ManagingAML

ASH 2020 Meeting Highlights in Acute Myeloid Leukemia

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Dr. Ross Levine: My name is Ross Levine, and I'll be your host, if you will, of tonight's program, *ASH 2020 Meeting Highlights in Acute Myeloid Leukemia*. I'm joined by two really fantastic and esteemed colleagues. One of my compatriots from Sloan Kettering, Dr. Eytan Stein, as well as our friend and colleague from Duke, Dr. Harry Erba. Thank you both for joining us this evening.

Dr. Harry Erba: Thanks, Ross.

Dr. Eytan Stein: Thanks.

Dr. Ross Levine: Great. What we'll try to do tonight is talk about really three different areas, and we'll go through some data relatively quickly from the meeting, and then we'll have a discussion of each of them. Then for the last 10 minutes, we'll try to answer some of your questions, and I can speak, I think for myself and my colleagues that, we're always here to answer questions, and also just discuss cases with everybody, because we think that AML is a hard disease, and every case has its challenges.

Just to give you some background, AML has been a disease which until I would say four or five years ago, had relatively static treatment with intensive chemotherapy and stem cell transplant for our younger or intensive therapy eligible patients with really no great standard of care for patients who weren't candidates for intensive therapy, who failed intensive therapy. In the last couple of years, we've seen a whole bunch of new therapies.

Whether it's VEN/AZA, venetoclax and azacitidine, or venetoclax hypomethylating agents more broadly. The use of liposomal daunorubicin cytarabine, CPX 351, and the beginning of targeted therapy era with FLT3 IDH inhibitors, and now, the beginnings of maintenance therapy. Tonight, the idea was to talk a little bit about what we're learning about these agents and how we're using them and what did we learn this past year?

We'll start with the elephant in the room, which is venetoclax-based therapies for AML. How do we use them? How do we monitor response and how should impact duration of therapy? There are emerging clinical scenarios or combinations which are emerging for particularly BCL-2 targeted therapy. For venetoclax, I thought we'd talk a little bit about a few different abstracts. This was one that was a collaborative effort led by Keith Pratz, which I thought was really important, because it talks about what it's going to be like to use these agents in real clinical practice.

This was an analysis of the VIALE study. The VIALE-A study was a study of azacitidine with or without venetoclax and with the intent of looking at a complete response and overall survival. There was even a post hoc analysis, which is what you'll hear about today. There were a whole set of dose modifications for cytopenias in this trial, including in patients who had significant cytopenias, either delaying venetoclax or the next cycle, or an AZA dose adjustment.

You can see all the details there and the details are not critical at this moment, but are available. The trial has been published. A couple of things we learned from this trial. First was that, in many patients we saw blast clearance in VEN/AZA more quickly than with AZA alone, but this resulted in a delay of the next cycle. Patients had a delay of an average of 10 days for VEN/AZA versus AZA.

Remember that you're trying to give it every 28 days, but the reality is it's not. Although you're getting more of a response, the fact that you're delaying is because patients also have delayed count recovery, and you could see the fraction of patients that actually have a delay is 74%. The most patients are not getting therapy like clockwork on day 28. If you look at when those events are, it's important to understand that the median time from remission to first-grade for cytopenic event was about 161 days for VEN/AZA, and if you look at the remission or response rate, you can see a higher incidence of complete remission, a clear remission with hematologic incomplete recovery. You also see an increased post-remission grade for cytopenia.

You're getting remission, but that's expensive mild suppression. A lot of the delay is due to cytopenias, and you could see that in VEN/AZA, that many patients had two or more cycles delayed. That's not seeing the AZA, where a lot of patients had no cycles delayed or at most one or two. If you look at the patients who got different regimens, whether they got a 21-day or 28-day, it did not look like that dosing regimen made a big difference. Again, with the idea being that most patients aren't even getting it every 28 days, it doesn't seem like accelerating that made a big difference with the caveat that that was not how it was designed.

The second abstract on VEN/AZA was a study from our colleges at MD Anderson led by Ravandi and colleagues, looking at measurable residual disease. These are MRDs, some people call minimal residual disease, but I think measurable is a better term, in venetoclax/decitabine in AML. This study looked at patients with AML treated at MD Anderson, 118 given decitabine. This is the 10-day regimen, which tends to have more cytopenia, so it's more aggressive. They had a significant remission rate. Then in the 97 out of 118 patients achieved at least a morphologic leukemia-free state or CR/CRi. They looked at MRD.

As you could see here, their CR rate was 60%, consistent largely with the published literature for this agent. About half of patients were MRD negative. You look at the time to response, it was about 1.4 months. The time to MRD negativity was a little bit longer, so first CR, and then MRD negativity. About one-sixth of the patients had a stem-cell transplant, and about 40% relapsed with an overall survival of 14 months. The VIALE trial, it was 14 months, so not that different. If you look at the likelihood of achieving a CR or a CRi or MLFS versus MRD negativity, in newly diagnosed AML it was 82% and 54%.

You can go across and see in different subtypes, for example, in secondary AML, though the response rate remains relatively high, or in cytogenetics, the MRD rate starts to drop significantly, suggesting that even if you're getting a response, they're not often as deep as they are in de novo AML. This didn't dramatically break out into subgroups with one exception, and that is P53 mutant disease. Where you have a lower response rate, although it's real, but a very significant lower rate of MRD, suggesting you're generally not clearing the vast majority of these patients.

If you look, as you might expect, the patients who achieved MRD negative CR do best of everybody. People who have a good response do better than people that don't. It does mean that if you're monitoring someone on a VEN HMA regimen, that knowing whether you achieve MRD or not is a powerful predictor for their overall survival. It should be informative as to what you decide to do with that patient. Then, this is looking at stem cell transplant, which also the patients who got transplanted. These patients often in MRD negative remission do well.

I wouldn't take this message that stem-cell transplant is the answer for everybody, but the people who got a transplant who were in good enough clinical and leukemia condition and get a transplant do very well. When they looked at multi-variant analysis, the two predictors for adverse outcomes are the persistence of measurable residual disease or p53 mutant. You know those have independent value, but they also have a related value. Then on the other side, IDH mutations actually predict for the likelihood of response. That fits with an emerging data, and maybe Eytan will comment on this, that maybe the IDH2 patients do better than all of the other groups.

Again, the patients who achieved CR/CRi, even versus morphologic leukemia-free state do better. Then the last is a study actually from our institution, which included both Eytan and I as co-authors, but was really led by Max Stahl and Aaron Goldberg. Which was looking at VEN therapy in the relapsed/refractory setting, so the second-line therapy. This was looking at off-trial use of venetoclax in either hypomethylation or low-dose Ara-C in 86 patients with relapsed/refractory disease. What was basically shown was that the likelihood of a response, if you got either AZA/VEN or decitabine/VEN--AZA/VEN being more commonly used, there was about a 49% aggregate response for it against CR/CRh MLFS.

The message here is that it's significantly less efficacious than in the upfront setting, but it's not without therapeutic value. For decitabine/VEN, it was a little bit lower. We don't know if that's a difference in the two drugs or just small sampling error. Obviously, the low-dose Ara-C, which we don't use very often, had the lowest response rate. I think that fits with most of our perspective.

If we look at overall survival, the best survival was in the AZA/VEN group, with a 25-month survival. The decitabine/VEN, with again small numbers, 5.4 months. I do worry about making conclusions, but there's no doubt that there are some patients of reasonably long-term survival, even in the second-line setting. I'm now going to turn it to my colleagues and ask them to react to this data. The first question is, which patient should get VEN HMA therapy. How do they decide? You could see there's three things I put up there, which were age, fitness in quotes in molecular subgroups. Maybe starting with Eytan, where do you think VEN/AZA or VEN/HMA therapy fits in clinical practice right now?

Dr. Eytan Stein: Thanks, Ross. That was wonderful hearing all those slides. In clinical practice right now, certainly, HMA and venetoclax is used in patients who are perceived by the treating clinician as being unsuitable for induction type chemotherapy, with things like 7+3, which is what is most commonly used. In the FDA label for venetoclax and AZA, it's approved for patients 75 and older, or younger than 75 with certain comorbid medical conditions. In practice, I think we sometimes lower that age to really anyone who the clinician feels is not an appropriate candidate for induction chemotherapy. I think there's a second group that we use it for, that I've been using it for, and that's patients who are biologically unlikely to respond to induction type chemotherapies.

If I've got a 60-year-old with a complex karyotype and a P53 mutation, I have started giving them HMA venetoclax as their initial therapy instead of giving them 7+3 or other intensive regimens, really making the kinds of cross-trial comparisons we're not supposed to make, which is that with 7+3, the remission rates in that patient subgroup is 20% to 30% while with HMA VEN, the remission rate seem to be in the range of 50% to 60%.

Dr. Ross Levine: What do you think, Harry?

Dr. Harry Erba: No. I agree with all of Eytan's comments there. I think it's the availability of a regimen like HMA venetoclax has really made decision-making a lot more difficult in this patient population. We know that the FDA has approved this regimen based on the Phase IB study, and now the VIALE-A study for patients 75 years of age or older, or those with comorbidities that preclude intensive chemotherapy, the unfit. I like to think about those who are inappropriate for intensive chemotherapy, and actually, also think about the other side of that coin, those who are appropriate.

I agree with Eytan. I put into my decision-making a kind of a model in my head of things like performance status, comorbidities, functional status, cognitive status, goals of therapy, but also the molecular features, and that helps quite a bit. As an example, you will see the occasional 70-year-old patient who maybe has a history in the past of coronary artery disease, but a nucleophosmin mutation without a FLT3-ITD, and definitely, without any of those high-risk features like RUX1, ASXL1, TP53. I might be thinking about a curative therapy for them with intensive chemotherapy and even consolidation and taking them on to transplant or not depending on their level of response.

On the other hand, I agree with Eytan, you have the other side of the coin where you have a 60-year-old who's otherwise healthy, but with really bad disease. I don't listen to the statisticians. We have a study that shows 50% to 60% response rate in P53 mutated disease there. Then we have the liposomal daunorubicin cytarabine data showing in that subset of patients only about a third of them respond, and it was even lower with 7+3. It's gotten more complicated. We need to evaluate this regimen based on its activity and tolerability in that population and randomized trials. Those studies are being designed in the NCI NCTN cooperative group setting.

Dr. Ross Levine: Ironically, I think you guys picked the two easy groups. I think the complex karyotype with the caveat that there's no gold standard randomized trial, there's a lot of data that you have a higher response rate and lower toxicity, and you know that the chance of curative therapy with an intensive regimen of P53 complex karyotype is really low. The core binding factor and NPM1 without bad co-mutation group. We know they're chemo sensitive, and I think you're right, Harry, we push the age. Or maybe not push the age. I would argue, the ALLIANCE data, for example backs us up on that. The problem is in that middle group. How do you, for example, reconcile the IDH finding?

Because those patients also are chemo sensitive, and I think that's the group that we're struggling with now. Until we have randomized data, it's back to where you both started, which is, do what we call the door test, and really try to thoughtfully look at the patient and figure out what makes sense for them. We all know it's a judgment call. Because, I think that for many of those groups, the IDH patients, some of them can do very well with chemotherapy too.

It gets to be a hard thing, and then you're asking, is the only question response rate or is it curability? How do you go from one to the other, and we just don't have a lot of data for

VEN/AZA followed by stem cell transplant yet except for the data you just saw. I don't know what you both think. I think that's the tough one. The people in the middle that don't have really bad mutations but don't have the really chemo-sensitive disease.

Dr. Harry Erba: If you don't mind, let me illustrate that. Right now on my inpatient service, I'm taking care of two patients. One, a 74-year-old guy, long ago, history of CAD, but otherwise, well and golfing and doing everything he wants to, has an IDH mutation. I gave him AZA/venetoclax. I didn't have the other mutational data back and by day 21, has cleared his leukemia and his counts are recovering.

On the other hand, there's a 58-year-old guy admitted the same time with the same, in this sense, mutation and IDH and no other high-risk features or good risk features. He was younger and otherwise fit. I gave him 7+3, and now his counts recovered, but so he's suffering from invasive fungal sinusitis and Aspergillus pneumonia, despite putting him on prophylactic antibiotics. I looked back at that decision, I was like, "Wow, was that really the right thing to do?" Unfortunately, there's no data to guide us as you said.

Dr. Ross Levine: Then, just to move on to some of these other questions, because, the other is, how do we use MRD testing in VEN/HMA? Are you using it routinely? Why are we using it? Are we using it because we're just curious, because we like to watch the pot boil, or does it actually guide us in how long do we use these drugs or whether to transplant and when to transplant? I don't know, maybe first Eytan. Love to get both of your thoughts on this. Because I don't think it's straightforward.

Dr. Eytan Stein: Yes. I think it's really not straightforward. I think the argument to use MRD testing in a patient who you think or you're going to take an allogeneic bone marrow transplant, I get that in that you get the MRD testing, I'm not sure what to do with that because hitting people with more AZA/VEN isn't necessarily going to make them MRD negative, and I'm probably going to transplant them anyway.

At the end of the day, I think it ends up providing information that may be prognostic, but not doing anything different in terms of therapeutic interventions when I see this MRD data. By the way, we get MRD flow on everybody at every minute of the day. Most of it is probably not necessarily clinically useful.

Dr. Harry Erba: Yes, if you're looking at the patients treated with HMA VEN in the labeled population, I'm looking for quality of life. That, for me means count recovery and tolerating the therapy that then I'm giving them. Yes, you could get this information, you make people feel better when it's negative, can make them feel worse when it's still positive. Outside of moving ahead to transplant where, again, I agree with Eytan, what do you do there? If they're MRD negative, do you just keep going or do you say, "Hey, this is a great transplant candidate with a reduced intensity preoperative regimen."

If they're positive, you say, "Hey, they're not going to become negative. Let's move on." I'll tell you the one place where I find the mutational data once I have a patient on HMA VEN helpful, and that is, I've had occasional patients who have FLT3 mutation with, in a background of others, including IDH. I have used the triple combination, in fact, I have a patient with an IDH and a FLT3 mutation who I got into remission with AZA/VEN, but counts just never got better, and then just kept adding on things like ivosidenib for the IDH1, and then gilteritinib for the FLT3, and ended up getting him into an MRD negative remission with this four-drug combination, makes the myeloma doctors salivate when you say that, and he goes on to transplant. There's no data to really guide you on that individual patient decision.

Dr. Eytan Stein: By the way, and from just a very practical perspective, because I'm sure we have a lot of oncologists on this call, it's very difficult when you get MRD data to explain that to the patient. A patient will come into my clinic and I'll say, "Good news, you're in complete remission, but you have MRD." They're like, "But you just said I'm in complete remission. What does it mean that I have MRD?" That's a difficult discussion to have. Sometimes it can be more confusing than helpful, especially for the patient.

Dr. Ross Levine: Yes, I agree entirely. I think that it is useful to look at, especially as we start to treat the younger patients with VEN/AZA, so say adverse risk group to see who clears their disease or not. There's two reasons. One is that if you get, for example, a complex karyotype patient and they clear their disease and they're MRD negativity, you should move.

I think you have a window, and I think that window is pretty small. I think in the adverse risk, like the ones that Harry described and you, Eytan, you described or pushing the age younger. I actually think there there's a pretty strong rationale because, our transplant colleagues will tell us that they only want to transplant MRD negative patients. We all know that that means they're transplanting the best group, that is the group that does best, but there may be a window in some of these people.

The 25% that do achieve MRD, they're probably not going to stay there that long. I think you do want to act. I think that's one group that I think you want to actually measure a lot, because you're doing it with a transplant in mind. Then I think the other is, you start to think about a patient who's done really well and they're 8, 10, 9, 12 cycles of VEN/AZA, and with a caveat that we don't really know what to do after that.

If you go to one drug, there are people that think you should go to the AZA and other people think you should go to the HMA. There may be patients where they did achieve an MRD or not, where you could make the argument that you've either maximized your benefit or you give them a break. I'm not saying we know exactly what to do, but you have to start thinking about more than just their bone marrow morphology to make those decisions. The former is more

straightforward. The P53 mutant patient, find the window, the latter is back to the soft call. I don't know if either of you have anything you want to add to that.

Dr. Harry Erba: I'll add, I think in this situation where you're thinking about transplant, it's not just transplant yes or no. We all know with various donors and importantly, different preparative regimen. If you're talking about the patients I see every day in clinic, and these are the older patients, you're thinking about a reduced intensity preparative regimen, because they'll basically melt if you could give them a myeloablative transplant, right. Now we have Chris Hourigan's data published in *JCO* 2020 from the BMT CTN trial that showed, if using an error-corrected next-gen sequencing profile, if patients were MRD positive and got a reduced intensity transplant, you might as well not transplant them at all. On the other hand, the myeloablative preparative regimen seemed to overcome that. It may be very helpful to the transplanters making a decision about what kind of preparative regimen to give.

Dr. Ross Levine: Another question, the third one was, what about the data? Maybe we'll ask Harry first because it's the Sloan data that we showed, but it's not the only data. I as Eytan knows, I was a bit of a nihilist about the VEN/AZA use in the secondary setting. I saw a lot of it being done off trial without any publication. I kept saying, that's not where we have literature. Right. But there's now enough data. I guess the question is, do we think there's a role for these VEN/HMA combos in the second-line setting, and what data are we ever going to get that will guide us?

Dr. Harry Erba: Well, good luck with that because we have no understanding or agreement from Phase III studies that have been done over 20 to 30 years of what is the optimal salvage regimen with chemotherapy. I do think it makes it an interesting question now of comparing intensive to a less intensive approach with a venetoclax-based regimen. We could talk about the number of studies that were presented at ASH and previously of adding venetoclax to intensive regimens, including CPX-351 and the FLAG-IDA regimen and 7+3.

It may be just having venetoclax in your chemotherapy regimen may be helpful. I will say to you though, I have used HMA/venetoclax in the relapsed/refractory setting. I know the literature is all over the board, 20% to 40% response rates, but then you look at MD Anderson data with 10 days of decitabine where they report a 60% response rate. It comes down to a little bit about, a lot about, patient selection and who we're really talking about, but there's clearly some benefit there.

Dr. Ross Levine: I think it does suggest that there's activity, and one of the challenges, of course, is that most of those people would be chemotherapy relapses and understanding what the previous therapy is and if they got HMA versus not, and obviously, VEN/AZA failures, which we know are a hot mess, to put it mildly, because they tend to be very active in times of the essence. Maybe let's get to that last question that Harry already started, which is, what emerging VEN combo data are you most excited about? I didn't show slides.

I'll go first. I actually thought the FLT3 VEN data, the Gilt/VEN data to me was really quite impressive. The Gilt data is and we'll get to it, is interesting, but the Gilt/VEN, thinking about using it, it gets back to Harry's point. It just makes other drugs better. That's the one that intrigued me the most, but of a lot of intriguing combinations. Eytan, what VEN combos are you excited about?

Dr. Eytan Stein: I think my worry with all of these VEN combos is that you're going to get a lot of myelosuppression that when you end up doing a larger study, will end up hurting patients with prolonged time to count recovery. I agree that the VEN/Gilt data is really impressive. A lot of those patients though had morphologic leukemia free states, and probably never had count recovery, and probably the way to go is, we need to think about how to modulate the dosing and how to build in dose holds, because I don't think we totally know how to do that.
I'm certainly excited about it. I think you're right. That VEN seems to make everything better. Given that the AZA/VEN IDH inhibitor combos are very interesting. Also, the problem there is that is AZA/VEN works so well in IDH mutant disease to prove that adding an IDH inhibitor is actually going to be any better, is very difficult to do.

Dr. Harry Erba: I completely agree with every one of those comments. It's really important when docs are thinking about throwing these drugs together because they have the mutational data. If you look at what our colleague, Naval Daver presented for the multi-center trial, it was an 80% overall response rate in these FLT3 mutated patients with the labeled doses of Gilt and the label dose of venetoclax 120 and 400 a day, respectively.

Here's the thing, just to Eytan's point, half of those responses, 40% were MLFS, no count recovery, and the others were CRs. But, that does suggest if you're trying to get one of these patients to a transplant, that might be great. If you're talking about your 80-year-old grandmother who you want her not to be in your infusion area getting transfusions or in your ED with febrile neutropenia, maybe not so great. When you start to use these drugs together and you see the cytopenias, what do you go down on? Do you go down on the duration of the VEN, on the dose of the gilteritinib? There's really no good guidance there.

Dr. Ross Levine: I completely agree. I could talk about this all night, but we're going to talk about some other topics. The others are going to be a little shorter because I think that in the community that we all live in of leukemia therapy, the VEN/AZA is the big one. Let's talk a little bit about maintenance therapy briefly. I think we are beginning to see some intriguing data with the oral hypomethylating agents. I thought it was worth a brief discussion to remind you all that we now have a randomized trial.

This was Andrew Wei's presentation of data that he and Farhad Ravandi, Gail Roboz and many others have led the QUAZAR trial. This was the trial of oral azacitidine versus placebo as a maintenance therapy. To remind you that patients got into CR, and they got variable amounts

of consolidation therapy and then got either oral AZA or placebo. The message is that there was an overall survival benefit.

It was seen probably most dramatically in the patients who didn't get consolidation, but it was seen across. It really is intriguing and, again, this data has begun to be spun in a lot of different ways. People have looked at it with conversion to MRD negativity. It just suggests that having an oral HMA does have the ability to reduce burden and potentially delay or prevent relapse. We can talk about that in the disease. So, I simply put, I think this is one where we still are trying to figure out in our heads what to make sense of it, but just to get your perspective, each of you on the oral HMA data, and whether you're using it or whether you're going to be using it soon, how do you think it's going to emerge in our practice? Like how is it going to impact your practice today or maybe in a year? I don't know, maybe starting with Harry and then Eytan.

Dr. Harry Erba: Okay. September 1st, 2020, now we finally have maintenance, oral maintenance. There've been other studies with the hypomethylating agents with a little bit of a glimmer that there might be something. There are German studies showing a lower relapse free survival with one year of therapy, but it's important to understand what the QUAZAR study was. These were patients, 55 years of age or older who were not candidates for transplant.

They did not go on to transplant, and if you look at the real benefit of oral AZA, it did not cure anyone who wasn't already cured by their induction consolidation. It delays relapse, and you could see that in the relapsed-free survival curves and these curves come together at about 20%. Really what you're talking about is, looking at the older patients who've gone through intensive chemotherapy and now they're in a remission and you want to try to maintain that remission as long as possible, which means, you want to maintain their quality of life in that remission for as long as possible.

What do we have? We have this drug. Okay, that's great, but 50% of patients get nausea, vomiting, constipation that has to be managed, and 50% of the patients develop Grade 3 neutropenia, 14% had febrile neutropenia leading to admission. These are patients who thought they were done with treatment. Who are going to be these people that I would treat?

Well, it will be really older patients that I've given intensive chemotherapy to. Okay. Well, based on my comments before, I'm really only going to give an older patient intensive chemotherapy if I think they have a chance of being cured with chemotherapy, core-binding factor leukemia's, rare, not included in the QUAZAR study, by the way, or a nucleophosmin mutation without other high-risk features or biallelic CEBP alpha mutation.

Then, I'll treat those patients because I'm not sure that I've cured them, and then I'll put them on this drug. Then the question comes up, am I really going to continue it indefinitely? My answer to that is, no. If that patient is still in remission three to five years later, they've likely already been cured, and so now I know that and I can offer stopping the drug. Then finally, the

biggest issue is what we just said about HMA/VEN, we're not using intensive chemotherapy as much in older patients. It's going to be a very small population of patients. All I could say is, it's added to my time in clinic, having this discussion with my patients.

Dr. Ross Levine: Eytan?

Dr. Eytan Stein: To really just to add onto what Harry's saying. I think really you got to the point of, this is a trial that was designed many, many, many years ago that had a very long time where it was accruing, and it was at a time where we didn't necessarily have donors for all of the patients we wanted to transplant. I mean, at Memorial Sloan Kettering, they now tell me our transplant service that we don't have an upper age limit for patients who we transplant. There's no age cutoff anymore.

Because of that and because of the fact that we now do haploidentical transplants, really anyone who I'm giving intensive chemotherapy to, whether they have intermediate disease or unfavorable risk disease, my intention is going to be to transplant them. If I'm not transplanting them, it's because something went dramatically wrong, except for those patients, obviously, with core-binding factor or nucleophosmin mutations, like you said.

I can just tell you, in my practice, since this drug was approved, I've prescribed it for one person who I felt was suitable for it. That person, unfortunately, actually relapsed after a month on the drug, having nothing to do with the drug, obviously, but it is a tough sell. I think it's a tough sell for people.

Dr. Harry Erba: To me, the two interesting scenarios will be in patients that are peri transplant, will we begin to use it after you've finished more intensive therapy if you have a delay to the transplant and, will there be a way to keep leukemia at bay where maybe you don't want to give an intensive regimen, like just to keep your window? I know that's not what this trial designed, but I think that's a group where I think we often wring our hands. Then I think the transplanters who are all about HMA as even prerenal as relapse prevention, I think we'll see a lot of data with the oral agents post-transplant remission. Again, I'm not saying that this trial would guide either of those, but I wonder if those scenarios may flash out ASH '21 and '22, I don't know what you both think.

Dr. Eytan Stein: I love that first idea, I haven't run into that patient yet, but definitely you have some patients who are so beaten up and they need to regain their performance status or look for a donor whatever it is. I think that makes sense, and along those lines looking at Gail Roboz's data that she presented, 40%, I think it was like 39% of patients who are MRD positive by flow became MRD negative. You may even be able to get a deeper response. Just parenthetically, I would say, isn't it interesting with placebo, 20% became MRD negative.

Dr. Ross Levine: That's right. It's one of the fascinating things in that data, that's right.

Dr. Eytan Stein: I think that's a great idea.

Dr. Ross Levine: Let's move on, we all have two more topics to cover. This is, I think a quick one, which is FLT3 inhibitor therapy. I thought it would be good to take a look at the data from this year. This was data from good friends and colleagues of all of us, Jessica Altman, Sasha Perl, Naval Daver, and a great fellow, Yazan Numan who's at Northwestern.

They basically looked at an interesting question, which I think wasn't addressed in trials, which is, if a patient got a FLT3 targeted therapy earlier in their disease, for example, midostaurin as part of upfront therapy and now they relapse, what's the use of a second round of FLT3 inhibition? It's sort of an interesting question, and so, to remind you all that the RATIFY trial was the trial that led to the approval of midostaurin for the upfront use in FLT3 mutant AML.

A heroic trial that was done over a real long time by a lot of investigators, and I'm sure Harry has some good stories to tell about how really the brute force it took to ultimately get that trial done in lots of places. Then the ADMIRAL trial was the gilteritinib experience, but the question is the ADMIRAL trial didn't include people who got midostaurin as part of their initial therapy.

This group looked at folks that got FLT3 inhibitors after a previous FLT3 inhibitor therapy. As you can see here, these are relapsed/refractory patients, they're mostly ICD. Most of them got midostaurin, but there is some sorafenib and others because there have been clinical trials that all of our centers have run with chemo. About a third of them had gotten a transplant before the Gilt, but most didn't.

If you look at ultimately how they got the FLT3 inhibitor therapy, most of them got it in single-agent, but some people tried combinations without the caveats, I know those are approved, and the average duration was 5.7 months. The median response rate was 51%, and I think this is instructive, because it does suggest although not maybe durable activity, but gilteritinib doesn't have durable activity even when it's given to patients who've never seen a FLT3 inhibitor. This has durable activity that's not dramatically different than the ADMIRAL trial. Of course, they've looked at mechanisms of resistance that the patients who had existing MAP kinase mutation, which we know is a bypass mechanism, that those patients relapsed. Just a few questions about this, the first is that, in the FLT3 therapy, do we believe that the gold standard remains what it's been? Which is midostaurin upfront and Gilt as our relapsed/refractory. Any comments, either of you on that?

Dr. Harry Erba: I can comment, I would say that I think the standard of care is currently just that. It's midostaurin in combination with chemotherapy, and then at the time of relapse in the FLT3 positive patients, it's gilteritinib. I think we're all awaiting the results of studies with second-generation FLT3 inhibitors that are combined with chemotherapy upfront.

There is a crenolanib with chemo study that's randomized against midostaurin with chemo, there is gilteritinib with chemo study that's randomized. There is a crizotinib that's randomized against just chemo called the QuANTUM-First. I think that's what we're waiting for, and the question is, does a more targeted, more potent FLT3 inhibitor than midostaurin lead to better outcomes than a multikinase inhibitor like midostaurin?

Dr. Ross Levine: I agree, we have to wait for those studies. Keith Pratz presented the final data from the Phase Ib study of gilteritinib with chemotherapy inductions and consolidations, and there are all sorts of cohorts. If you put it all together at the end of the day, there was a 70% response rate. I'm sorry, 80% response rate. It was equally divided, again, between CRs and CRis, and they define CRis as potentially neither the platelets nor the ANC recovering. I think I wouldn't use this outside of a clinical trial until we actually know how best to use that combination, and if it's actually better than what we already know improves survival.

I think the point about gilteritinib is, yes, it is now a standard of care. We need to do better. The median survival was improved. At one year, twice as many patients were still alive, but by two years, those survival curves come together, which is not unexpected given that a FLT3 mutation is typically a late event in leukemogenesis, and it's really just causing the proliferation. You knock off that clone, but you get resistance through other FLT3 mutations if you're using a type 2 inhibitor, or the RAS/MAP kinase pathway.

We have to see if we could do better in terms of responses, depth of response, and most importantly, duration of response with what we know how to do, combinations, and we get back to Ross's comment about Gilt with a BCL2 inhibitor. That may be something to look at more closely in this relapsed/refractory setting.

Dr. Ross Levine: I think this data clearly shows that patients who got midostaurin can respond to Gilt. I think, the two questions I thought would be good, we covered the emerging combinations, I guess. We can talk about IDH, FLT3, which just like Eytan, I've been excited about for a while. I thought maybe there are two. One is like, in the relapsed/refractory setting for our FLT3 mutant patient, do you think there are other considerations that you'd go for? Or, if you have an ITD patient, is Gilt your standard first choice in the relapsed/refractory setting versus an IDH inhibitor versus VEN/AZA? Eytan?

Dr. Eytan Stein: That's a tough question. Certainly, you know, in a FLT3 IDH patient who's relapsed, the ADMIRAL study would suggest you should give them gilteritinib. I think the real question here is, there are some patients who are younger who could get more chemotherapy. What happens if you were going to combine in the relapsed and refractory setting a chemotherapeutic agent or chemotherapeutic agents with gilteritinib? I think that's the question that's being answered with crenolanib.

I believe they have a study in the relapsed setting combining crenolanib with chemotherapy. Whether if a patient has both a FLT3 and an IDH mutation, we've been very interested and we finally have a trial that's going to be opening very, very soon combining FLT3 inhibitors with IDH inhibitors, a long-suffering trial that's finally opening. The question is going to be, well, maybe in that setting, we know that HMA/VEN, as we've talked about, has some efficacy, so should we be doing the triplet? Things have become more complicated, but it's certainly given us more work for us to do. We're not going to run out of work before we retire. That's for sure.

Dr. Ross Levine: Maybe one last question before we talk about CPX for a few minutes, for Harry, what was your reaction to the last thing, which is the negative data on the Gilt/HMA combination? I don't know. I was surprised.

Dr. Harry Erba: The negative data?

Dr. Ross Levine: Yes.

Dr. Harry Erba: You're talking about the LACEWING? That study, Eunice Wang, a great colleague of ours, and she is really a proponent of that study. In that study, it has safety run in of 15 patients, with AZA/Gilt, the Gilt was at 120, the AZA was the typical seven days. There were only 15 patients. The CR rate was 30%/35%, was five patients and CRi was another five patients. Overall, a 67% response rate, a median survival in that group of about eight months. That was supposed to then go on to a randomized Phase III study of Gilt alone versus AZA/Gilt versus AZA alone.

They've dropped the Gilt arm, not quite clear why the Gilt alone was dropped. I can't imagine it did a lot worse than AZA/Gilt. They kept the AZA open. Of course, the biggest criticism of that is what we've been talking about. You can get response rates of about 70% with AZA VEN there. What Eunice pointed out at ASH is, if you look at the hazard ratio for survival in that subset of patients with FLT3 mutations in the HMA/VEN studies or the VIALE-A study, it favored AZA/VEN, but it was not statistically significant. Those investigators are moving forward, but I agree with you. That did not seem to be the way to go forward, but AZA/VEN/Gilt, like I said, I've used it off trial and I've seen success. One thing that I do when I'm combining these regiments is, I like the idea of starting with one and then adding drugs, because then I can get an idea of what's the toxicity and the benefit.

Dr. Ross Levine: I know we're have a couple of minutes for Q&A. I'm going to quickly go through CPX and just make two quick points, and then I want to ask questions. The first was a really nice study from our colleagues at Jefferson, Margaret Kasner and her group, where they looked at outpatient use of CPX. I just want to make the point that the patients did well with very little mortality, and had a very high response rate. Suggesting that you can give liposomal daunorubicin, and we can talk about the COVID implications pretty safely.

Then the other is the data from our colleagues in Canada looking at high-risk disease. These are secondary P53 mutant patients. I just want to get to the punchline, which is this. Which is, what they showed was that really the only people that have long-term benefit from CPX are when it's consolidated by a transplant.
Again, we've only got a couple of minutes, but get your perspective on those things, which is, when and how do you use CPX? What's your thoughts on outpatient use? Do you use it a lot in the transplant eligible population? Maybe get each of your reactions to that quickly.

Dr. Harry Erba: If Eytan's thinking, I'll jump on that. Yes, it's a long discussion. It's typically a patient who's had MDS. You've known him for a while, they've progressed into AML. You've talked about curative options and it's basically transplant. They've already had HMA. You're not excited about HMA VEN. There's a patient I'm going to give CPX-351, try to get them in remission, get them to transplant. Completely agree with your point, Ross, about the benefit of transplant here. That's where I really think we see the benefit of CPX-351.

In fact, Jeff Lancet had gave the five-year update of that Phase III study. The survival in patients who got transplanted was quite impressive, but if you look at the sensor marks, most of the patients in the entire study who were out there at five years were the same patients who were transplanted basically. You really need the transplant if you're going to go with that. In terms of outpatient administration, there's no reason why you can't give it as consolidation as an outpatient when the patient has good counts.

For the patient who's newly diagnosed, it's the same criteria used for HMA/VEN, they have to be reliable, have a caregiver, live close to us, not be at risk of tumor lysis syndrome, so their white counts are not high, and, of course, not already have a complication of their AML like febrile neutropenia or infection.

Dr. Ross Levine: Eytan, you want to add anything to that?

Dr. Eytan Stein: No, not really. I would agree with everything that's being said. We've started routinely giving this to patients who meet the criteria that Harry laid out in the outpatient setting for induction. There's a way in which patients actually probably do better when they're not in the hospital, when they're not getting woken up every four hours for vital signs and getting stuck at 4:00 in the morning and getting a good night sleep. I agree with everything Harry's said.

Dr. Ross Levine: In the COVID world, we actually see how much of we want to move our therapy to the outpatient setting as well. Obviously, we've all gotten much better with testing in our hospitals. I think we learned a lot out of expediency about how to keep our patients well and safe outside the hospital pretty quickly. We certainly did in New York, especially, don't you think, Eytan?

Dr. Eytan Stein: Absolutely.

Dr. Ross Levine: That pivot I think actually has changed our practice in New York. What I think in New York, unlike other areas, commutes to bridges and things, it can be hard even for a reliable patient to be close enough if they get really ill. I think we've got a little more comfortable with our ability to manage our patients and to monitor them, and to use some further away sites to keep tabs on people in between therapy.

I have some take-home points. I know that there may be some additional questions. Maybe we'll start with the second and third bullets. I think we've covered the first one really well, like how these data impact practice is what we went over again.

What do you think are the trials you're waiting for, Eytan? What are the one or two results you think that the field needs that are actually going to deliver? Maybe thinking about ASH 2021.

Dr. Eytan Stein: Well, let me tell you about two things. The target that I'm very excited about is menin. There's a lot of excellent preclinical data on the use of menin inhibitors when it comes to, as you know Ross and you know Harry, in patients with MLL rearranged and NPM1 mutant disease, we saw a sliver of data from Kura Oncology at ASH 2020, and certainly, we're hoping to see more data from other compounds in 2021.

The other thing I'm really excited about is, I actually think that there're going to be more and more studies looking at using HMA/VEN in intermediate- and high-risk patients that are younger than 75 in real studies. I'm going to go out on a limb and predict that five to seven years from now, our induction regimen for acute myeloid leukemia with intermediate- and high-risk disease is going to be HMA/VEN, and it's not going to be 7+3 or 7+3-like regimens. That's what I'm excited to see.

Dr. Harry Erba: I agree, Eytan. That may be true and the cooperative group system through MyeloMATCH is actually designing those exact studies looking at MRD negative remissions as the primary endpoint comparing intensive and less intensive regimens in younger patients. I'll take the other low-hanging fruit then since he talked about menin inhibitors, I'm going to mention, obviously, CD47 as a target. Throughout oncology, we don't have time to talk about it now, but some very exciting data with various CD47 targeting agents in combination with hypomethylating agents. That's exciting, and I would not give up on eprenetapopt or APR-246. This is a really cool drug. It's a pro-drug, gets infused, and what it does is, it gets metabolized to something that refolds mutant P53 into an active confirmation. In combination with HMA in P53 mutated MDS and AML, there's been some really remarkable data that's been presented. Many may have seen the top-line results of APR-246 with AZA versus AZA alone in high-risk MDS. It failed to meet its primary endpoint, which was a pretty high bar with a small study of trying to improve CR rates by 50%. Came close. Didn't quite make it, but this is not the end of that drug.