FAQs From the 65th American Society of Hematology Annual Meeting and Exposition

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Transcript

Mary DeRome: Welcome and thank you for joining us for today's session, frequently Asked Questions From the American Society of Hematology Annual Meeting and Exposition. I'm Mary DeRome, senior director of medical communications and education at the Multiple Myeloma Research Foundation.

Today, I'm joined by Dr. Ajai Chari from the University of California, San Francisco. Later, we will also have Dr. Paul Richardson from the Dana-Farber Cancer Institute in Boston, Massachusetts. We've invited these faculty to be here today to answer some of the frequently asked questions we've received from patients and caregivers about the data presented at this year's ASH meeting. Let's get started.

We saw numerous studies that described the use of biomarkers and other indicators as predictors of treatment outcomes or adverse events for newer therapies like CAR T and bispecifics.

Dr. Chari, can you help us understand the implications of these studies: what were they trying to determine, and what did they show?

Dr. Ajai Chari: Thank you, Mary.

To set the stage, many in the audience will be familiar with bispecifics and CAR Ts, which are paradigm shifting. We're taking patients' T cells—and we thought that these T cells really wouldn't even work in patients with advanced myeloma who've had many therapies—and we're now getting response rates of 60% to 100%; 60% to 100% is the new 20% to 30%. With the biomarkers, we're trying to understand, how do we do better and who's not fully responding. The other thing we have to keep in mind is that though responses are important, even more important than response is that you're maintaining that response, what we call progression-free survival (PFS) and overall survival (OS).

What we're trying to unpack is that we have these great new tools, but how do we figure out who's going to respond or not? At a high level, the limitations of these new studies is that most of them have been approved on the basis of single-arm studies.

We have a couple of randomized studies for CAR T. The reason I bring that up is that when you do a single-arm study, anything that happens on that study, good or bad—it's hard to delineate whether that's due to patient factors, like did you put really sick patients on the study? Is it due to disease; is it really bad myeloma? Or is due to the treatment? One of the ways we can start unpacking that is to look at these biomarkers, which are basically various tests that are surrogates. Like if you have a certain laboratory test, does that predict better or worse outcomes?

One theme we're seeing across many of these abstracts is inflammation. Inflammation is evidenced by certain blood tests—ferritin can be very high, C-reactive protein can be high, fibrinogen can be low. when we have these inflammatory markers, those have been shown in several studies that were presented at ASH to confirm worse outcomes.

Both in terms of potential risk of death but also remission duration. We need to understand. One of my majors in college was psychology. What I always remember from that was that correlation and causation are very different. If a laboratory is correlated with a particular outcome, okay, that's a particular association. But whether intervening makes a difference has yet to be seen.

When we talk about these observations, we need to make sure that patients don't take away the message that because this is high, we need to do something about it. Because that is a next level of evidence. The current level of evidence suggests that patients with high markers can have less-durable remissions and potentially inferior outcomes, and potentially also more blood count problems.

Particularly, we see with CAR Ts that it can take up to 6 months to recover your counts. One of the features may be these high inflammatory states also starting with low blood counts. One thing that is not coming up consistently is the expression of the target. One of the unanswered questions right now is, you have three major targets that are being explored with T-cell redirection therapy, which is the broad rubric of either bispecific or CAR T. The three targets are BCMA, GPRC5D, and FCRH5. One of the questions that's being asked is, when patients get these therapies, and you're getting 60% to 100% response rates, why do patients eventually relapse? Because if these therapies are so good, what's the mechanism? That is another area of exploration. We talked about the inflammatory markers predicting outcomes on the current one, but then what leads to progression?

Some of that, again, you can break it down into patient, disease, and treatment. One of the things that one might infer is that, disease-wise, this is an arms race against myeloma. When you target a particular antigen or target or protein, does the myeloma lose that target as a mechanism of escaping? So, for example, if you're repeatedly targeting BCMA, does the myeloma say, fine, you think you're

going to come after me with BCMA, I'm just going to lose BCMA and escape your mechanism. That is probably more seen as a general rule with bispecifics than CAR Ts.

Bispecifics are repeatedly getting dosed, which puts a lot of pressure—what we call antigenic pressure. With CAR T, it's more of an expansion and disappearance. We're not seeing so much of loss. There were a couple of papers looking at the loss. But we have to understand that the target is a complicated structure.

You can have loss at the gene level, so the protein's not even being made. It can be after the protein's made that there could be mutations in the protein that can affect binding of the mechanism. Like if a bispecific is no longer binding to the myeloma because the protein has changed, that would be another. That's another theme that we're looking at.

I would say that the third part of this maybe relates to the patient. We talked about patient, disease, and treatment. The patient factor in particular that seems to be coming up across multiple abstracts is the immune health of the patient.

What we're talking about is how good are your snipers, your T cells that kill, but also how good are your cloaks. There are also T cells that block the immune system from killing. That balance of your sniper to cloak, if you will, is another theme that's coming up as a potential risk factor for outcomes. But—those are probably some high-level themes.

But how do we take that into the clinic, and do we change inflammatory markers—does that help? That's a major question. Can we do something about the immune microenvironment making the snipers more angry or getting rid of the cloak cells that protect the cancer? Those are going on. The thing that's probably the closest to prime time that we've seen in studies is that it does seem to make a difference about lowering the disease burden. If you go into CAR T with a bulky disease, that correlates with more inflammation, it can correlate with more of what's called cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), which are neurologic issues and even some of those delayed neurotoxicities.

That's one thing that we are really mindful of, particularly with CAR Ts, because you don't get a redo. Like you get that slot, you collect the T cells, you prime the patient, get everything teed up, and you can't take it back.

You have to really be thoughtful about when to do the CAR T. With the bispecifics, it may also matter, but the difference is that it's an off-the-shelf product and you don't have to give another dose. It's not like you're trapped into a corner like, okay, you've got to give it now or not. Those are some of the themes in the biomarkers.

Mary DeRome: This is the first time that I've seen in a meeting where they're looking at biomarkers around these immune targets, around CAR Ts and bispecifics. But that type of work has been ongoing with other drug classes for quite some time. The CoMMpass data that we've collected over the years for patients who have been taking some of these—the immunomodulatory drugs (IMiDs) or the proteasome inhibitors—and looking at all how patients have done based on their genomics, then trying to use genomics to predict which patients will respond best to these therapies and which patients will relapse quickly.

Dr. Ajai Chari: There was a really interesting paper that was published in *Nature Medicine* this year looking at what happens to patients after bispecific and CAR Ts, from Nizar Bahlis's lab in Canada.

They used the CoMMpass data set, because if you want to ask the question of how common might the loss of BCMA or GPRC5D be, you need a data set. They actually went back to CoMMpass and looked at BCMA and GPRCs on newly diagnosed patients and found that for BCMA, about 3% of patients have a loss of one copy. Keeping in mind that we have two copies of all the genes, about 3% of patients are missing one copy of BCMA and about 10% can be missing one copy of GPRC5D. Those patients may be more susceptible to the double loss after bispecific therapy. That's a good example of why we need to do these kinds of biomarker studies and collect that data and why CoMMpass is so helpful.

Mary DeRome: It's been used so extensively, throughout this ASH in particular.

I believe we had 34 abstracts that utilize CoMMpass data for many different things. It was involved in 12 oral presentations, and this is why we did this study. People need this data to be able to figure things out and really help patients. And it's working and it's being utilized exactly as it was intended.

Let's move on to minimal (measurable) residual disease (MRD). Several researchers are trying to expand the utility of MRD either by using peripheral blood instead of bone marrow biopsy, which would be great for patients if we could do that, or by pairing MRD with other sensitive techniques such as mass spectrometry.

Could you briefly review what MRD is and what data from the recent studies that we saw at ASH might mean for patients?

Dr. Ajai Chari: I would set up my response to this question as if our therapies are getting better and better, and we're getting 60% to 100% response rates, and the remissions are getting deeper and more durable. The techniques need to keep up, because it's not just enough anymore to get rid of your M spike or light chains; you need to get deeper measurements to understand the potency of these new therapeutics. There was an interesting abstract coming from the Spanish group that's done a lot of the work on MRD. They looked at this minimal amount of disease not in the marrow but in the blood.

If you ask patients whether they like getting bone marrow biopsies, no one's going to raise their hand. We need to move away from this technique. So they looked at it in three different ways from the blood. One is by flow cytometry, and it was a pretty sensitive technique; they claimed that it was 10^{-7}. That's one in ten million cells being able to pick up myeloma.

A second technique they looked at is with microscopic particles of DNA coming from the tumor. Then the third technique they used is immunofixation mass spectrometry, which is basically what you see on shows like CSI: somebody's been killed, they want to study the blood, and they use mass spec to figure out what the proteins are to identify potentially the poisonous compound. It's the same technique. Then we have these really fancy protein-detection techniques, and because myeloma is a plasma cell and it's a protein disorder, you can use these really sensitive techniques.

Their question was, how do these blood-based techniques fare compared to the bone marrow–based techniques? They didn't sample too many patients for DNA; they mainly did flow cytometry and immunofixation mass spec.

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What was interesting is that being negative by both those techniques correlated with the bone marrow being negative in 86% of patients. What that means is that you could potentially save 86% of patients from having a bone marrow biopsy.

There was another technique that looked at this mass spec. One of the challenges with mass spec is that it's so sensitive that you can also get other interesting findings. For example, this other technique from the other group from Chicago looked at mass spec, and they were interested in seeing how early you can see the mass spec becoming negative after transplant and whether it correlated with prognosis. One of the things they noticed is that if you're going to do it after transplant, you may need to wait up to 18 months. The reason is that the proteins that are made for myeloma, number one, can take a long time to clear. That's what we call a half-life issue. Even if you take a magic wand and got rid of all the myeloma, the protein that's made may take a long time to clear especially by these very sensitive techniques. If you use more rudimentary techniques, you may see it clear quickly. But the more sensitive you are, the longer it can take.

Then the other reason they reported that it could be happening is that when you have a transplant and your immune system is recovering, you may have favorable features. Your immune system may be recovering favorable clones that are actually not necessarily myeloma but they're antibody fragments coming from the immune recovery. That can be a good thing. Because of all of that noise, it can take up to 18 months to recover.

This is a really exciting field. What is the take-home message about MRD? The challenge with this test is how to use it correctly. No one will disagree in the myeloma field that it is correlating with prognosis, meaning that it's a prognostic test. The deeper the remission, the better we think these patients will do. MRD negative will do better than MRD positive.

The challenge is how do we make that usable at the bedside? To go from a prognostic test or predictive test? Again, does changing somebody from positive to negative—how much value does that add? And at what cost? Because if you're already doing very well, how much additional therapy do you need to throw in to get this person to convert to negative? Conversely, can you start backing off?

There are some limitations of MRD, which it is important to talk about and why we caution patients to not overinterpret these results. This is what the FDA and the health authorities are wondering about. In the clinical trial that we've done so far, you're not testing every patient. We're only testing people that we think are in complete remission. It inflates the sensitivity of the test, because who cares if you're MRD positive, if you're MRD negative in the marrow, if you have disease in the blood, the urine, on imaging. The second part is, is it sustained?

That's the hard part about doing bone marrow MRD; you're not doing it every week or every month. You're doing it every now and then. There can be sampling issues; if you get a pocket of myeloma, you'll hit it. On the other hand, if you just got blood because it was a more dilute specimen, you're going to get a false negative. Then, finally, it seems to matter what kind of patient and disease you have. If you have high-risk disease, the MRD negativity really needs to be sustained, and it may not be enough. We may need more tools. Likewise, extramedullary myeloma, which is outside of the bone marrow.

What I'm getting at is that there are some nuances to MRD that make it a challenging test. Part of the reason the marrow will be helpful in the future is not so much just for the myeloma but for the immune microenvironment. Because that's the test that you can't get from the blood. These new techniques will evolve to the point of getting it in the blood, but whether your immune microenvironment normalizes is something that only the bone marrow can tell us. That is in very early stages.

Mary DeRome: We'll move onto your next question, which is on new treatment combinations. There were some results presented from studies looking at daratumumab combinations in newly diagnosed patients, including the Intergroupe Francophone du Myélome (IFM) 2018-04 study and the PERSEUS study.

Could you review those for us?

Dr. Ajai Chari: The field has been evolving. Many people ask us about bispecifics and CAR Ts, which are currently approved for four or more lines of therapy and wonder why they can't move up to earlier in treatment. You need clinical trials, because it's one thing to show activity in the heavily treated population; it's another thing to show that it's superior to currently available therapies for patients who haven't been heavily treated.

With the CD38 monoclonal antibodies, daratumumab and isatuximab in particular, the question is, for transplant-ineligible patients, the MAIA data was great: Dara, Revlimid, and Dex in newly diagnosed myeloma patients shows really amazing results.

What's been unclear is, what about using these newer treatments in the transplant-eligible population? Because usually you're getting chemo, transplant, and then maintenance. Then what's the value of a monoclonal antibody like a CD38?

In the U.S., there are folks in two camps. There are the early adopters that have been using it, and many of us in the academic world have been using it on the basis of what's called a randomized phase 2 study known as GRIFFIN. That was a 100-patient study, and the primary goal was to show that it deepened the response, which was positive. But many people want to see more than that, they want phase 3 study results: larger numbers, a longer follow-up, and PFS. That's what PERSEUS gave us, so it's bortezomib, lenalidomide, and dexamethasone (VRd) versus VRd plus daratumumab (D-VRd)—triplet versus quadruplet. After transplants, patients got a couple of cycles of consolidation, and then maintenance.

The interesting part also is that the maintenance is nuanced. If you were assigned to get daratumumab, you got it in an initial therapy and induction, and then in consolidation and in maintenance for 2 years. But after 2 years, you could potentially stop if you were MRD negative. It's not that you get daratumumab forever.

Because it's a lot to ask of patients to be getting an injection for a long period. Many people are like, okay, I'm going to do my few cycles of initial therapy, I'm going to do the transplant, and taking a pill for maintenance is one thing. But then to be asking people to go in forever for an injection is a tougher sell.

Mary DeRome: It's a cost issue, as well. Some of the questions after PERSEUS was presented was about the cost of therapy. Because Darzalex is a fairly expensive therapy. If patients don't need it, should they be having it? It comes down to being able to use biomarkers to determine who needs to have the Darzalex and who doesn't.

Dr. Ajai Chari: Just to add that the addition of daratumumab in the study showed a 60% reduction in the likelihood to progression or death. That was the main

take-home message. How people interpret that in terms of how long to use daratumumab is the main question we need to get more information on. But that's why there was so much excitement.

Mary DeRome: Dr. Richardson, we're going to talk about smoldering multiple myeloma (SMM).

We saw some results from studies treating intermediate- and high-risk SMM. In an effort to determine whether there's a benefit to starting treatment for these patients, we also saw some data on the genomics of high-risk SMM.

Can you tell us what we learned about managing this precursor condition, and specifically Immuno-PRISM?

Dr. Paul Richardson: Omar Nadeem from our team presented the Immuno-PRISM data. What has struck us about teclistamab use in the SMM high-risk population was the remarkably low rates of toxicity, which was obviously critical to the success of the project. What we wanted to avoid at all costs was excessive toxicities and any infections and so forth that could be prohibitive. Instead, what we saw was a favorable picture of far fewer infections than we've seen in the relapse/refractory setting, which was encouraging.

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Above all, the remarkably high response rates and the MRD-negative rate—you couldn't do much better. The reality was that it proved feasible and, so far at least, relatively safe, which is essential. Now, it's still a relatively small number of patients. The next phase of the study now is the randomized portion where patients are assigned to lenalidomide-based therapy or to teclistamab. That will help us understand the value of teclistamab going forward. But I'm personally very excited by this.

There is another initiative from Irene Ghobrial and Omar Nadeem looking at CAR T therapy in this group of patients. I'm a little cautious about that, because though CAR T is phenomenally active, there are toxicities that can be unpredictable and, rare as they are, I'm cautious about that. But in terms of the teclistamab experience, I'm really excited. My group is, too, to see the progress that's being made.

Mary DeRome: It'll be interesting as they begin to move these immunotherapies into earlier lines. The FDA had some comments about secondary malignancies that might be resulting from some of the CAR T therapies. We'll talk about that later.

Dr. Paul Richardson: It's wonderful to have Dr. Chari's perspective here, as someone who's really been in the trenches with CAR T, both at Mount Sinai and now at UCSF. My experience has been very favorable with regards to outcome in a select group of patients. But unfortunately, my experience with CAR T, I have

lost a couple of patients to treatment-related toxicity, including most importantly late Parkinson's in one patient, which has left me a little bit sobered.

She was in complete remission, MRD negative, and had done well actually through the procedure itself, but then very sadly developed the late Parkinson's, which was not treatable and not reversable and she passed. We have to be careful.

Mary DeRome: Let's talk about some of the autologous stem cell transplant data that was discussed at ASH. There were a couple of presentations on transplants; one looking at factors behind patients who might refuse to have a transplant, another looking at global differences in age distribution of patients receiving transplants and how this affects outcomes after transplant.

Dr. Richardson, what were some of the take-homes from those presentations?

Dr. Paul Richardson: Transplant remains a standard of care for transplant-eligible patients in the global sense, especially in health care jurisdictions that don't necessarily have access to the novel therapies that we're lucky enough to have available in the U.S.

It's a mainstay of therapy, particularly in Europe and elsewhere.

The field is evolving. There was a presentation at last year's ASH, an oral presentation by Christian Straka, that caught my attention. It's going to be published in a manuscript, hopefully fairly soon. This was a German trial looking at elderly patients receiving a lenalidomide-based induction regimen and then early transplant versus delayed. I was expecting to see a PFS benefit to the trial, but there was none—not only no PFS difference but no OS one that would be expected.

The absence of a PFS benefit was interesting. The important point was that this was tailored to an elderly population. It was a randomized trial, well conducted. It was the German group who are rigorous and tend to do a very good job.

I'm thinking about this and saying to myself, well look, what should we learn from DETERMINATION? Clearly, PFS wins, hands down. But survival, especially if you have access to novel therapies in relapse, remains equivalent, recognizing we've got follow-up. A 10-year follow-up may be a little more definitive.

I look at the success of CAR T therapy and I look at the success of bispecifics and, in particular, bispecifics supported by immunomodulatory drugs. There was a wonderful presentation from Jeff Matous on talquetamab followed by pomalidomide, for example. The results were outstanding. I'm left with this feeling that perhaps we should be thinking very carefully about high-dose melphalan, given its excellent value, but at the same time looking to the future. That's where I'm looking at this more broadly.

Because cellular therapies really did impress me, and T-cell redirection was particularly impressive, especially the work that Dr. Chari and I saw together on Monday afternoon.

Dr. Ajai Chari: I just wanted to add quickly that I completely agree with Dr. Richardson. But the variables we have to consider are efficacy, safety, convenience, cost, and patient-reported outcomes. Those are the five determinants of whether something's going to be used or not. It's essential that we have randomized studies to move the field forward. I don't think anybody's wedded to transplant, but we need to displace it in a thoughtful fashion, because if the access is limited, especially globally, transplants are very cost effective and have long-term follow-up data. As Dr. Richardson's already alluded to with CAR Ts, we are not fully aware of the long-term data yet in terms of the toxicities and Parkinson's.

We really need to let the data guide us and not have these emotional attachments. I'm happy to displace either one, but I would just want to see which one is better. Because there's so much emotion wrapped up with these topics. Some people are really pro-CAR T and anti-transplant or vice versa. We should let the data guide us in a thoughtful manner, moving forward.

Dr. Paul Richardson: I so agree, Dr. Chari, it's very true. But I also think we have to be very aware now that we're in a lucky space with myeloma where we can think strategically—that our patients are living 10, 15, 20 years. We have to be very thoughtful about what that means. Certainly, one aspect of high-dose melphalan that we have to be thoughtful about is the long-term consequences from the standpoint of myelodysplasia. And, obviously, the rare but real incidence of acute myeloid leukemia. It's important to bear that in mind.

I was impressed at last year's ASH, Dr. Chari, with your group and the 70-patient real-world experience for cilta-cel and ide-cel. In that group you had a number of patients who had myelodysplastic syndrome, didn't you? They had received a lot of prior chemotherapy, as well as transplant. I think it requires us to be thoughtful; my bias in this is to be tailored to the patient. Because I agree with you, Dr. Chari: the patient-reported outcome is everything. The quality of life, the toxicity considerations, all of these things matter.

But at the end of the day, I'm also persuaded by the fact that melphalan provides an ability to target stemless. You need to do, especially in high-risk disease that's resistant to quadruplet therapies. If you don't get where you need to go with your quad, and you have higher-risk features, I fully agree, Dr. Chari, that the data would suggest that that's a person in whom intensification with high-dose melphalan should be offered.

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Mary DeRome: There were several presentations on new and emerging agents being examined for their effectiveness in treating myeloma. For example, there was a phase 1B2 study for sonrotoclax, a new BCL2 inhibitor that is more potent than venetoclax, and HPN217, a trispecific T-cell engager.

Dr. Richardson, what can you tell patients about these newest agents?

Dr. Paul Richardson: I'll take the BCL2 and perhaps Dr. Chari can opine on the trispecific. The BCL2 inhibitor was fantastic, I really liked the data that was presented by Dr. Hang Quach. She's based out of Melbourne in Australia, and she's terrific. It was really compelling. I firmly believe in the value of targeting BCL2 in t11;14 translocation.

The story of venetoclax is a cautionary tale in some ways but also frustrating in another, because clearly we all feel that venetoclax works, and it provides real benefit to our patients. Unfortunately, given the challenges with the BELLINI study, the first phase 3 in that setting, followed by the unfortunate failure of the CANOVA study.

We're in a situation where we know it works but we haven't proven it. It makes the likelihood of venetoclax being approved by FDA extremely low, frankly. I do understand why.

The flip of that, though, is these next-generation drugs. This is one, and actually there is a second one coming from AbbVie, which is now under study. The important point is that these two next-generation inhibitors will be more active and safer—and what Hang presented was extremely active.

I'm very excited. It was a great step forward, and just an oral therapy, which has real-world promise.

Mary DeRome: Dr. Chari, what about the trispecific?

Dr. Ajai Chari: It's a really exciting time in myeloma, because we used to have so few drugs. But now with the BCMA-targeting therapies, not only do we have two already approved, teclistamab and elranatamab, but there are also multiple other ones in development, including linvoseltamab. There's also an AbbVie compound, and there's also this one called Harpoon-B17, which was presented. This is a different molecule that's actually a very small protein. it's so small that, to make it stay in the system longer, they have to add a third component, which is albumin. It's just called a half-life extender.

But it's such a small molecule, and it's targeting BCMA like everything else. If you look at the whole space, there are six different products—it feels like the statins of myeloma. Like how many do you need? But the good thing about this is that it will hopefully drive down the cost and make access better. Because, again, globally we need these products to go to all patients and not in restricted safe

areas. I would say, efficacy-wise, it's striking how concordant they are. Their responses are 60% to 70% across the board.

The PFS is interesting. Teclistamab is the first one out and has a PFS around 11 months. What was interesting at this year's ASH, elranatamab was updated and has a PFS of 17 months. So, quite compelling. But we want to avoid direct cross-study comparisons. There may be some slight difference there, but there are always differences in the patient populations and the lines of therapy and all of that.

What I mean by that specifically is that, with this class of products—and this was true of the Harpoon as well—we do see infections with this class. Because when you target BCMA, yes, you get the myeloma down, but you also get unusual infections, including severe infections.

Teclistamab was the first on the market, and there is a rate of infection with the most recent data cut of 55% with about a 2-year follow-up. Because of that, we've learned that you need to monitor for infections, hold the therapy if there's a severe infection, and give intravenous immunoglobulin as a preventative.

Those interventions may be leading to better outcomes with the newer therapies, because it's not like we're treating these people in absentia. We're learning from each product, and so the safety signal maybe looks a little bit better. Whether that's due to the product or our experience is the unanswered question. But convenience is another difference across the products, some are IV, some are subcutaneous, some are monthly, some are weekly, some have a step-up dose, some don't, so that's another differentiating factor. Then the last one I would say is that the cytokine release with this Harpoon compound was quite low; it was only about 25%. Most of the other compounds are 60%, 70%, and so how the dust settles will be interesting. But it's good to have choices in the shorter term.

Dr. Paul Richardson: I would agree. I just wanted to add a couple of comments.

Correct me if I'm wrong, Dr. Chari, but the infection signal was quite favorable, correct? People have gotten smarter at handling all the infections. But I got the impression that the Harpoon platform and the rates of infection were perhaps lower than we've seen with other studies. Do you think that's just time frame and not being necessarily enrolling during the pandemic and that kind of thing?

Dr. Ajai Chari: Absolutely that's part of it. But I'll say the big thing I always look at if you're going to make cross-study comparisons: a follow-up duration is essential. Because the infections keep adding up. if you've only had an early data cut, you really can't say too much.

Dr. Paul Richardson: Yeah.

Dr. Ajai Chari: Between the learning, because these newer compounds have less follow-up, that's probably major differentiating.

Dr. Paul Richardson: Excellent point.

Mary DeRome: Our last topic is the next generation of IMiDs, the CELMoDS. Some presentations provided insights into their mechanism of action and looked at their effectiveness as maintenance and also preliminary efficacy from a study that you authored, Dr. Richardson, using mezigdomide, daratumumab, and dexamethasone in relapsed/refractory patients.

What did we learn about this class of compounds?

Dr. Paul Richardson: Most importantly, it's great to have oral options for patients. We've already touched on the BCL2 inhibitor earlier, and the value of having oral options improves patient convenience above all.

Then access, because essentially you've got a truly outpatient therapy. We had the really nice work down led by Sagar Lonial with iberdomide, and we followed that with a mezigdomide story. They moved in parallel, but there were slightly different populations. Dr. Lonial showed with iberdomide that we were getting around a 26% to 30% response rate in triple-class refractory BCMA-exposed patients. With mezigdomide, it was slightly more heavily pretreated patients, and our response rates were more robust. This reflects the differences between them.

I would caution against thinking of them as glorified IMiDs. They are not; they are true CELMoDS. What that means is that they're in the degrader class. That's actually quite distinct; they're what's called molecular glues. But the immunomodulatory class in terms of their molecular size are substantially smaller, and their engagement of the cereblon E3 ligase complex reflects that.

Let me give you an example. If you close the cereblon E3 ligase complex, it turns on the degradation rapidly of Ikaros and Aiolos, which are key transcription factors that not only control central pathobiology in myeloma but also activate the immune system when you degrade them. This is an incredibly important switchboard. What happens is, with pomalidomide, there's about a 20% closure of the cereblon E3 ligase complex. In contrast, with iberdomide, it's around 50%, and, remarkably, with mezigdomide, it's 100%.

The degrading that mezigdomide drives is much, much, much, much more rapid, aggressive, and effective, as reflected in preclinical models. What's been gratifying is to take this to the clinic and see it actually translate for patients to their benefit. What we've been struck by is that iberdomide is very well tolerated.

We have great data from Niels van de Donk looking at iberdomide as a new strategy post-transplant; it's well tolerated and driving up response rates and quality of responses, dramatically more than we've seen historically in different settings with lenalidomide.

Again, to Dr. Chari's points, we've got to be careful about cross-trial comparisons. Nonetheless, the complete response rate improvement that we saw with iberdomide is remarkable.

Another interesting point about iberdomide is that it may not be associated with second cancer risk, as lenalidomide or pomalidomide is—pomalidomide perhaps less so.

But lenalidomide interacts with what's called a *P53* mutation in a way that can be quite challenging. For that reason, iberdomide may be a new step up with less second cancer risk and more efficacy. Mezigdomide goes even further; it has the same properties in terms of second cancer risk hopefully being less.

But above all, it's exquisitely active. In our study, we looked at daratumumab combined with mezigdomide and mezigdomide combined with elotuzumab. When we combined mezigdomide with daratumumab, we looked at various doses and schedules and we compared 0.3 to 0.6 milligrams of mezigdomide and, at the same time, did the same with elotuzumab. The elotuzumab cohort of patients were all daratumumab refractory, essentially, so heavily pre-treated daratumumab refractory. In that group, we saw excellent tolerability and about a 45% response rate, which was pretty respectable and encouraging but still relatively modest.

What really struck us is with the daratumumab cohort. Now, they could be daratumumab exposed, but their patients in that study could not be daratumumab refractory. They weren't truly triple-class refractory; they were at least double-refractory. Still, an aggressive patient population and meeting the three prior lines.

With that in mind, we saw response rate approaching 90% in one cohort, around 84% in another, and around 65% in the third, recognizing that that third cohort was early. The overall response rate was 78% across the group as a whole. But I was particularly struck by the 89%.

What really captured our imagination was the duration of responses. In the lead cohort, our lead patient saw 41, 42, and 43 months on therapy. Now, that's over three and a half years. Basically, our lower boundary of our duration of response (DOR) was 24 months. That means that this DOR is going to be long.

This is so exciting when you compare it with what we can generate from bispecifics and what we can generate from CAR Ts. What we can think about here is that mezigdomide may really enhance the activity of bispecifics and may be a fabulous option to enhance the activities say of a CAR T, particularly in higher-risk patients where the likelihood of relapse may be greater.

Really, mezigdomide is showing that it can partner with different doses and schedules. We were able to look at the pharmacodynamics and

pharmacokinetics in the study quite comprehensively. My colleague, Tracey Chow, was a lead author on this. She showed that you saw powerful effects on natural killer cells and T cells, which corresponded to the responses that we were seeing.

Mary DeRome: I have one final question for each of you.

[0:44:58]

Thinking about what you saw in ASH this year, what were you most excited to hear about? Is there anything that will impact the patients that you manage sooner rather than later?

Dr. Chari, I'll let you go first.

Dr. Ajai Chari: For SMM, I really like Immuno-PRISM, with the caveat that it's a small single-arm study, so we don't have a control arm. But the potency of efficacy was unprecedented: we're looking at 100% response, 100% MRD negative. Those numbers are great. This has always been my issue with treating SMM. Because we don't have perfect models for who's going to progress. I have issues with starting a whole bunch of people on therapy for a long period of time, and we don't even know if we're helping them. It's much more palatable to do a fixed duration of therapy.

Because that's what our colleagues in lymphoma are doing. There are some cancers where they're going for curative intent and they're treating for fixed duration. To be treating everybody with everything forever it's just not a winning strategy. I would say that was super exciting.

The CD38s in the front line, to see the PFS data. was exciting.

Then to see the biomarkers and the real-world data. What's also striking is these T-cell redirections that we talked about today. The clinical trials are really cherry-picking patients. Because you have to have perfect disease and no health problems.

And that's why the real-world data set is so important, too, as a companion. We're seeing really good results, but we're actually treating even sicker patients, obviously, in the real world. There was one study that showed that 80% of the patients who got teclistamab were actually not eligible for the study as it was originally designed.

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That just shows why we need these deliverability real-world studies to partner with the clinical trials. A lot of exciting data. Hopefully, we can piece this together. The hottest unanswered question is about sequencing. How do you go from A to B to C? We're starting to see some signals on that.

Mary DeRome: Dr. Richardson?

Dr. Paul Richardson: I 100% agree with everything Dr. Chari said. Those were highlights for me, too. In addition to what Dr. Chari mentioned, there are a couple of things to add. Pivoting back to the CELMoDS, with the promise that these are well-tolerated oral agents, I see the promise of bispecifics really being enhanced by the integration of oral therapies. That's to Dr. Chari's point about fixed duration of therapy; you minimize toxicities of a bispecific and then an oral therapy that can maintain remission for a long period of time.

Just acknowledging my colleague, Tracy Chow, in our work: what she showed was this incredible effect on T cells and natural killer cells from these oral agents. As we think about myeloma being truly an immunological disease controlled by inflammation and all sorts of complex interactions, we've now got a toolbox that directly addresses that. That's incredibly powerful.

As we tailor therapies, we need to be very aware of how complex the pathobiology of myeloma can be and how individual it can be. In that spirit, there was a presentation by my colleague Jeff Zonder on our patients in the DETERMINATION trial who were African American.

It really caught my attention, because it's an area that we've been trying to understand. We were looking at Duffy-null to better understand what Duffy-null means. Duffy-null, you can be Duffy-positive or Duffy-null if you have West African heritage. Believe it or not, Duffy-null occurs in up to 60 to 70% of people of West African heritage.

It's specifically West African. It doesn't just control leukopenia; it does a lot more in the context of cytokine homeostasis and inflammation. As we think about treatment, I'm just using this as an example, we can think carefully about tailoring our choices now for our patients as we recognize the complexity of pathobiology of each individual patient.

For me, it was a great ASH. There was the Duffy-null story on the one hand, which is a small piece, the incredible breakthroughs that Dr. Chari spoke to, and then, finally, I just wanted to share one thing that was the talk of the meeting amongst the investigators.

That is that belantamab mafodotin obviously released its results of DREAMM-7 as a press release showing that, truly, belantamab mafodotin does have even survival benefits in a large randomized phase 3 trial. We're eagerly awaiting that data.

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But it really was great to see a drug that I've always believed in actually reestablishing itself. That's another message that this it is never a zero-sum game. We need all the drugs we can possibly have for our patients, because it's

such a complex disease. it was great to see belantamab really stepping back into the therapeutic armamentarium.

Mary DeRome: Belantamab was approved for a period of time and then it was taken off the market. Do you anticipate it coming back on the market?

Dr. Paul Richardson: Yes, I do, based on the results of DREAMM-7 and the fact that it conferred survival benefit against a very strong comparator. This wasn't a weak comparator, this was dara-VD versus belantamab-VD. To see a survival benefit, particularly for older patients, one could envisage a patient receiving daratumumab, lenalidomide, and dexamethasone as part of the MAIA regimen up front, enjoying, God willing, years of disease control before relapsing.

A perfect choice for frailer patients in whom bispecifics or CAR T may not be appropriate could be belantamab-VD. If that can engender years of disease control, you can see that sequencing and choices really matter. We need to think creatively about that, because being held to the standards of CAR T and bispecifics is a tough one, actually, because it's so good.

But the point is, for many of patients, that's not the best choice practically, socially in every respect. Having the ability to really pick and choose is so, so good for us to help our patients the best.

Mary DeRome: Patient quality of life is really coming to the fore, because there are so many different therapies that patients can take. Patients and doctors want to make sure that the next line of therapy is going to be agreeable to the patient based on his or her particular qualities—what's going on in their life, the things they like to do, the things they want to do—versus limitations that will be put on their activity based on whatever therapy they're going on.

So, okay, on behalf of the MMRF I'd like to thank Dr. Chari and Dr. Richardson for joining me today.