Dr. Eytan Stein: Hi there, my name is Eytan Stein. I'm the Chief of the Leukemia Service at Memorial Sloan Kettering Cancer Center in New York City. And I'm very excited to welcome you to this educational activity entitled *Changing Standards and Evolving Strategies in AML Patients Unfit for Intensive Chemotherapy*. I'm joined by two eminent colleagues, so I'm going to allow to introduce themselves right now. Marion, do you want to start?

Dr. Marion Subklewe: Yes, so hello also from my site. My name is Marion Subklewe. I'm an attending at the LMU in Munich, Germany, where I'm taking care of AML patients. I'm also heading the Flow Unit in the Lab of Leukemia Diagnostics. So, I'm involved in MRD diagnostics per flow in AML patients, and I'm also heading a Lab of Translational Cancer Immunotherapy. So, clearly a focus on immunotherapy approaches also in AML.

Dr. Stein: Great, thanks so much. And David?

Dr. David Sallman: Yes, so really a pleasure to be here again. I'm David Sallman from Moffitt Cancer Center in Tampa, Florida. I'm the Myeloid Section Head, so predominantly overseeing all the clinical investigations for patients with myeloid malignancies. My personal focus is on patients with myelodysplastic syndromes, acute myeloid leukemia, a particular focus around patients that have P53 mutant disease, and then I dabble excessively in the correlative space, particularly around IO therapy, and then some MRD, predominantly more from a sequencing perspective.

Current Standards of Care for AML: Intensive Chemotherapy

Dr. Stein: Okay, great, thanks so much. And it's really wonderful to be joined by such preeminent leaders in the field of the treatment of acute myeloid leukemia. I think one of the things that may have changed between when we all started doing this a number of years ago, in 2024 is how we think about the types of patients that should be getting intensive induction chemotherapy, drugs like 7+3 or FLAG-Ida or other intensive regimens.

And I was just wondering, David, could you take us through really quickly, you know, in this advanced day and age, who should be getting intensive chemotherapy and how should we be thinking about that?

Dr. Sallman: Yeah, so I definitely had more hair when some of this discussion was being started. And I think really that, right, this is the major point of today's discussion amongst the three of us. And I think, unfortunately, I think it's getting increasingly complex. I think really back in the day, there was some sort of arbitrary age cut off on what could be fit or not fit. And then again, if you were “fit”, you should get 7+3 induction chemotherapy. And if you weren't, you should just maybe get something, and that was obviously modified down the road. But really now, I think you have to really incorporate multiple different components that I think we'll talk about in detail.

I think you, yes, you still have “the age of the patient”, but much more than that, what is the fitness? What is the comorbidity status of the patient? What are the patient’s goals?

Does the patient really seek a curative therapy, independent of risk? Do they focus more on quality of life, inpatient, outpatient discussions? I think these are major components. And then I would say equally important is that what are the biological underpinnings of the patient's disease? And again, there may be fit young patients that shouldn't get intensive and then vice versa. And I think there's not an easy answer. I think the big key is to really develop a personalized approach for these patients, a center approach for these patients. And ideally, if at all possible, to have all of these kind of variables in front of you before making a final treatment plan. Because that first treatment plan is most pivotal in ultimately improving the outcome of your patient.

Dr. Stein: So that's great. And Marion, one of the things that David touched on a little bit is that the biology of the patient's disease might influence whether you give that patient intensive chemotherapy or not. I mean, how do you think about that? Are there certain younger patients where traditionally, 15 years ago, we might have given them intensive chemotherapy where you would no longer do that? Or are there certain older patients where you might give them intensive chemotherapy, whereas a number of years ago you might not have?

Dr. Subklewe: Yeah, so I think it's really difficult to answer this question, but I think one additional aspect is, is a patient fit for intensive therapy and allogeneic stem cell transplantation, or is he only fit for intensive treatment? So, I think a large quarter of patients, sort of a little bit older still somehow fit, I would say they are fit for intensive treatment, but probably not really suitable for allogeneic stem cell transplantation . It was also difficult sometimes, you know, through the disease, they are in a worse state and, you know, they might recover once they're responding and you have to reassess. But clearly in those patients where we think due to age, performance status, and clearly also patient wish, they are not heading for allogenic stem cell transplantation. I sometimes even hope to make it easier for the decision that they come out with adverse genetic risk profile. And then it's sort of easy that we don't go for intensive treatment, but rather say, this is a patient for a clinical trial of an AZA non-intensive.

So, I think in principle, in a lot of patients, we really have to await genetic diagnostics to make the first sort of talk with our patients to put out the options and make a treatment decision. And I think it's beyond just the genetics we need for deciding, you know, targeted therapy or what we should include in addition to 7+3, for example. But it's also sort of thinking already about post-remission treatment options, that the genetics also determine our initial path. And in principle, I think all the scores, we're assessing frailty score and what kind of different scores we address. I think it's always really important to see the patient. It's nothing you can make in a board decision or something. And you have to get a

feeling of the patient, the family, the entire situation to decide which path this patient wants to go. But then, sorry, just one more thing. I think it's still really challenging because in a lot of patients, they rely on your guidance, right? So, I mean, we can always say patient wish, but the way you talk to the patient and they trust in you, there's a high responsibility in the way you talk to the patient and sort of show him his options.

Dr. Stein: So, what about this issue that has come up? Maybe this is the whoever wants to take this one can jump in. We have this issue now that the WHO and the ICC have sort of changed how we define acute myeloid leukemia. In fact, there are some patients have a genetic abnormality and not have an increase in blasts who will now have a diagnosis of AML. And I think the question becomes if you have a patient, for example, this is a patient I saw yesterday, a patient who came to me with an NPM1 mutation and an SF3B1 mutation, but no increase in blasts. And the question is, that patient is AML according to one of the classification schemas, but not the other one.

What do you do with a patient like that? How does this ICC-WHO thing get in the way or not get in the way of whether we should be giving intensive chemotherapy?

The Role of Diagnosis and Genetic Testing in Treatment Decisions

Dr. Sallman: Yeah, I mean, that's an extremely rare patient that Eytan….

Dr. Stein: It's true. I didn't just make it up for this talk.

Dr. Sallman: So, I think what I really like about the ICC classification part is there's no question there's a major overlap based on the underlying biology. So, somebody that's a 19% blast and somebody's a 20% blast, we can show these to multiple expert pathologists, they'll all disagree on what the percentage is. Some call AML, call MDS. From the trials, it can be like, I really feel like this blast count is less than 20 because this patient is optimal for a MDS trial or vice versa in AML from that. So, I think on one side, that harmonization in that, if I have a biological patient that I think clinically fits into one basket, I would treat them the same across different blast thresholds.

Now, I guess my question back to you is, I would presume that your patient that presented yesterday-his neutrophils and platelet counts may be okay. And so what is...

Dr. Stein: You would presume wrong, Dr. Sallman.

Dr. Sallman: Oh man, struggle.

Dr. Stein: The patient is pancytopenic…

….they came to me for a second opinion, pancytopenic, transfusion dependent, but when they had a marrow done two weeks ago at an outside institution, which I'm assuming is correct, they only have an NPM1 mutation, SF3B1, and a TET2-ASXL1 without increased blasts. So, now what, now what? Marion, would you want to say something?

Dr. Sallman: Okay. No, well, so I think my one important, there are definitely patients that have AML-defining genetic lesions without an increased blast that, like, are not clinically presenting that way. And this can happen with, you know, rarely, inversion threes and some others, and there's arguments about this. So, I've had patients that have potentially been AML-defining, some of which I followed for years without any therapy whatsoever, or I've done low risk therapies. I think with a patient like that, obviously, what is the mutation frequency? Is this a subclone or not a subclone? But in this patient, I think likely, this is probably a rapidly evolving AML-like state. And so just repeating a bone marrow biopsy and truly seeing, is there a rapid increase in blasts? Again, if you have a patient that is presenting with severe pancytopenia, transfusion dependence in NPM1, I would personally then treat that patient as an AML. And I would be very surprised if they truly stay with this lack of blasts, but these are personalized.

I think it's also, what is the goal of the patient? So, this is a high-grade myeloid neoplasm where I'm thinking of curative therapy. I think the nice thing is HMA-venetoclax has great response rates in this setting. So, it would be a very reasonable approach. You could say, hey, I'm still treating similarly across MDS and AML – granted, off label in the MDS setting. So, I do think the biology trumps everything else. I think, my hypothesis would be this would potentially more rapidly evolve. I've never personally actually had a patient presenting like yours stated yesterday.

Dr. Stein: Marion, what about you? How would you approach this?

Dr. Subklewe: Yeah, so I think one and I'm not surprised that the blood counts were sort of abnormal, right? So, I mean, nobody gets a bone marrow just for nothing. So, I think these cases are very rare and somehow constructed that they have less than 10% blasts and have genetic abnormalities, because otherwise, you don’t look into the bone marrow. But I think in principle, half of us and all the people that have guided us, that the number of blasts in the bone marrow are rather arbitrary and probably can have a recount, but I would do a repeat bone marrow because I would feel more comfortable if we get this threshold above the 10%, but otherwise I think pancytopenia, NPM1, for me this is an AML and I probably would like to confirm it prior to initiation of maybe intensive chemotherapy. But I think it is also very important to know, I think it has been shown at ASH that secondary mutations in NPM1 patients, these patients remain favorable. So I think this would be important in this patient that this intensive therapy result–allogeniec stem cell transplantation–has a curative approach, so this would be the way that I would go.

Dr. Sallman: Dr. Stein, what was your recommendation? We'd love to hear your thoughts as well.

Dr. Stein: Well, I was really struggling with this. It's a good thing that you brought that up. I was really struggling with this one because, like Marion said, there is this data from, I think, Christoph Rollig's group showing that the SF3B1 or the secondary mutations still remain favorable. But I think there was conflicting data from Curtis Lachowiez and using the UK Biobank showing the exact opposite. Now, of course, it must be that those patient populations are different in some way.

So, I really struggled with this. I certainly felt that giving someone like this intensive chemotherapy may be overkill. So, I thought maybe AZA-VEN . But I raised the question to my fellow, who thought I was an idiot, but maybe you could take the patient, is there a role of taking a patient like that straight to transplant? And someone who doesn't have increased blasts, do you need to eliminate the NPM1 clone and you can give them a myeloablative transplant?

What's the role there? And now, of course, if they have favorable risk disease, maybe you could spare them a transplant. So, I wasn't sure. The outside institution had recommended AZA-VEN, and that was as far as they got. They couldn't decide whether the patient needed a transplant or not. So, it was a very interesting case, and we're going to present it at our case conference this week.

The Current Standard of Care in Patients Unfit for Intensive Chemotherapy

Dr. Stein: So, I think the question becomes then, OK, we talked a lot about, or we talked a little bit about the patients who are getting intensive chemotherapy, but in 2024, I guess, what is the standard of care for patients who aren't going to get intensive chemotherapy? I think everyone's going to say AZA-VEN. I'll throw it to Marion. So, I guess the question is though, is AZA-VEN the standard of care in those patients who can't get intensive chemo? Or are there patients where something else might be the standard of care? Whether it's a targeted therapy, hypomethylating agent monotherapy, some sort of triplet. I know that if we all lived in Texas, we might be giving triplets to patients. Or is AZA-VEN really the standard that community oncologists should be giving to their patients?

Dr. Subklewe: Yeah, so maybe also coming back to the question, which patient should get intensive care and you know, which are the patients who will get non-intensive treatment. I just want to say probably Europe or at least Germany or Munich, we are pretty conservative. So, we've still given a lot of intensive therapy to our patients. And I'm always saying, if we sort of don't know, then we say no, the patient is probably somebody who should receive VEN-AZA. So, this is sort of my recommendation now to residents and whatever to fellows when we look at the patient. And I think we are moving sort of towards lower or less old patients that are actually also getting VEN-AZA and we are not as strict anymore. So, when we started, it was really patients that were really unfit. And now we're giving more patients on the VEN-AZA and even opening up the road that these patients might go to allo transplant, which at the beginning was sort of a no-go. We said intensive treatment is going to be allo, and patients who are not eligible for this are also

no allo transplant patients. So, that has changed definitely in the past, I don't know, two years. But for us, VEN-AZA is sort of the gold standard, but clearly before, we would always try to get a patient into a clinical trial based on genetics. We enrolled a lot of patients in the magrolimab trial and what other trials and triplets that are evolving. So, the gold standard would be a clinical trial. Second would be VEN-AZA. We hardly do ever any cytarabine plus venetoclax. So, we always do VEN-AZA. And then we always have a debate if there's an IDH mutation, how to move forward. Mostly we go with VEN and AZA, I must say, at this time point. So, yeah, I'm curious how David is seeing that. But yes, this is the gold standard in our center.

Dr. Stein: And can you get VEN-AZA for any age patient or is there an age cutoff where insurance will not reimburse it?

Dr. Subklewe: No, we can get it for every age.

Dr. Stein: Okay, David, what about you? You're giving VEN-AZA to everybody who's not fit for intensive chemo?

Dr. Sallman: Yeah, I think the two big groups where I would say, no different, I think one, you know, just Marion alluding to the IDH1, I would say there's no, there are some now active prospective trials, you know, I think one maybe within the [BDML] group with sort of sequencing of therapies and potentially another one. But you know, again, I think choosing what's the best therapy from the get-go and also thinking about sort of the longitudinal sequencing of options, you know, that way, what we may have. So, although they are cross trial comparisons, you know, the AZA-IVO frontline had a median OS of 29 months, the AZA-VEN in that group was about 19 months. So, that to me is a big delta. Again, lots of discussion on differences in patient populations, et cetera. But these were both true elderly unfit patient populations.

The other, and again, there's been multiple cohorts, although each one of them is quite small. You know, patients that get AZA-VEN have had much worse outcomes, at least with ivosidenib even from a response rate perspective, they had OS. Potentially, olutasidenib is different, although, again, these data are just emerging. Whereas, vice versa, HMA-VEN doesn't seem to be much more impacted. I think also just from an ease, at least in the US, where a high percentage of patients are treated in the community, AZA-IVO doesn't require much from a titration.

And again, you can just sort of leave patients on. Yes, you still have to follow them very close with counts and differentiation syndrome, but there's not this extreme titration month by month by month by month that's required. And so, from our standpoint, we view AZA-IVO as the standard of care frontline for IDH1 mutant elderly unfit patients. But again, maybe some prospective trials will help more definitively answer that. I do actually occasionally use IVO for the patient that doesn't want to come to the center, or the lady that's three, four years on single agent IVO with AML who's very afraid of the medical system.

The other big group I think is P53, and this group clearly has no standard of care. So, to Marion's point, they need trial, like one, two, three, four, five, because their survival in AML is less than six months in every single cohort. Standard of care are not published today, and that's clearly not adequate. I would say what we do off of trial, is we don't use actually venetoclax. We use only single agent hypomethylating agent because the morbidity is quite a bit less and the outcomes are the same. And I've actually a fair number of patients that have done reasonably well. So, I typically will slightly favor, although I don't believe the data of single agent decitabine in that setting. But I think HMA, monotherapy, and a P53 who's not fit for, especially not fit for allogeneic stem cell transplant, is what we're using . So, those are the two big groups that were, I would say, currently definitely changing therapy.

I think the last one is that FLT3 group, and we can talk more, does bad also. You know, to really the standards, you know, HMA-VEN would have been negative, HMA-GILT was a negative trial. So, we have actually moved much more either into a frontline triplet or a sequence where they get AZA-VEN and we add GILT. This is because of insurance issues, like into the end of cycle 1/cycle 2. And we've been doing much more triplet in our FLT3 unfit patient population, either again sequenced to some degree or a combination if we can get all agents up front. There is [two ways of end GILT] and there's a DAC-VEN-Quiz. We're a part of or going to be a part of the DAC-VEN-Quiz triplet study to help answer that maybe more definitively.

Dr. Subklewe: David, can I just ask one question to the P53? Do you differentiate in any way, you know, what kind of mutation there is or, or something?

Dr. Sallman: Yeah, yeah, this is the article I'm currently working on. I think, I mean, in AML, I mean, there's no study that actually shows really almost any impact. Now I do think from the Haferlachs, they published two papers like in parallel with *Blood Advances*. And if you still look at the single versus, it's basically bad versus really, really bad. So, I don't think from necessarily a treatment perspective, there is a major impact.

Dr. Sallman: Again, the vast majority of these patients are going to be a multi-hit or multi-hit equivalent. Again, complex karyotype with P53 is equally as poor. I think the only patients is, again, if you truly have a non-complex karyotype and P53 in a subclone, I do think you could consider intensive chemotherapy. There's a couple of publications to support reasonable outcomes. I would still go with like a non-7+3, more of a higher dose, CLAG, FLAG, plus or minus venetoclax, because they're often a myelodysplastic-related change , but maybe that rare patient that P53 in a subclone, I may consider intensive chemotherapy, but those patients are quite unusual.

Dr. Subklewe: Yeah, if I also just may add, so also the other group, we are sort of trying to put on clinical trials or integrating some kind of triplets or something are the patients just IDH and NPM1 negative, so not mutated. So, I mean, because they just do in general, was not as terrible as a P53, but those are the patients we are trying to get into clinical trials.

Obtaining Genetic Testing Results in a Timely Manner

Dr. Stein: Okay, so bottom line, Marion, you have a patient. So, I think actually before we get to the bottom line, I think that what you're both saying highlights the importance of knowing the genetics of the patient before you start on the treatment, right? So, how quickly can you get back sort of your cytogenetics, FISH and I guess P53 mutation status, you know, in Western Europe or maybe in Germany, which is where you are Marion and in Tampa, Florida, which is also in some ways a different country. So, Marion, how fast can you get your data back?

Dr. Subklewe: So, I really think not fast enough actually. We still have some delays. So, we do sort of a FISH screen. So, we get some of the adverse karyotypes within 48 hours. We get the important mutations within three to five days, but sometimes depending on the weekday, we actually do the bone marrow and so on. We sometimes have to wait 10 days until we have all the markers back. We are trying to do it within one week, but sometimes it takes a few days longer, and it's actually a huge problem. Also, from a psychological point for the patient, for the doctors, but also from a sort of financial point to keep the patient in hospital, to give them best supportive care while we are waiting and waiting. And sometimes actually, if they are stable, that's sort of still something I didn't learn when I started this, discharge the patient, right? And call them in once we have all the genetic data back. So, I think from the options we have that's absolutely necessary. I think there's a lot of data that in most patients, at least, it's safe to do. But sometimes you have these patients right there too sick to be discharged and neutropenic, they need sort of platelets transfusions or whatever, and they're just elderly and you don't want to have them one hour away from the center. That is a problem, actually.

Dr. Stein: Okay, David, how about you?

Dr. Sallman: Yeah, I mean, we're not, you know, like two hours later, like the Sloan Kettering group, you know, are with it. But I would say we're almost identical.

Dr. Stein: No, we're not nearly that good.

Dr. Sallman: We're almost identical to Marion. You know, really, it's about a week. But again, based on lots of things, both cyto and NGS can, I would say, push back as late as 10 days. You know, we, I do a lot of begging and rushing with my genomics lab, like getting it on the next run. Because it is, yeah, it does matter.

We will potentially send the FLT3 PCR still separately just because that can turn around more in the three-day timeframe, either for trial or for not on trial. We don't have any rapid IDH turnaround, so to the importance of that, we're waiting for NGS in all of the circumstances. And again, I think Marion highlighted a really important point because some people say, well, am I not going to give chemo at my institution. Again, for these P53s, I think we can make a very strong argument. And of course you have your history, but to what you put up, I mean, really most centers have the ability within one or two days to at least turn around an MDS FISH panel, especially like these broad FISH panels, like they include probably almost half of chromosomes, you know, once you include eight, 21, 16, 15, like again, even if the probes aren't meant for that, they may pick up things that if you start to see multiple FISH probes, you know, popping positives, it's supporting a complex karyotype.

The other thing, and it's been a little bit more, I would say, validated in the MDS, but we see in MDS, AML the two other things. One is P53 immunohistochemistry So, if you're really struggling with turnaround, it's a really good surrogate. It's not perfect, but the concordance is over 90%. It's having P53 IHC staining correlate with potential of P53 mutation. Even the VAF levels can actually correlate. So that can be one thing.

And also if you see a lot of ring sideroblasts and sort of excess blasts, MDS, AML states, much more common in P53. I think – any of those red flags, 100% halt on that. Actually, and I think she brought up another great point, actually; I think a lot of patients can be discharged and brought for an expedited follow-up. We'll say if hospitals stays, all of our hospitals are at a major bed crunch. For us, if we're not intensively treating, we actually do this entirely as outpatient unless there is a critical reason, proliferative disease, et cetera, just because of bed availability. I know that's different from actually, a decent number of centers in the US. But again, thinking about all these things, really getting everything and potentially a quick discharge, having them come back within a week can be reasonable in some cases.

Assessing Performance Status: Geriatric Assessment Versus the "Gut Feeling"

Dr. Stein: So, bottom line, David, for the community oncologists, they see a newly diagnosed AML patient a little bit older, they get the FISH back from a commercial lab that shows multiple, multiple chromosomal abnormalities, and then they find out they have a P53 mutation. Let's say this patient, I forget if I, I may have just said older patient, but let's change the age. Say, the patient is 60 years old, transplant candidate, how are you going to treat that patient? You're giving them AZA monotherapy? What are you doing? And you don't have a clinical trial available, you're a community oncologist.

Dr. Sallman: So I think if there is no way for the patient to get, I mean they still need to get to the academic center because, if we're going to think about curing, the only chance is transplant, there's no other question. So, what's not okay is you treat them for six months, you send them in as they're relapsing and then you have no option, period, in that setting. So, they need to be seen very, I argue even peri, that first round of therapy, but if it's truly not possible, and I think they could go to transplant, I will give them HMA-VEN, because the response rate is both quicker and at least a little bit objectively, higher from at least a blast clearance, although the quality true CR is about 20% between HMA and HMA-VEN. So, if I think they're a transplant candidate, I will give them HMA-VEN off study. If I think they don't or borderline, then that's when I'm going HMA monotherapy.

Dr. Stein: And Marion, in Germany, someone's not so close to Munich. They're in maybe a smaller area, a smaller town, and they see a local oncologist there in the local hospital. How would you advise them for this kind of patient? 60 years old, complex karyotype P53 mutation, newly diagnosed.

Dr. Subklewe: Yes, so I think a new patient is really an individualized decision. So, we would highly argue that this patient has to be presented at our site and we have to see him. So, it's not enough to just have the genetics and sort of some scores. We really have to see the patient and talk to the patient and get sort of an idea.

So, what is the concept? I mean, you know, in certain countries, they don't even do allo transplant in P53. I mean, the prognosis even with allo transplant is dismal. So, you have to sort of get sort of a feeling for the entire patient. So, that would be the first. I think all AML patients have to be seen or consulted, if at least an allo option is possible, at an academic center, maybe at least presented at a board meeting, even if there's not an allo option for these patients.

And then probably we would advise for a VEN-AZA, but we also sometimes treat these patients with intensive treatment to get them in the best remission prior to transplant.

Dr. Stein: Okay, that's great. I mean, I think that what we're hearing from or what I think we're all saying, because I agree with my colleagues, is that, even though it is easier to give treatment for acute myeloid leukemia in the community setting, where it wasn't before, where before you really had to admit them to a hospital to get intensive chemotherapy, really the ideal thing to do for the patient's sake, is at least to have them be seen once or multiple times at an academic center or a center of excellence so that an appropriate treatment plan can be put in place because AML has become complicated. It didn't used to be complicated. It used to be 7+3 or AZA or supportive care. And now it's really as complicated because we understand the genetics a lot better. So, I agree with my colleagues. And I think that that's something that I would really try to hammer home to the folks listening to this, is that if you can, it's a really good idea to send the patient for a second opinion, at least initially.

We talked a little bit about delaying treatment, but I wanted to dig into that a little bit, because like Marion said and David concurred, there are financial pressures for keeping a patient in the hospital while we're working them up, but there are certainly some patients who shouldn't be discharged.

So, what are the things you're looking at? Because we don't want to discharge a patient and then find out that they go home alone and they fall and something bad happens. So, who are the patients who really shouldn't be discharged from the hospital and should stay there until you have the genetic information back to make a treatment decision? Both biologically and from a fitness perspective. Either one of you, feel free to grab that one.

Dr. Subklewe: I think the fitness of the patient is important, but clearly sort of the setting, is he living alone or does he have somebody living with them that can sort of get help? So, I would be more concerned if it's an elderly patient who is sort of, you know, Echo-2 oxygen or something and is living alone, so, I think that wouldn't be responsible. And then clearly, you know, his whole risk profile for infections, bleeding and transfusion dependency is something that has to be taken into account. What is his risk profile for, for example, for pulmonary infection, you know; is he a COPD patient with cardiac disease and so on? And hemoglobin is already, you know, somewhere around seven.

I would feel a little bit more uncomfortable and needless to say, it's a huge difference if he's living like, you know, 30 minutes around the hospital or he's like one and a half hours driving and I don't know any hematologist close by who's taking care of him. So, it's a mix of sort of personal familiar, a family setup, distance to the center and then sort of infection, bleeding, transfusion, dependency, that guide our decision. It's very individualized. We don't have, like, one score that we can apply.

Dr. Stein: So, David, how do you then do you advise based on what Marion was saying, if you've got maybe a physician who doesn't treat a lot of AML, how did they decide who to discharge and who to keep in the hospital? In this environment in the United States and maybe in other countries where maybe you send a patient home from the hospital, there's a bad outcome before they come back and maybe there's litigation that ensues. How do you do that? Is that another reason people should be coming to academic medical centers? Like, how do we handle that?

Dr. Sallman: Yeah, so at least I would say in Florida, it may be more Southeast US, and again, maybe Eytan could speak to practices in the New York area. I mean, it's pretty unusual that induction chemotherapy is given outside of large hospitals in the area. And so, I think that's one thing. So, usually there is a call regardless to transfer the patient. And so, I think it's, I would recommend at least that call at all times.

And then again, if they meet all the logistical and other issues, what we'll do is rapidly expedite an appointment to where they're going to see us, let's say within a week or

less. And I think if they're, if there is a clear plan, then it's very easy, straightforward. I think there's a fear, oh my gosh, the patient has 30% blasts, but they have, you know, counts are not that bad. They're completely functional. Like it's some emergency, you know, patients sometimes go months with a diagnosis of, you know, an AML and are completely fine.

So, there are some very clear patients, but I think the key is again, the quick call in, hey, this is what the patient has or may have, can you get them quickly? Because again, it's really that first decision and then we can co-op manage together, I think, quite easy. Again, it's the P53 patient, these are a lot, they are often oligoblastic-type patients, many of them may be seen as an outpatient. And then we put in all this effort, a patient may be waiting two weeks to transfer to our hospital and in the end, we're not going to induce them anyway and only give them more outpatient-based therapies or trying to avoid that. I think one of the challenges, and I think something that we could improve a lot, at least within the United States, is if we could get these standard of care technologies, NGS, FISH, cyto, to also rapidly turn around in the community. That would then give us, I think, all the answers. I think a lot of times what we're stuck with, are a lot of times the calls I get, hey, my patient has AML, I can't do any of this testing, or it will come back forever from now. And so that puts us in a little bit of a weirder conversation.

So, in general, we just try to rapidly get them to our center and then we'll repeat everything from baseline just because it will be quicker for me to repeat than for me to wait. But that's not optimal. And I think we could, I think if we could all get a, really a standard of care workup in an expedited fashion, that would allow us to co-op manage better.

Dr. Subklewe: Can I just add one thing? So, I think, in principle, also arguing that every patient has to be seen at an academic center is that, unfortunately, the likelihood is really high that these patients will die of their AML. And for the patient and the family, it's really, I think psychologically, sort of, of value that have then been seen at a, you know, big center and every decision sort of were confirmed, even if the treatment is then done in a community center or something. Because then later on, you get these desperate emails that they want to be presented at the academic center when they have relapsed of whatever and are in a bad state and there's nothing to offer. I think it's also sort of, in that sense really helpful for everybody to be presented at an academic center.

Dr. Sallman: Eytan, any key differences? Obviously, you're in a large city, we would consider, with hospitals every three or four feet or blocks or however you speak. So, thoughts on maybe on differences or not in your area?

Treatment in an Academic Center Versus In the Community Setting

Dr. Stein: I think there are differences. Yeah, I was just going to say that. You know, like you said, in New York City, in Manhattan, we have hospitals, you know, we have a hospital across the street from my hospital that's a large academic center. But what I found recently, part of the reason I asked the question is that, we are seeing patients getting true induction chemotherapy in community hospitals where I wouldn't have expected it . Places that are, you know, community hospitals that really, you know, they will have community oncologists on staff treating a lot of solid tumor patients. They might be hospitals that specialize in orthopedics, but they will...patients have started getting intensive chemotherapy in these hospitals. And it's interesting, we've even seen...I mean, this is a completely different topic, but we've seen patients who've been getting, adults with acute lymphoblastic leukemia, which is a much rarer disease in adults, getting intensive chemotherapy at sort of community hospitals out on Long Island or New Jersey.

So, I do think there's a shift. And I think the other thing that comes up when we talk about less intensive therapy is that I think many community oncologists, appropriately, are feeling comfortable starting patients on AZA-VEN because they gave patients AZA and now they think, now we're just going to add the venetoclax. But then we run into the problems that we all struggle with, which is, well, what do you do after cycle one of therapy when the patient's in remission but they’re pancytopenic?

And I think that, that's where it becomes a little bit more difficult. I don't want to waste too much time on topics that might not be of interest, but I think one topic that is of interest that always comes up is, and I think it's come up throughout this discussion, is sort of this individualized approach to patients, or individualized approach to, you know, who can be discharged from the hospital, who can get intensive chemotherapy, who can't. And I once heard one of our colleagues describe the way we make this decision as using the oculometer. I think Hagop Kintarjian describes that, which is that you look at the patient and you make a decision. I know in Seattle, they have geriatric assessments or some sort of assessment that they do, but I don't know anyone….so, how do you make that, I mean do you do a geriatric assessment? Like in Germany, are people doing geriatric assessments of their patients, get up and go tests, or sending them to a geriatrician, or it's really what you think, Marion, when you see that patient in the office?

Dr. Subklewe: So, I think there are actually also studies that have shown that gut feeling is very similar to all the official scoring. So, I mean there are centers in Germany that do that but it's not very prominent also in the SIL, IML, CGE study group. So, we are not doing it but we've just now started using the sit to stand test and the gait speed on 10 meters burst. We thought maybe it is interesting at some point to have some objective measurements, so we are doing that. We haven't looked at the data yet, but I think in principle, we rely on gut feelings, sort of, you know, talking to the patient, seeing the patient, you know, having him move through the room and, you know spending some time. So, you know, you cannot rush in and out. But I think it gives you a very, I don't know, good assessment of the patient fitness. Yeah, it's very unscientific, but that's what we mainly do.

Dr. Stein: And David, in Moffitt, is there a committee of Rami Komrokji, Jeff Lancet, and David Sallman that sort of does a race with the patient? How do you, do y'all sit around and how do you decide?

Dr. Sallman: Yeah, I mean, I'm in the gut feeling camp. So, definitely any of those papers, I would be strongly supportive of. I think part of the challenge is, is that every case, again, these are rare cases, but it's not just the fitness. What was the fitness of the patient one month ago, three months ago? What's the kinetics of the change? What's the patient's living situation? They have 18 family members that could do anything or they're homeless and even transportation logistics. And the process, all of that happens like, almost every case there's something unique. What are the goals of the patient? Even just, I feel more comfortable in the hospital versus not in the hospital, like that. I do often, I will sometimes discuss, especially this, I think to me, one of the biggest questions is, is HMA-VEN or is

IC+ whatever, the better option for the fit 60- to 75-old? It's a big question. There are some trials that are going to help answer that, but I do, I don't have a sort of a dogma where you have to get this or you have to get that.

Sometimes we choose that and even how we actually get to that final treatment may be based again on all of these other things. And that's why I think if you just have one measure, hey, this is your frailty, geriatric, biological, whatever, I think the data gets very muddy in the end. And it's unfortunately all of that together. So, I'm a team gut feeling.

Rapid-fire Round: Key Points

Dr. Stein: Okay, so with that, I think we're coming to the end of our discussion. We're running out of time. I do want to have what we're going to call a rapid-fire round. We'll give David the first chance at the rapid-fire round.

You have two minutes, only two minutes, you're going to have to really limit yourself to 120 seconds with a community oncologist. Florida cancer specialist has called you and they want to know in two minutes, what are the most important pieces of advice for them about a newly diagnosed patient with acute myeloid leukemia and what they need to know? Go.

Dr. Sallman: Yeah, so I think to start, just a standard workup and working with the lab to have cytogenetics, FISH panels and next gen sequencing to be able to, no question, get a sense on all patients, maybe a FLT-3 PCR on top of that and just get that routine because that's going to help everything even if this is going to be a patient treated at academic.

To me, I think number two is, it sparks an immediate call to a colleague at one of the academic centers. And I think I have some really great relationships with a number of FCS practices, and we will literally discuss every new AML high-risk MDS case. In some of the cases, it's impossible for them to see me, and they will maybe just solely get there, and we can give it.

But I think that first, comprehensive workup, two, call to the center, ideally number three, at least that one-time eval for potentially HLA typing, allo transplant, start. Again, is there a trial? What is the best optimal therapy?

And then I would say, sort of having this tag team approach. I think realistically, there's going to be a lot of barriers for some of the speeds of some of these things. So, for us, for example, all of our post-cycle one of whatever combination, like we do all of the bone marrow is at our center. So, therefore, we can get all the data in a day. We haven't even talked about MRD, which is extremely critical in all of this. And we can kind of help dictate, hey, how should we transition therapy? So, thinking of really a team approach, not having a one size fits all, working with your academic center. In the end, they're going to be doing a lot of, or a brunt of the work and that's going to be the way to most optimally manage these patients.

Dr. Stein: Okay, Marion, I just went on Google Maps and I saw that there's a small town named Geisenfeld, Germany. A little bit, not so far from Munich. You've got a community oncologist in Geisenfeld that calls you. What are you going to tell them? Two minutes that you might give them that David hasn't said already.

Dr. Subklewe: Okay, that's going to be difficult. But the first thing I would say, you know, waiting is okay. So, that would be sort of, I will stress that waiting is okay. So, you wait for genetics; and that's important. We'll make you know, will depend on how we'll treat this patient. So, stay calm and give hydroxyurea and watch your patient and wait for the genetics. Second, right send the patient to an academic center so we can evaluate the patient for clinical trial, which is still the best option in lots of cases, and we can advise on the treatment . And maybe third, and maybe that hasn't been said by David, if this is a patient, which commonly happens in this case, who's receiving VEN-AZA, please be aware that although we always say it's non-intensive treatment, it can be very toxic treatment. And there are certain things that have to be watched out. Only give venetoclax for 28 days. Look at bone marrow aplasia and response. You can stop venetoclax early. Think of applying GCSF and talk to us while you give the first cycle and are thinking, when to initiate the second cycle, if you want to initiate the second cycle.

So, don't be misled by this non-intensive treatment approach, which is somehow misleading, and would advise on posaconazole or antifungal prophylaxis dosing and all these kinds of things. Just send him a short reminder how to do this.

Dr. Stein: Okay, so thank you so much to both of you. This concludes our discussion of the changing standards and evolving strategies in AML patients who are unfit for intensive chemotherapy. I'd like to really thank David and Marion for talking with me today, especially Marion, because of the time difference, I believe it's close to 10 p.m. now in Germany. David and I are in the same time zone. In our next webinar, we'll be talking about the advances in non-intensive therapies that we're anticipating in AML from CD47-targeting agents to bispecifics and T-cell redirecting therapies to CAR T cell therapies. So, please don't forget to complete your continuing education evaluation to claim CE credit. Thanks so much for your attention.