukemia as quickly as we can, because we don't want to sit, you know, for weeks and weeks before we start treatment. Of course, AML is often a cancer where we really want to start treatment in a timely fashion.

So, when we're talking about kind of diagnosis, the first thing, of course, is the morphology. So when a patient is presenting, you know, we're doing a bone marrow, we're looking for elevated blasts of the myeloid lineage, right? If they're the lymphoid lineage, they're ALL. So an AML, which generally is defined as greater than 20% blasts, but can be less than 20% blasts if there's an AML-defining genetic abnormality. So certain fusion transcripts, for example, like the core-binding factor leukemias. Even if it's less than 20% blasts, that still defines a patient with AML.

And then we're looking at different kind of CD antigens on the surface that are that are standard for patients with different myeloid leukemias. And it helps kind of in the kind of old-fashioned FAB classification, but it's still useful. And then what is particularly impactful now is kind of the cytogenetics and the molecular abnormality. So, you know, things like standard routine cytogenetics, you talked a lot about that, that helps us identify patients with complex cytogenetics that are in that adverse-risk group, patients with core-binding factor leukemias that are in the favorable-risk group.

But you know, there are, you know, multiple different somatic mutations that are recurrently mutated in our patients with AML. And these are really important to know. And I think it used to take us, on average, like, three to four weeks to get these type of panels back, and it's becoming faster. So for instance, in academic centers, like we have access to, it often is only taking like 3 to 5 days, whereas send-out places, it's still more like 2 to 3 weeks. And so definitely, you know, the sooner we get this information back, the more helpful it is to put treatment plans in place.

One thing that's also kind of helpful to do is to assess for the possibility of extramedullary disease. It's not as common in patients with AML to have kind of foci of leukemia outside of the bone marrow in the circulation, but it certainly can happen in like 15 to 20% or so of patients. And so that's something to be aware of. Often, when the white count is elevated above like 50,000 or especially if a patient happens to have like a FLT3 mutation or an elevated LDH, they may have an increased risk of having CNS involvement. So thinking about an LP or evaluation for extramedullary disease is important.

We can get some of the genomic information off of the peripheral blood. So that's something that can be done in patients who have circulating leukemia, but often at diagnosis, you know, we're really wanting the bone marrow, because we want to see morphology. We want to know cellularity. There's a lot of kind of pieces of information that are essential in that bone marrow, at least for diagnosis.

And then, you know, what is the goal of treatment? Well, of course, the goal of treatment is to, you know, first get the patient into what we call a remission, and then hopefully a long-term remission leading to a cure. And so what do we mean by remission? You know, remission is, there's many different types of remission according to our classifications. A complete remission is kind of the gold standard, and that means that they have less than 5% blasts in the bone marrow, they are no longer requiring transfusions, their neutrophil count has recovered, their platelet count has recovered, so a neutrophil count above 1,000 platelets above 100,000. And a complete remission that doesn't have full count recovery can be called a CR with partial hematologic recovery, that's called a CRH, and that's if they have a neutrophil count above 500 and a platelet count above 50, they haven't met that true full CR criteria. Or we also have a CR with incomplete hematologic recovery, that's called a CRI, and that's when you have all the criteria of a complete remission, but either the neutrophil count isn't recovered or the platelet count isn't recovered. So those are kind of just different kind of nuances of our different CR criteria, with a true CR being full count recovery of all the lineages. If you don't have any count recovery, but you still have no evidence of leukemia in an informational bone marrow, meaning that there is cellularity there, you don't see any leukemia, but the counts haven't recovered, that's called a morphologic leukemia free state. And a partial remission, which we don't see that often in leukemia, but it exists, and rarely you'll see it, maybe with differentiating therapy as patients are kind of slowly differentiating, where you'll see full normal count recovery, the true CR count recovery criteria, but still some leukemia blasts there, somewhere between 5 to 25%, and less than 50% from when they started.

So those are kind of the definitions of remission. And then, you know, that is kind of what we used for, you know, years and years. But I think more and more we're realizing the importance of something called MRD, or measurable residual disease. So a patient with a complete remission, a CR, can have either a CR that's MRD positive or MRD negative. And an MRD status is really just, it's a better estimate of residual disease, because even if you have less than 5% blasts, maybe 1 to 2% of those blasts are leukemia, or maybe they're normal. So just getting to a deeper sense of, you know, below the limits of morphology, what our pathologists are seeing, is there still leukemia there that we can detect with fancier assays.

And we know through following both patients receiving intensive chemotherapy and with lower-intensity therapy, that having persistent MRD is associated with shorter remissions and a higher chance of relapse. And so that's kind of – it is an increasingly important endpoint that we are paying a lot of attention to. Because, you know, we know if a patient is still MRD positive, and they've completed maybe their induction consolidation therapy, they're probably going to relapse because there's still leukemia that we can detect.

And so there's different ways that we can detect MRD, the two most commonly used, one is called PCR, qPCR or RT-PCR. This is a

very standardized and highly sensitive way of looking at residual disease, but you have to have kind of a specific genetic abnormality to PCR, and so that's about 50% - 40 to 50% of our AML patients. And that's a fusion transcript, a core-binding factor leukemia, NPM1 mutations can be perfect for PCR analytics. And so PCR is the most sensitive and the most standardized if available for your patient with AML.

Across the board, we can do something called flow cytometry or multiparameter flow cytometry. This actually comes back faster. It can be resulted in only like a day or two, but it's a little bit more challenging for pathologists. There's a bit of a learning curve, and so it's difficult to standardize with a lot of kind of user interpretation, but it is relevant and applicable for all patients with AML. So often, we will do flow cytometry for everyone, and then PCR in patients where that is available and it is complementary. And studies have shown that doing both can be complementary.

And there is also increasing interest and validation of using next-generation sequencing, or NGS, for MRD. That's not yet standardized. It allows you to check kind of the different mutations in that patient. You know, in the setting of remission, have those mutations disappeared? Or can you still detect them? It's a little bit challenging, because, you know, you talked about clonal hematopoiesis, there are patients who have CHIP clones or like pre-leukemia mutations, like DNMT3A, TET2, ASXL1. If those are still persistent in remission, does that mean it's MRD, or is that just a pre-leukemic clone? So some of those types of nuances are important when you're thinking about NGS, and that's some of why it's not yet fully standardized.

But you can do MRD testing in either peripheral blood or bone marrow. Bone marrow is, of course, a bit more sensitive, but both are appropriate. And we now have guidelines, primarily from the NCCN and ELN criteria telling us that in patients with kind of core-binding factor leukemia, NPM1, these mutations that are associated with favorable-risk leukemia, you know, we should be monitoring. And if we're still seeing persistent MRD after two cycles of therapy, that actually indicates that a patient who wouldn't otherwise go to transplant, may actually benefit from a transplant, because they have such a high risk of relapsing. So these are really important for us, and are changing the way we think about kind of classification and treatment decisions, not just at diagnosis, but also as time goes on during therapy.

So then in terms of kind of treatment. So the, you know, big question about, you know, how are we going to decide what treatment to do for our patients? I think, you know, we all trained in the world of kind of two different options, right? It was, you know, 7+3 for patients who were fit for intensive chemo, and then like azacitidine, decitabine, or low-dose AraC, for people who are not kind of appropriate or fit for intensive chemotherapy. And that's definitely changed. We still think about patients who are kind of fit for intensive chemotherapy, but if you're fit and appropriate for intensive chemotherapy, we're thinking, are you favorable risk? Because if you're favorable risk with the core-binding factor leukemia, we know we want to add gemtuzumab to your chemotherapy. Do you have a FLT3 mutation? Because if you do, then we want to add a FLT3 inhibitor, either midostaurin or quizartinib are approved in the frontline setting. Do you have a therapy-related MDS, a therapy-related leukemia or AML from a prior MDS or antecedent hematologic disorder? If you do, then liposomal 7+3 is approved and has shown benefit in that patient population. So all of these are important. You know, we want to know this information before we start treatment, because it really impacts what we're doing.

And then, you know, patients who are going to transplant, that tends to be all the adverse-risk patients appropriate for transplant. Intermediate patients who you think are a benefit, that's more of a risk-benefit discussion. Or favorable-risk patients who remain MRD positive, we're thinking about transplant, and if we're not thinking about transplant, that's where oral azacitidine is approved and a great option to improve relapse-free survival and overall survival in young patients getting intensive chemo, not going to transplant.

And then for our patients who are not appropriate for intensive chemotherapy, that's where, you know, we've had really quite a shift with the addition of venetoclax to azacytidine or decitabine or low-dose AraC, it's approved with all of those three backbones, and has improved survival, and is, I think, really kind of a key update for and availability for our older patients with AML. But also, you know, this is where mutational testing for IDH1 is really important, because if you have an IDH1 mutation at diagnosis, the approval of azacytidine and ivosidenib is approved with phenomenal, you know, increased survival rates compared to azacitidine alone, with good tolerability.

Relapsed patients, you know, this is where we need to know, do you have an IDH1? Do you have an IDH2? Do you have a FLT3-ITD? A FLT3-TKD mutation? Because we have targeted therapies for all of these. And it's also important to realize that, you know, just because you had a FLT3 mutation a diagnosis, for instance, it's not always going to be there at relapse, because clones can shift, and therapy can change the type of leukemia. So kind of doing mutational testing at different timepoints is really critical so you're using kind of the best treatment for that patient.

So key principles that help guide treatment decisions, you know, I think there's kind of a number of them, but just to highlight some of them is, you know, realizing that that relapsed/refractory AML is, unfortunately, a primary cause of mortality, that age is not the sole determinant for therapy intensity. And just because a patient is, you know, maybe younger, but they have certain comorbidities, you

know, maybe we should be thinking about lower-intensity combinations, or vice versa. An older patient who's very fit may benefit, especially if they have a core-binding factor leukemia, and we know they could be cured with intensive chemotherapy. So that's why, you know, evaluation of comorbidities is really important. Geriatric assessments can be incredibly helpful to provide, you know, treatment and prognostic insights.

It's really important to talk about goals of care early. Talk to your patients what's important to them to know, you know, how to best, you know, treat the patient in front of you, know the kind of desires of that patient, and that's really, you know, of course, important to make sure that we're all working together and making sure we have the same kind of goals and endpoints.

Transplant is really important. We've got to think about, you know, transplant early for all of our patients, really, regardless of what therapy they're getting. You know, are we thinking about a consolidative transplant. If we are, let's get transplant involved quickly. Let's get that, you know, let's figure out who the right donor is, and kind of get that process started. And remembering, again, that that response to therapy is dependent on kind of the genetics. And so genetics is really important for defining the best treatment approach and the anticipated outcomes.

So in summary, most patients with AML have at least one driver mutation that affects prognosis, relapse risk, treatment options, and response to treatment. AML risk is divided into kind of three different categories: adverse, intermediate, and favorable risk using genomics, right, this the standard cytogenetics as well as mutational abnormalities. MRD is increasingly important, and it means measurable residual disease. It refers to persistent treatment-resistant leukemic cells that can increase the risk of relapse and are there below the limits of what we can see with standard morphology. And we can test for MRD with qPCR, with flow cytometry, with NGS. Each method has advantages and disadvantages. And in the future, I suspect we'll be using many of them at the same time. It's most beneficial when it's measured sequentially. So it's not just, you know, a one-time MRD, yes/no. You're monitoring your patient over time, during and after induction therapy, before transplant, at other treatment-specific times. And remember that the 2024 NCCN AML guidelines recommend specific therapies based on cellular molecular cytogenetic biomarkers.

Dr. Fathi:
All right. So Courtney, in your view, what patient factors affect a patient's eligibility for intensive induction versus non-intensive therapy in the upfront setting?

Dr. DiNardo:
Yeah, I wish it was an easy answer. I wish it was like a very simple, you know, this is what you need to do. But it really depends a lot, you know, on the patient's, I mean, we say performance status, because that really makes a difference. Is the patient walking into the appointment? Are they kind of fit? Are they able to, you know, get back and forth to appointments easily? You know, these types of things are really important. Do they have comorbidities, especially underlying heart disease, that would affect their ability to receive an anthracycline? Do they have kind of underlying lung, liver disorders, kidney disease? I mean, things like this are all important. Age is, of course, important, but age is just a number, and that's part of the picture.

I think the other thing that's really important is the genomics themselves, right? So, you know, we talked about this a little bit. If a patient is a favorable-risk, core-binding factor leukemia patient who's on the borderline, I'm going to, you know, think about intensive chemotherapy for that patient, because I know they can be cured with intensive chemotherapy. Whereas, if they have, you know, complex cytogenetics and a p53 mutation and they're borderline, you know, I'm not going to push them for intensive chemo, because they're going to do just as well or just as poorly, I should say, with a lower-intensity therapy. So, the genomics actually matters for me also.

Dr. Fathi:
That's great, Courtney. Brian, I think in line with that, some of this information that helps us make these decisions are related to mutational testing at time of diagnosis and sometimes during the course of the patient's history of their AML. Tell me a little bit about your approach to diagnostic testing on presentation, and also how often you check mutations over the course of your treatment of the patient's disease.

Dr. Jonas:
Yeah, thanks, Amir. I think that's a super important question. And you know, when I was discussing earlier about the biology of AML, we really need to be getting, with every patient that's diagnosed, not only just standard cytogenetics, which has been something we've been doing for as long as all of us have been practicing, but also these next-generation sequencing-based broad myeloid mutation panels, and I think those are very critical for understanding the biology of the disease.

Dr. Fathi:
I'm sorry, one quick question that I want to run by Courtney. More and more now, because of the diagnostic testing that we have, we

actually do not pick up only one potential targetable mutation, but two or now maybe three. How do you approach these scenarios? I know there's not a perfect answer to this question, but this is a predicament that we run into now.

Dr. DiNardo:
Yeah. Oh, it is. And it is going to be all the more confusing in another couple months when, you know, there's potentially the approval of menin inhibitors for patients with KMT2A rearrangements and NPM1 mutations. And it's going to be even more complicated, in a way.

But in terms of multiple mutations, you know, I think for me, if it's a FLT3-ITD, for me, that takes precedence. So if I'm trying to choose between, you know, an IDH mutation or a FLT3 mutation in particular, I usually kind of go for a FLT3 mutation in that setting, just because those patients are often quite proliferative and in need of a FLT3 inhibitor. And that's just been kind of our experience and recommendation.

But otherwise, you know, it's surprising to me – we didn't talk that much about clone sizes, for instance. Like you can have a relatively small FLT3 mutation, or IDH1 or IDH2 mutation. They can be at like 10%, 15% so you would think that maybe they wouldn't respond to an IDH inhibitor, for instance, but actually, you know, they can respond just as well. So I tend not to use the clone size as I'm determining which treatment to choose. And if a patient has a target, has an IDH1, an IDH2, or a FLT3 mutation, I will use those targeted therapies if appropriate for that patient, regardless of clone size.

Dr. Fathi:
Great. Thank you so much.

I would like to provide an overview of the current landscape of therapies for acute myeloid leukemia. As has been mentioned, there has been a sea-change in the therapies that are currently available in AML, with multiple agents being approved over the course of the last decade, and many currently in clinical trials for further investigation, which will hopefully become available for our patients in the years to come.

In terms of the classes of these drugs, some of these are small molecules, some of these are antibody drug conjugates, some of these are naked antibodies. But suffice it to say that our small molecule inhibitors have had a substantial impact on the treatment of AML, both in the upfront setting and in the relapsed/refractory setting.

I'll start with drugs that impact DNA methylation. Those that target the isocitrate dehydrogenase genes, IDH1 and IDH2, are incredibly impactful in that they have been studied both as monotherapy in the relapsed/refractory setting, but also in combination with upfront therapies. The IDH1 inhibitors ivosidenib and olutasidenib, are currently approved for therapy in AML. The IDH2 inhibitor, enasidenib, is also approved for relapsed/refractory AML.

Hypomethylating therapies in the form of oral azacitidine is now approved as a maintenance strategy following upfront intensive chemotherapy. The small molecule BCL2 inhibitor, venetoclax, in combination with azacytidine, as well as low-dose cytarabine, has also been approved, and has really changed substantially the therapy of older patients with AML. Gemtuzumab ozogamicin, the antibody drug conjugate, was initially approved many years ago in the relapsed/refractory setting, then pulled voluntarily by the sponsor, and is now back and approved in multiple different settings, including the upfront settings in combination as well as a monotherapy in the relapsed/refractory setting.

Finally, the receptor tyrosine kinase inhibitors, the FLT3 inhibitors, both the earlier generation, nonspecific FLT3 inhibitor, midostaurin, as well as the newer next-generation, more specific and efficacious FLT3 inhibitors, gilteritinib and quizartinib, have also been approved in various different settings for patients with FLT3 mutations.

Let us start with venetoclax, the novel small molecule BCL2 inhibitor that, when combined with our standard upfront therapies for older patients, has really made a substantial difference in the care of these patients and has improved their survival. Much of the data has really emerged from phase 3 studies that have combined venetoclax with upfront strategies for older patients, including azacitidine and low-dose cytarabine. The famous VIALE-A study, the phase 3 study that is led by my good friend and panel member here, Dr. DiNardo, combined venetoclax and azacitidine and compared it with azacitidine and placebo, and showed a significant survival advantage. Not only that, the composite's remission rate was 66% with the combination versus 28% with the placebo combination.

The randomized phase 3 study that looked at low-dose cytarabine also showed an advantage in terms of overall survival, although I will say that more and more patients are using the hypomethylating combination in favor of the low-dose cytarabine combination in their treatment of older patients with AML, given better tolerability in general.

There are unique tolerability aspects to the care of patients who do receive venetoclax combinations. In other hematologic malignancies, the therapy with venetoclax oftentimes leads to a potentially life-threatening complication called tumor lysis syndrome. This can also happen in AML, but the likelihood of it is quite low. In fact, it's less than 10%.

Nevertheless, it is important to monitor patients closely. Our patients at Mass General Hospital are admitted to the hospital for close monitoring of tumor lysis syndrome. There is a dose escalation initially that allows you to gently increase the dose so as to mitigate any effects of potential severe tumor lysis syndrome. And then we monitor patients closely by monitoring their electrolytes, kidney function, LDH, and uric acid.

There is also important considerations when it comes to concurrent CYP3A4 substrates that are oftentimes used in patients who have AML that can impact the circulating levels of venetoclax, increasing it and putting patients at risk. The most common agents that we deal with in this setting are azoles. So many patients who receive prophylaxis for fungal infections or are under treatment for fungal infections receive azole therapies. And in that scenario, the dosing of venetoclax needs to be adjusted, meaning decreased.

The combination of azacitidine and venetoclax, as well as low-dose cytarabine and venetoclax can lead to significant marrow suppression, and this is important because prior to the advent of the hypomethylating agent combinations with venetoclax, older patients were treated with hypomethylating agents as monotherapy. In that setting, suppression of blood counts did occur, but not to the degree as you see with this combination. And therefore, we should monitor these patients very closely over time. And things like neutropenia and thrombocytopenia can be substantial, leading to complications like infection and bleeding that can be severe and potentially life-threatening. Close follow-up, potential use of GCF antibiotics as needed, admissions when patients have fevers, and potentially extending cycles and decreasing the duration of venetoclax are incredibly important aspects to the care of patients who receive combinations with venetoclax.

Now, let's move on to the more targeted inhibitors in patients with targetable mutations such as IDH mutations. Ivosidenib is an IDH1 inhibitor, the first IDH1 inhibitor that was approved for acute myeloid leukemia in an open-label, phase 1/phase 2 study that looked at both the dose finding as well as exploration of efficacy of ivosidenib. It was shown that in relapsed/refractory patients, the composite remission rate of just ivosidenib monotherapy, not a combination, led to a composite remission rate of 30%, a CR rate of approximately 20%, and an overall response rate of approximately 40%. These were quite phenomenal response rates in relapsed/refractory patients, and led to a median overall survival in patients, many of them heavily pretreated of approximately a year. Since that time, ivosidenib has also been combined, also with azacitidine, leading to high rates of composite remission and a markedly impressive prolongation of median overall survival over a placebo-controlled cohort in a phase 3 study called the AGILE study.

Another IDH1 inhibitor has been more recently approved by the regulatory agencies, olutasidenib. It is also a very potent IDH1 inhibitor. That too, leads to a composite remission rate of approximately 30%, a similar CR rate as ivosidenib of 20%, and a similar overall response rate of 40%. The combination of this drug with azacitidine has also been studied, but in a more limited manner. What's intriguing about this compound is it appears, not in comparison to ivosidenib, but in its own phase 1 and phase 2 study, is a durability of response that is quite remarkable, and at least, in terms of historical comparison, longer than what was seen with ivosidenib. Whether that is true, will require comparative studies, ideally in the phase 3 setting. And I'm not sure if that's going to happen, but nevertheless, we have these two IDH1 inhibitors that are currently available for patients who have IDH1 mutations.

Let us not forget about IDH2 mutations. Now there, as Dr. DiNardo mentioned, IDH1 and IDH2 are proteins, one residing in the cytosol, the other one in the mitochondria, both of them can be mutated and altered, leading to the progression and formation of myeloid neoplasms, including AML. I talked about IDH1 inhibitors for IDH1-mutated patients. Well, we also have an IDH2 inhibitor, enasidenib, that is approved for use in patients with IDH2-mutated AML. This was studied in a similar fashion to ivosidenib in a dose-finding and dose-expansion phase 1/phase 2 study leading to its approval as a monotherapy in relapsed/refractory AML. And at a dose of 100 mg, which is ultimately determined to be the recommended phase 2 dose and the currently approved dose, it too led to a median overall survival of approximately 9 months. And patients who had responses, even if they were non-CR responses, did remarkably well with even longer median overall survival.

So in summary, IDH inhibitors can be quite effective in patients with IDH mutations, can have an impact on response rates and overall survival, and are currently approved in various settings. However, like venetoclax, there are unique toxicity profiles to these agents. The commonality in terms of tolerability and safety is related to this entity called differentiation syndrome. The mechanism of action of IDH inhibitors relates to the triggering of differentiation and maturation of white cells, and sometimes that can be too robust and lead to an inflammatory cascade, presenting a nebulous fashion in patients, such as fevers, pulmonary symptoms, pleural effusions, rashes, adenopathy, and when severe, it can lead to a significant morbidity and even mortality, oftentimes a respiratory failure.

Because differentiation syndrome can mimic many of the conditions that we see in AML, such as the leukemic infiltration, infections, volume overload, it is important also to treat all those other potential sequela, but at the same time, keep differentiation syndrome in the back of our mind, and if we suspect it, treat it.

Differentiation syndrome typically occurs about 10 days to 6 months after start of treatment. That part of it is not easily estimated, but if

there is a suspicion, the recommendation is to treat it with steroids. We typically recommend dexamethasone 10 mg twice a day, and then as patients improve, which they should if it is indeed differentiation syndrome, a slow taper over time. But to monitor for differentiation syndrome, recognize the typical symptoms, initiate prompt mitigation with steroids is important, and sometimes DS, as is short for differentiation syndrome, can occur with leukocytosis, which means an elevation in white blood cell count, typically neutrophilic. That would require cytoreduction, and the most common form of cytoreduction is hydroxyurea. So this is the typical approach to differentiation syndrome that we see in patients who receive IDH inhibitors and have this manifestation occurring in about 10 to 20% of patients.

There are also unique toxicities with individual IDH inhibitors that I will briefly go through. For example, ivosidenib has been associated with QT prolongation, so close monitoring of QT interval is very important. Hepatic toxicity in the form of transaminitis has been seen with olutasidenib, and it can be quite severe, including grade 4. That needs to be also monitored for and dose adjustments and dose discontinuation may be needed. A benign form of bilirubinemia, usually indirect, has been seen with enasidenib, the IDH2 inhibitor. Typically, dose adjustment and dose discontinuation is not needed because it's most often a benign condition, but nevertheless, close monitoring of bilirubins in patients, particularly those who have a history of Gilbert syndrome, is recommended.

Now, let's move on to FLT3 inhibitors. FLT3 inhibitors have a longer history in the treatment and management of AML. FLT3 mutations were discovered more than a decade ago in AML, and they come in two varieties, as was earlier mentioned by Dr. DiNardo, ITD and TKD. The ITD mutation is more common, occurring in about 1/4 of patients. Another 7 to 8% of patients have various TKD mutations, the most common number which is the D835 mutation. And that is important because the FLT3 inhibitors, which are the small molecule drugs that inhibit the altered FLT3 enzyme have differential effects on whether you have an ITD mutation or TKD mutation. Some FLT3 inhibitors have minimal effect on TKD mutations, for example.

The first generation of FLT3 inhibitors were actually developed for other cancers, because, as you can imagine, other alterations and amplified receptor tyrosine kinases are oftentimes a trigger of other malignancies, and small molecule inhibitors that have been developed for them also happened to inhibit FLT3. And midostaurin was one of these first-generation FLT3 inhibitors, nonspecific, promiscuous, not particularly potent, but nevertheless inhibited FLT3. And it was studied initially as a single agent, then in combination with a great shot promise when it was combined with upfront intensive chemotherapy for younger FLT3-mutated patients, and ultimately, in the phase 3 RATIFY study where, in a placebo-controlled setting, it was superior in terms of median overall survival, although the remission rate was not significantly different. Because of that survival advantage, it was approved for use in FLT3-mutated patients, both ITD and TKD, and is currently a standard of care in patients who have FLT3-mutated patients and are newly diagnosed ineligible for intensive therapy.

Much more recently, a more targeted second-generation FLT3 inhibitor, quizartinib, has been studied in a similarly designed phase 3 placebo-controlled study, and that too was shown to be superior. This study was slightly different in the sense that the age range was different, whereas the RATIFY study with midostaurin went up to age 59; quizartinib went up to age 75. And in addition, quizartinib is not particularly effective in TKD-mutated patients, so the focus of this trial was only on ITD mutated patients. Nevertheless, these positive results led to the approval of this drug also in ITD-mutated patients who are undergoing induction chemotherapy for their disease. So now we have two FLT3 inhibitors, midostaurin and quizartinib, in combination with 7+3 or induction chemotherapy for newly diagnosed FLT3-mutated patients available to us. We have, increasingly, at our hospital, started to incorporate quizartinib because we think it's slightly better tolerated than midostaurin in terms of Gi toxicities. But of course, it's not particularly relevant in patients who have TKD mutations, so we have to also keep that in mind.

Gilteritinib, another next-generation FLT3 inhibitor with market sensitivity against FLT3-ITD, but also somewhat active in TKD, was studied in the relapsed/refractory setting in a phase 3 study, not in the upfront study, at least that data in the upfront study has not been published in manuscript fashion. But the ADMIRAL study that looked at gilteritinib in the relapsed/refractory FLT3-mutated setting, compared gilteritinib with various forms of salvage chemotherapy, and found gilteritinib to be superior to them, and that led to the approval of gilteritinib as a monotherapy, not in combination, as a monotherapy, for patients who have FLT3-mutated AML, which is either relapsed or refractory. Subsequent retrospective analysis looked at gilteritinib, particularly in patients who had previously been exposed to other FLT3 inhibitors, an increasing population as you can imagine, as we start to incorporate FLT3 inhibitors into the frontline setting, and found gilteritinib to retain its efficacy in those patient populations.

FLT3 inhibitors have also been studied in the maintenance setting, particularly in the post-transplant maintenance setting. As you can imagine, patients who undergo treatment for AML are oftentimes initially treated with what we call induction chemotherapy to achieve a remission, and thereafter go on to consolidated approaches, the most common of which is transplant. Once they undergo transplant, part of the challenge with FLT3-mutated disease is its propensity to relapse, and relapse often. So the incorporation of FLT3 therapy following transplant as a monotherapy given continuously for a period of time was to suppress the potential for relapse in that setting.

The first drug that really was assessed for this was sorafenib, another multitargeted, nonspecific, promiscuous FLT3 inhibitors developed in fact, approved for other cancers, such as liver cancer and kidney cancer. But in this setting, also highly suppressive of FLT3-ITD, and showed in a phase 2 randomized study called the SORMAIN study, to be superior in terms of relapse-free survival, so that many individuals and many centers, based on this data, began to give sorafenib to patients who had undergone transplant for FLT3 AML, in an effort to suppress relapse.

And then the more recent data has been with, again, the more targeted agent, gilteritinib, in the maintenance setting, in the MORPHO study, which was a randomized phase 3 study this time, double-blinded following transplant in patients with FLT3-ITD disease. And this study was not positive in terms of its key primary endpoint, which was overall survival and barely so. So the p value was 0.0518, as you can see here. And because of that, this was a negative study. Nevertheless, the assessment of FLT3 MRD prior to transplant and after transplant, but prior to initiation of gilteritinib following transplant, in those settings, if patients had MRD positivity, they did substantially better, significantly better, if they received gilteritinib versus placebo. So there is a lot of discussion now in the transplant world and patients who undergo FLT3-mutated disease in terms of how to interpret this data. This study was powered for all patients, not just for MRD-positive patients, but I would say for most of the individuals I talked to, the data on MRD-positive patients who benefit, or appear to benefit with gilteritinib here, this seems to be quite impressive. And most individuals at my center, at least, who undergo transplant currently receive gilteritinib if they are MRD positive, either prior to transplant or right after transplant.

So as we did with IDH inhibitors and venetoclax, just to briefly talk about the potential unique toxicities seen with various FLT3 inhibitors that are currently improved, midostaurin in combination with induction is what we generally use. It can cause marrow suppression. It can cause QT prolongation, although it's not common. But the main challenges we see with midostaurin, in my experience, are GI and liver, so nausea, mucositis, abdominal pain, diarrhea, liver enzyme elevation are, unfortunately, quite common and lead to dose interruptions, dose adjustments, dose discontinuations, and one of the big challenges with the addition of midostaurin.

Quizartinib, the new kid on the block when it comes to the addition to 7+3 is, in my opinion, better tolerated than midostaurin. But again, we can only use it for ITD patients. The unique toxicity with this drug is its propensity to potentially cause QT prolongation, and that was seen in the phase 3 trial as well, although the number of patients who had grade 3 or higher QT prolongation was not very common. Nevertheless, managing QT prolongation is important when you are giving quizartinib, and close monitoring is provided in terms of guidance in the package label.

Gilteritinib is currently approved, as I mentioned, in the relapsed/refractory setting, as monotherapy. That has been associated with GI issues, liver enzyme elevation, QT prolongation, differentiation syndrome has also been reported with FLT3 inhibitors. Nevertheless, in my experience, gilteritinib is fairly well tolerated, and adverse events seem to mainly occur in terms of marrow suppression and sometimes liver enzyme elevation. I do not see substantial GI burden or QT prolongation in the vast majority of patients I treat with gilteritinib.

Sorafenib is also provided here, although I have to say we do not use it significantly anymore, since the advent of gilteritinib and other more potent and specific FLT3 inhibitors. But nevertheless, sorafenib, because of its nonspecific multitargeted nature, has a broad range of toxicity, including GI toxicity, skin toxicity, secondary cancers, myelosuppression. But nevertheless, it can be used in certain settings, particularly in the maintenance setting, if gilteritinib is not available at my setting.

Finally, in terms of targeted agents, I'd like to also mention that it's not only small molecules that have been approved in recent years for AML, gemtuzumab ozogamicin, the CD-33 antibody drug conjugate was, as I mentioned, initially approved about more than a decade ago, I can't believe it, and then promptly removed because of potential for increased mortality in a phase 3 study. But then it came back after multiple studies looked at it in combination with upfront treatment as well as single agent in the relapsed/refractory setting, where it showed a survival advantage. In my practice, I generally tend to use gemtuzumab ozogamicin in combination with induction chemotherapy in patients who have core-binding factor leukemias or favorable-risk cytogenetics. Because in various studies, as well as in meta-analyses, it has been demonstrated that the patient population that seems to benefit the most from the addition of the CD-33 antibody drug conjugate seems to be those patients. And the unique toxicity, which I can turn to now, of gemtuzumab, is really hepatic toxicity, particularly sinusoidal obstructive syndrome, which is a liver entity similar to veno-occlusive disease that is associated around the time of transplant, particularly with higher doses and with ablative conditioning regimens with transplant. So in patients who are candidates for transplant, oftentimes, we think twice about using this drug for the experience we have seen in clinical trials with liver toxicity. In addition to liver toxicity, gemtuzumab can also be associated with infusion-related reactions. Those are not too uncommon in my experience, as well as marrow suppression, particularly thrombocytopenia.

FLT3 inhibitor therapy is not the only maintenance strategy in AML. In recent years, oral azacitidine has also been approved as maintenance, but not in the post-transplant setting, rather in the post-chemotherapy consolidation setting, where it has shown advantage versus placebo in a randomized phase 3 study called the QUAZAR study. And in that study, older patients who were in first remission,

who received either induction or induction with cycles of consolidation, were given oral azacitidine following completion of intensive chemotherapy. And those who received oral as azacitidine did substantially better in terms of overall survival with a difference of approximately 10 months compared to placebo. And as a result, oral azacitidine is now approved. We use it, although, because we end up transplanting so many of our patients, in a relatively low number of patients who are not either candidates for transplant, do not want to proceed to transplant, or they initiate it as potential candidates but are no longer because of toxicities during induction, and in that setting, we have to be very careful about using oral azacitidine following transplant, because – I'm sorry, following induction chemotherapy, because it can trigger cytopenias and GI toxicity. So dose adjustment, dose management is very important.

And that gets to this table that looks at the various AML therapies that I've talked about, including venetoclax, IDH inhibitors, FLT3 inhibitors, gemtuzumab ozogamicin, and oral azacitidine. And I think what comes across from the table like this is that, as opposed to intensive chemotherapy which gave us a platter of toxicities which were widely shared, you know, mucositis, nausea, vomiting, fever, skin, rash, each small molecule or targeted agent here has its unique toxicity profile. Whether that's QT prolongation or differentiation syndrome or GI toxicity or liver toxicity or tumor lysis, I think it is important to be thoughtful when you're using these drugs either as monotherapy or in combination. And I recommend everybody to study the package insert and to reach out to experts in the field and academic centers which treat a lot of AML and myeloid neoplasms, to get better sense of how to approach patients who you are considering for novel therapies.

So I'm going to shift a little bit and talk about other factors related to the management of patients with AML, and I'm going to talk specifically about factors that we look at prior to recommending a patient for transplant. And transplant has really become the main consolidative option for younger patients and more fit patients as a modality of consolidation, because it has the potential to cure, as opposed to many of the other options that we may have that are less likely to do so. And particularly in patients who have intermediate-risk disease, those who have persistence of MRD, and those who have adverse-risk disease, certainly if they have a donor, if they are sufficiently fit and appropriate in terms of organ function, we do recommend transplant. And factors that impact the transplant a success, as well as choice of conditioning therapy depend on multiple factors, including the donor and the recipient, age, comorbidities of the patient, HLA mismatch between the donor and the patient, history of hereditary AML. So as mentioned earlier, if a patient has a hereditary mutation syndrome, you want to be thoughtful about family members you may want to choose as donors or not choose. And that's at the source of the donor cells, whether it's a match-related donor, unrelated donor, and/or a half-matched donor, for example. And then the thought process around persistence of MRD following induction and consolidation, as well as age, because it would make a difference in terms of choice of non-myeloablative versus myeloablative conditioning prior to transplant. And then the choice of post-transplant maintenance, as was mentioned before for gilteritinib, is also an important consideration MRD.

The adverse effects of transplant are multitude and variable, and they could be related to conditioning, such as sinusoidal obstructive syndrome, mucositis, GI toxicities. They can be related to graft failure, graft versus-host disease, cytopenias that develop shortly after transplant, infectious sequelae of all sorts, pneumonitis that can be severe and overwhelming, as well as idiopathic pneumonia syndrome. And then the long-term effects, and that's why we have so many survivorship clinics now emerging in various cancer centers across the country, chronic GVHD, chronic and recurrent bacterial infections, reactivations of various viruses including zoster, infertility, lymphoproliferative states, and chronic pneumonitis.

So transplant and the discussion around transplant requires a lot of consideration of the patient, their disease, as well as donor sources. And I think some of that goes to balancing the treatment benefits and toxicities of AML, not just transplant that I just mentioned, but also the treatment that precedes it. And we have, I think, made a substantial amount of progress in recent years, even before the rush of approvals that we saw, you know, 10 years ago, over the course of last 10 years, I should say. There was an incremental improvement over time in survival, which was really due to supportive care, managing patients, expert transfusional approaches, so that patients now getting treatment for AML are much better managed in terms of nausea control, mucositis control, transfusional support, social supports that allow them to get through intensive and long-term therapies.

So I think we have a lot to provide patients who undergo treatment for AML, including upfront therapies, relapsed/refractory therapies, and transplant-based therapies. But nevertheless, as we've talked about over and over again, the tolerability and safety issues are very important and paramount, can be overwhelming, and need to be considered in every case, because there is a risk-benefit consideration in almost every discussion for the patient.

And that brings us to the shared decision-making aspect of all this. We talk about the diagnosis with the patient. We talk about the molecular markers that allow us to make decisions regarding what we're going to incorporate into the upfront setting versus the relapsed/refractory setting, and sometimes in the maintenance setting. And look at the data that supports that. And then talk about what we would expect to get from therapy and the potential toxicity and safety issues that emerge. And with that, we try, at least I try my best, to engage in a back-and-forth with the patient, to come up with a shared decision regarding what best fits their goals and their needs.

And my job is really to provide the information, provide my recommendation, but also hear what the patient has in mind regarding what they understand and know about effectiveness and safety, their concerns about side effects, their fears and anxieties regarding relapse and potential death and complications that may emerge from their disease. And then talk about quality of life, of course, and they also have financial considerations here, which I think is a good idea. I mean, this is becoming more and more an issue as many of these drugs that are emerging are highly, highly expensive and require, oftentimes, a significant amount of paperwork and effort by our support staff at the hospital so that patients can afford it and take it.

The best practices in terms of shared decision-making in our management of AML patients require close consideration, so talking together as a team, providing options for patients, and coming together in terms of decisions. And there is this method called the PACES method, that I maybe don't use as much as I should, but I think it's a useful method, method of presenting information, making sure the patient understands what you're saying, checking their understanding, asking questions, allow them to ask questions, express appropriate concern and support, and then go through the preferences that the patient has. So and I think if you follow that guidance, and I think many of us do probably, but this sort of a checkmark type approach to discussions with the patient and a shared decision-making approach, I think you're more likely to have a fulfilling discussion and a satisfactory outcome.

So in summary, most patients with acute myeloid leukemia have at least one driver mutation that affects prognosis, relapse risk, treatment options, or response to treatment. AML risk is divided into adverse, intermediate, and favorable risk categories using mutational or cytogenetic abnormalities. Measurable residual disease refers to persistent, treatment-resistant leukemic cells that can increase the risk of relapse. MRD can be quantified with qPCR, flow cytometry, or next-generation sequencing. Each method can have advantages or disadvantages. MRD is most beneficial when measured sequentially, including during and after therapy, before transplant, and at other treatment-specific times. The 2024 NCCN AML guidelines recommend specific therapies based on cellular and molecular biomarkers. The novel treatments we have for AML target genetic vulnerabilities that impact DNA methylation, cell growth, and apoptosis, tumor suppressor as well as tyrosine kinase activity. Recently approved therapies improved patient outcomes, including survival and composite remission rates. Transplant is the only curative treatment for the majority of cases of AML, not all, but the majority. And transplant is not available to all patients due to various reasons, including their functional status, their age, the availability of donors, and the availability of transplant. With an increase in novel therapies and targeted therapies, patients face potentially more complex decision-making, and must balance the tolerability, efficacy, prognosis, and quality of life concerns in coming up with a decision that hopefully is a shared making approach with their physicians.

That's all the time we have for today. I would like to thank doctors DiNardo and Jonas for a great presentation and lively discussion. I would also like to thank our sponsors for their support of this program. We would like to ask the learners to please fill out this evaluation and post-test to receive CME credit. This provides us with valuable feedback that will be used for the planning of upcoming programs. Please follow Iridium CE on X, Facebook, and LinkedIn, so you will be sure not to miss any updates.

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