Managing Myeloma

ASH 2020 Meeting Highlights in Multiple Myeloma

Joshua Richter, MD
Assistant Professor of Medicine
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
Director of Myeloma
Blavatnik Family Center at Chelsea Mount Sinai
New York, New York

Adam D. Cohen, MD
Director of Myeloma Immunotherapy
Associate Professor of Medicine
Abramson Cancer Center of the
University of Pennsylvania
Philadelphia, Pennsylvania

Nina Shah, MD
Associate Professor
Hematology-Oncology
University of California San Francisco
San Francisco, California

Dr. Joshua Richter: I am Dr. Joshua Richter. I'm joined today by my amazing colleagues, Dr. Nina Shah and Dr. Adam Cohen. Today, we're going to talk about some of the latest updates from the recent American Society of Hematology meeting discussing some of the unmet needs in the land of multiple myeloma, both in the newly diagnosed and the relapsed and refractory setting. For today's activity, we're going to go through some of the lead abstracts that were discussed. Many of them were discussed by some of the colleagues and participants on today's webcast.

At the end of the discussion, we're going to open up to questions and answers. I'd really like to welcome everyone and kick off this session today for newly diagnosed myeloma and hand it over to Dr. Nina Shah, to take us through some of the data from the IFM 2009 trial.

Dr. **Nina Shah:** Great. Thanks so much, Josh, for having me. Thank you also, Adam, for joining us today. I wanted to talk a little bit about the abstract you see here from IFM 2009 trial. This is actually one of my favorite abstracts. Autologous stem cell transplant in newly diagnosed myeloma, the long-term follow-up analysis of the IFM 2009 trial.

You can see that patients with newly diagnosed multiple myeloma were originally randomized to either get early versus late transplant. Early transplant means that they are in arm B and so they get their three cycles of RVd and then they go on to stem cell collection, transplants, and then get to consolidation cycles. If not, if they go to late transplant, then they just get RVd, they do get the collection, but then go on to five cycles of consolidation, and then maintenance. This is early versus late, not yes versus no.

The primary endpoint was progression-free survival. You can clearly see, and this was presented before, that the patients who got transplant early did have an improvement in progression-free survival over those that got transplanted late. Now, remember, most or at least half of the people who were in the transplant later arm actually ultimately went on to transplant. Again, this is early versus late not transplant yes versus no.

You can see additional data. This is the PFS-2. What this means is what happened after the first progression, so starting from transplant, and then following through the first progression, what happened to the second progression. You can see that there are actually no differences between the two populations. This is not surprising given the overall survival data.

You can see that although the transplant or the early transplant arm had an improvement in progression-free survival, they actually did not have an improvement in overall survival. What does this mean? This means, like we always say before, this can actually improve the time that the patient will stay in remission getting the early transplant, but it won't improve the time that the patient is alive overall, again, maybe because a lot of these people ended up getting a transplant.

One of the interesting things that you can see here is the MRD analysis. I want to point out that this MRD analysis was done after the patients had had transplant and consolidation or just their consolidation, and before going to maintenance. You can see, as we know, that the MRD negative is definitely better than being MRD positive. That's true, whatever group you're randomized to, but it seems like getting to MRD negativity is probably more likely if you get early transplant as you can see in the PFS curves here.

What the conclusions were from this is that high-dose melphalan transplant did reduce the risk of progression or death by 30% compared to later transplant. Actually, very nicely with a lot of follow-up time, 60% of the patients are alive. I agree that frontline transplant is still our choice for newly diagnosed myeloma, not necessarily waiting to the second time, but it also does cause us to think about what we'll do maybe with things going on like COVID, et cetera, although I think we've figured that out a little bit better now. It is important to know that patients achieved MRD negativity more so with transplants. We don't know yet because this is an older trial really in comparison to what we have, how this is going to fare in the setting of novel agents as well as quadruplets.

What are some implications? I said it before, and I think this is really important that this is a study of upfront versus delayed transplant, so it's not transplant versus no transplant. I think the FORTE trial is a better example of transplant versus no transplant, and we can know the upfront transplant is better than delayed if you look at PFS. I still try to take my patients to transplant in first consolidation. My rationale for this is that the patient is the youngest the day that you meet him or her. That day is the day they're ever going to be the youngest that they are. It's almost easier to take patients when they're less heavily pretreated, less beaten up to the transplant. You're more likely to

get the full dose of melphalan 200 in them at that time. There's no data on high-risk patients. There's probably a reason for that. There are fewer in the study, and it wasn't stratified necessarily with that data presented to us, so we don't know about high-risk patients and what the role is in transplants. That's always a big question. It's unclear if the change in induction regimens that many of us have applied, some people are using KRd**,** some people are using daratumumab-VRd, as we'll see later, would change these results.

Dr. Joshua Richter: While on this subject, I think this is really amazing data. I think it stratifies some of the data we already knew before. Nina, I'm going to have to ask you the hard question. I apologize for it ahead of time. This really looked at MRD rates as part of the whole picture. Knowing that you take patients to autograft and first relapse, I do the same. Does MRD affect your desire? If someone is MRD positive at the end of induction, do you really, really need it? Do you not need it if they're MRD negative?

Dr. Nina Shah: This crowd did not answer that. I still take them to transplant, even if they're MRD negative. I am a true tried and true transplanter.

Dr. Joshua Richter: Absolutely. I actually share the same policy. Adam, just to throw it to you. I think one of the things that Nina brought up is that they didn't really in this trial, address high risk versus standard risk. We have some of this information from the FORTE trial, albeit a little bit different. There's some information from the endurance trial that VRD and KRD, at least in standard-risk non-transplant eligible, may be somewhat equivalent. Does this data impact how you're inducing people now?

Dr. **Adam Cohen:** I don't think this data does per se because it doesn't really answer that question. For me, I actually agree with both of you in terms of the role of transplant. I'm still a believer in transplant, and we do try to do it upfront as well. Even if patients are MRD negative after induction, I think that the data supports more durable remissions with an upfront transplant. In every trial, including this one, there's always 20% to 25% of patients who never get to the transplant. Something happens before, and they're never able to get the benefit of it. That's why I think it's reasonable to prefer to go up front as long as they want to.

Dr. Joshua Richter: I think one of the things that this trial really enforces is the role of a referral to a transplant center regardless of your initial instinct of transplant or not. Whether or not you're in the San Francisco area, want to see Dr. Shah, you're in the Philadelphia area and you want to see Dr. Cohen, or you happen to be in New York and want to see me, I do think there is a continued roll to send essentially everyone for transplantation evaluation.

Let's move on to the second abstract, which is the in-class transition from parental bortezomib to oral ixazomib, basically, this is called the MM-6 trial, also called Switch.

Really, what this trial is looking at is that many people in the early setting of their myeloma treatment receive VRd or something akin to VRd, but ultimately, patients do not continue on the proteasome inhibitor long term. They either go on to transplant and then lenalidomide maintenance, or for the older patients, they tend to transition from something like VRd to either lenalidomide alone, or lenalidomide plus dexamethasone. We do know that long-term therapy with proteasome inhibition does improve outcomes. We know this from a variety of prior studies.

What this really sought to do was take patients who would otherwise switch over to something like lenalidomide/Dex after bortezomib-based induction and continuing them on the oral proteasome inhibitor, ixazomib. Patients were allowed to go on study if they received greater than or equal to stable disease after three cycles of a bortezomib-based induction regimen, something like RVd or CyBorD, and then the patients transition to continued proteasome inhibition with IRd, ixazomib, lenalidomide and dexamethasone.

Patients were at an average of 73 years old. A lot of this came from some of our VA hospitals. These were patients who had some comorbidities. One of the things that I thought was really applicable about this study data is that these are patients very akin to the patients we see day-to-day in our clinics. These are patients who had cardiac issues, neuropathy, metabolic disorders, renal disease, and essentially were able to achieve a lot by transitioning from something like lenalidomide/Dex to IRd.

The benefit here is not just increased overall response rates, but the depth of each response level was significantly enhanced, going from about 6.9% to 28.7% CR rate. That's a humongous improvement. We really recognize that especially early on in your journey, the deeper remission you achieve does correlate to more durable remissions. It's not so much that more people are responding, which is true, but those MRs are becoming PRs, the PRs are becoming VGPRs, and the VGPR are becoming CRs. Again, the progression for your survival rate, the data is still relatively early, and luckily, most patients are doing well in either arm.

Ultimately, patients are continuing to deepen their responses. Now, always what we want to know is, are we sacrificing toxicity at the benefit of efficacy? It's really not what we saw with the transition. Although we did see notable class-related toxicities, the majority of which were Grade 1 and Grade 2, very few Grade 3 and Grade 4 toxicities. As we can see here in this plot, most of the Grade 3 toxicities were in the single-digit range for things like diarrhea, peripheral neuropathy, asthenia, and edema.

Overall, this is a really heterogeneous and "real-world" US myeloma population. These weren't the healthiest of the healthy. These are patients with comorbidities, who are older. What this really shows is that one of the options that we currently take with older patients is to give them induction with VRD, or a similar regimen, and then abandon the triplet for long-term doublet therapy to avoid the need for parenteral treatment. We do recognize that for some of the patients, we unfortunately sacrifice the benefits they

receive from prolonged proteasome inhibition. What this early data shows is that we can deepen overall response rates and depth of response by continuing patients on an all-oral regimen that includes the oral proteasome inhibitor, ixazomib.

Throwing it out to you guys. I'll go over to Adam first. Are there patients right now that are older that you give VRD, switch over to lenalidomide, that you wish you could give them long-term proteasome inhibition, but the need to give them either bortezomib or carfilzomib becomes an issue?

Dr. Adam Cohen: Yes, absolutely. I think there are certainly patients where travel back and forth to the center can be a problem. That's one part of it. Patients who maybe have a partial response, but you really want to deepen that response, so you want to continue a triplet therapy. Or people with high-risk disease, who you think would benefit from the dual PI IMiD maintenance. Any of those patients, that would be appropriate for this type of approach.

Dr. Joshua Richter: Nina, with your use of ixazomib, any tips or tricks about how to get around any potential AEs, or any experience that you'd like to share?

Dr. Nina Shah: Yes. I think it's important to remember that with ixazomib, there can be some peripheral neuropathy, there can be some nausea, there can be some low counts. It's pretty well tolerated. You can modify the doses. Actually, some of my patients like to take it at nighttime on that Monday that they take it. It's definitely tolerable. It does cause a little bit of fatigue too. I think it's something that, like Adam said, the patients that I think this really could benefit would be the people who maybe don't go to transplant, but need longer-term PI maintenance because of high-risk disease, but would not want to be getting bortezomib long term. I think that would be a good match for this type of population. I'm glad that they did this study, because it's not the most exciting study we could ever see, but it's actually very real-world applicable, which actually ends up being very exciting.

Dr. Joshua Richter: I couldn't agree more. We'd love to see all these great bi-specifics, tri-specifics and CARTs, but we all do have to get down to the nitty-gritty that the average patient is getting VRD and then going off on to some other therapy. I still find this interesting that even though the upfront IRd study did prove out to not fit statistical significance with a *P*-value of 0.07, especially with COVID rates varying in different parts of the country and the world, having an all-oral triplet PI IMiD steroid combo is rarely advantageous.

At this point, I'd actually like to switch gears over to the GRIFFIN study. I believe Nina, I think this is all you.

Dr. Nina Shah: This is one of my also favorite abstracts, although this has been presented and represented so many times. Each time, I like to get a little layer. This is

the GRIFFIN trial looking at daratumumab-RVd versus RVd in transplant-eligible patients. I think daratumumab needs no introduction; CD38 monoclonal antibody, which specifically targets myeloma cells, and it can act through ADCC, but also other immune mechanisms.

You can see the trial design. I think it's really important to remember, this is a randomized phase 2 trial. Patients who were transplant-eligible, newly diagnosed, were randomized to receive either daratumumab-RVd or RVd for four cycles. All patients went on to stem cell collection and transplant. Then there were two cycles of consolidation, and then maintenance therapy. If you were in the daratumumab arm, you stayed in the daratumumab arm throughout with induction, consolidation and maintenance. If not, you just got RVd, and then ultimately, lenalidomide maintenance alone. The primary endpoint here was achievement of stringent CR after consolidation. Very important. It's not PFS. This is not a randomized phase 3. It's a randomized phase 2, but sometimes we just like to get our answers as quickly as we can. What happened here?

You can see that, indeed, the trial did meet its primary endpoint. You can see that at every single point, that blue bar is higher on the left than it is on the right. That means that every single cut of data, which is either after induction or transplant, consolidation, maintenance, the patients who had quadruplet therapy did better as far as achieving a deeper response. Why do we care about this? Because we know that deeper responses are associated with improved PFS, and sometimes we're a little impatient and we don't want to wait for PFS.

You can see that there's also data on MRD negativity. Again, I want to point out this is at 10^{-5}, which is like the old school, it's almost like the iPhone 10 now that you want to have actually 10^{-6}. Be that as it may, at any single time or any single way you slice the data, take your CRs or your MRD negatives, or your less than CRs, or however you slice it, you can see consistently that the MRD negativity rate at any group of these patients at any time was consistently higher in the patients who had quadruplet therapy versus just RVd. Why is this important? Because we are very quickly beginning to adopt MRD as the other vital sign in myeloma and analysis. We know that MRD negativity usually predicts for better progression-free survival and potentially better overall survival based on retrospective data. It's important to keep this in mind and keep tracking this.

One thing I just want to point out for subgroup analyses - and of course, the analyses, everyone loves to hate - but one thing I want to point out is that they don't - and it's on the bottom right there, the high-risk disease actually was not favorable for either group. I say this because if we think about, where are we going to put this? Where are we going to put daratumumab-RVd and quadruplet therapy? We'll talk about this in the discussion, but I just want to point out that there's been some rumors about using this in high-risk, but I don't know if that's necessarily evidence-based. In most other subgroups, it did seem to favor the daratumumab-RVd group.

Of course, the money in all this is progression-free survival, and we don't have that data, actually, fortunately yet because all the patients are doing fairly well. As a median follow-up here of 27.4 months, you can see that there's no difference yet for progression-free survival of daratumumab-RVd versus RVd. The median hasn't been reached in either arm. I think that's actually very encouraging to know that we're doing well, no matter what we pick.

In conclusion, you can see that daratumumab-RVd then followed by daratumumab maintenance, actually improve the rate of response as far as stringent CR goes and depth of response, including MRD negativity. I want to point out that the safety profile actually was very well tolerated. We didn't talk about it, but there was no difference in stem cell collection success. There were some AEs, including some cytopenias in the daratumumab group that're generally well-manageable. The bigger issue here is that is this going to change our practice? We'll talk about this, because this is a randomized phase 2, with an endpoint of stringent CR not PFS. There are other trials going on, including the PERSEUS Trial, which is a phase 3 trial, which is going to examine this.

Just for a panel discussion, if I would say 40 is new 30, is four the new three? Do we want to give more drugs and more drugs better? We know that depth of response ultimately correlates with PFS, but are we willing to make the jump just yet? Maybe we should wait for the PERSEUS Trial. As I mentioned, no issue with stem cell collection, so that's reassuring. What is not reassuring is the cost, because this is a long time for daratumumab. The question is, could you get there with the triplet? Could you get there with KRd? That's a controversial question in itself. I still don't know who's right for this regimen. I think some people like to say high risk, but that's not necessarily supported by subgroup analysis. Remember, it's a lot of daratumumab. These people are on for induction, consolidation, maintenance, 32 months. It's a lot of daratumumab and you can't use daratumumab again.

With that, let's have a panel discussion about this.

Dr. Joshua Richter: I think this is, you look at this data at face value and how deep the responses are, how much, you can't argue with how great it is. The thing you brought up is I would say the million-dollar question, but with the cost of a quadruplet could be the billion-dollar question, who needs or who should get daratumumab-RVd? Nina, since this is yours, I have to ask, are you giving daratumumab-RVd? If so, who gets it?

Dr. Nina Shah: No, I'm not giving it yet. Sorry. I don't want to disappoint some people because we don't have PFS data yet. I just think that that's one thing. The other thing is that the bortezomib in this trial was given on 1, 4, 8, and 11, and that does cause neuropathy for some patients. You're going to take a trial, you got to do it the whole way. You can't just give daratumumab over four cycles upfront and then not do it on the consolidation and maintenance. That's how the trial was designed. They have to

stick to it. That's why I haven't quite adopted yet. I'm not ready to swallow the quadruple pill just yet.

Dr. Joshua Richter: Adam, how about you? Are you all in with four is the new three?

Dr. Adam Cohen: Yes, I actually share a lot of what Nina's saying. Her question is, I don't know who to give this to, I think is accurate. I'm not doing it for everyone. It hasn't become my standard.

I will say there are some patients though, who are just exploding with disease. They have really high tumor burden, they're hypercalcemic, they're really symptomatic. Those folks, I want a quick response and I am sometimes starting with all four in that group. I know that's not how the trial was designed. I'm also sometimes starting with VRd and then adding daratumumab in in patients who fail to get a good response within the first few cycles. That's the extrapolation to real-world practice. That's not really evidence-based as of yet. I think, though, if the PERSEUS Trial shows a really strong PFS advantage and not a significant increase in infections, which I think there is always some hint of that with all the daratumumab studies upfront, then we'll probably adopt it, but I'm waiting a little bit.

Dr. Joshua Richter: I, like you guys, am not all in with the quadruplets. The handful of people that I have is the people that show up to the hospital with horrible renal failure, big burden that I give daratumumab-CyBorD, get them out of the hospital. I feel like in for a penny, in for a pound, I switch them over to daratumumab-RVd. Adam, I'll just want to ask you your experience. I've actually had a little bit of trouble collecting stem cells from some of these people, not failures per se, but it took four or five days, not two to three days. I don't if you've had similar experience.

Dr. Adam Cohen: Actually, I meant to mention that as well. I've had the same experience. We've had a few patients where the collections have been slower, suboptimal, not as much yield. That was seen in the trials and probably can be overcome with plerixafor and other things, but that's another cost to potentially add in here. It's more time to collect.

Dr. Joshua Richter: Absolutely. I think a TBD, whether or not this is going to take over the world of induction therapy. The next venue we're going to go into is the relapsed/refractory setting. This is the really big meat of what was presented at ASH. A lot of great new drugs on the horizon. Some really great novels, CELMoDs, some bi-specific antibodies, some new novel alkylators, some really impressive data of the drugs that are going to be approved, somewhere between days and years from now. Kicking us off is going to be Dr. Shah, looking at some of the data coming out with iberdomide. Dr. Shah.

Dr. Nina Shah: Great. Really exciting to see this phase 1/2 trial of iberdomide plus daratumumab/dexamethasone or bortezomib/dexamethasone.

This is just part of the study design. Basically, this was looking at patients with relapsed/refractory, multiple myeloma. Depending on which arm you win, you had to have at least two lines or one line. The iberdomide, which is a new CELMoD, a newer cousin, younger cooler cousin of lenalidomide and pomalidomide was paired with either daratumumab or bortezomib for relapsed/refractory in multiple myeloma.

You can see here some of the baseline characteristics. I just want to point out on the bottom right that in the daratumumab group, there were people who actually had received daratumumab before. I think that's important because the responses that you see, we can maybe ascribe to iberdomide, maybe, because we know that daratumumab retreatment usually isn't that great. Just a note there that these patients were generally very heavily pretreated, especially in the daratumumab arm.

The safety, I think one of the things about lenalidomide safety that concerns me always is the diarrhea and the yuckiness. This seemed not to be as much of a problem here. Obviously, there's a little neuropathy with the bortezomib, but I thought that overall, this actually showed some pretty good safety profile. I will remind you that this is an oral drug. That adds to the oral group, oral class which is important now that we think about keeping patients away from the medical center.

What can we say about the efficacy? Actually, you can see here that in both groups--these are not comparative. Remember they're just different cohorts and they reported them out simultaneously. They had a pretty nice response rate considering the patient population has relapsed/refractory myeloma, particularly in the daratumumab arm. You can see some pretty nice responses despite the fact that the patients had, a lot of them, about half of them had had daratumumab before. The bortezomib patients were a little bit less heavily pretreated. What does this mean? It means that people can get a response with this new IMiD, the new CELMoD that allows us to have another tool in our myeloma bank here.

In this phase 1/2 trial, the iberdomide given in combination with daratumumab or bortezomib and dexamethasone was pretty well tolerated, favorable safety profile, something that you wouldn't necessarily not expect. The results also suggested that there's good antimyeloma activity of this agent when it's paired with another agent, whether it's bortezomib or with anti-CD38 and antibody. Of course, there's ongoing other enrollment, other cohorts looking at iberdomide 1.6 milligrams per day looking at their final recommended dose for combination therapy. Just again, pointing out this is an oral therapy. This trial actually supports further evaluation of iberdomide-based combinations in relapsed/refractory myeloma, and phase 3 trials are planned.

I think this trial gives some interesting things to talk about. This is a new image. Could this have an identity crisis? It's really hard to replace lenalidomide. I always call lenalidomide like the Coca-Cola of myeloma, it always wins. If you're going to replace lenalidomide, you better be willing to have a giant trial because it has cornered the market here.

Where could this go? I think maybe this could be something like post-CAR T maintenance, maybe for patients who have already had exposure to lenalidomide. I do want to point out, it's well tolerated. If someone was to show me a small trial where iberdomide beat lenalidomide in anything, or was the same, but was better tolerated, I would take that. We have patients on lenalidomide forever, and a lot of them don't really like it that very much. I think that's important to know that there was efficacy in the daratumumab refractory population, although the subgroup analysis wasn't really clear on that. It's just that we know that there were daratumumab refractory patients in the daratumumab group. Again, it's an oral drug, so it adds another tool that is user-friendly. Josh, what do you think?

Dr. Joshua Richter: Every time a new drug comes out, some of the things you brought up pop into my head. If I had all of my druthers, I could pick any drug I want. Where and when am I going to use it? If RVd is good, is IRd with iber-vel-dex even better, or daratumumab iber-dex in the upfront setting? I think this drug is extremely active as you pointed out. It's an oral therapy, which is great. I think you bring up a couple of really interesting potentials, which is, could it replace lenalidomide? We're going to need to see some data for that. Post-CAR T maintenance I think is just an amazing thing. To date, unfortunately, we're not curing the lion's share of patients with myeloma-based CARTs, is the answer to massively improve outcomes with something like this? What do you think may be the optimal combination? Is it with a bi-specific, tri-specific? Is there some magic sauce we need to mix with it?

Dr. Nina Shah: I think it'll be a good combination with any of these. I think we all know that myeloma combo therapy is usually better. Like I said before, if this is better tolerated than lenalidomide, I'd like to see it move up because quality of life is a huge, huge deal. For patients that can't tolerate lenalidomide, if this is better tolerated, I'd rather have them get something like this. I know that's a fantasy right now because that trial will be very difficult to design, but that would be my preference.

Dr. Joshua Richter: Adam, how about you? Where do you see this fitting in because we're probably not going to see an iberdomide versus pomalidomide, or iberdomide versus lenalidomide study in the near future. You have someone who's on lenalidomide maintenance, and progresses, and the FDA says you can give them daratumumab-pomalidomide or daratumumab-iberdomide. Do you have a thought of where you would go?

Dr. Adam Cohen: I don't think I know enough yet to make that call. Honestly, I have thought of this as more of a rescue drug after they're refractory to lenalidomide and pomalidomide. Pre-clinically, there's some data that it might overcome resistance to those agents. You can argue or ask, "Why do we need a third IMiD?" But actually, a lot of us end up going back to these drugs and new combinations down the road. If I had a new CELMoD or IMiD that actually has better activity after someone's progressed on pomalidomide and lenalidomide, I would use it in a heartbeat. To me, that's why I'm thinking of it. The others though , are the combination with the T-cell engaging therapies, either post-CAR or with bi-specifics. This would be perfect with a bi-specific in a patient that's already refractory to triple class or penta-drug refractory.

Dr. Joshua Richter: Absolutely. We're going to get the drug approved and then figure out the optimal way to use it. Even beyond this is the next CELMoD, so this is CC220. Where does 480 fit into this, the next CELMoD after that.? We all have our work cut out for us trying to figure out the optimal sequence.

Let's move on to the next one. The ANCHOR Study. ANCHOR looked at melphalan flufenamide also called melflufen, either in combination with daratumumab or bortezomib in relapsed and refractory myeloma. Melflufen is a peptide drug conjugate. Essentially think about it as fancy melphalan. Much in the same way that daunorubicin and cytarabine use the classic 7+3 in a novel way to get better drug delivery to tumor cells, melflufen gives better drug delivery of the melphalan to the target plasma cells. It's an intravenous drug given once a month.

Here we can see part of the schema, the combination of melflufen, along with bortezomib. Here, these are patients who had early- to mid-relapses, one to four prior lines of therapy, refractory to an IMiD and/or PI. Here, the melflufen was given once a month, along with bortezomib on days 1, 4, 8, and 11. Again, we're looking for primary response rates and comparing different doses of melflufen, either 30 milligrams or 40 milligrams, as a flat dose.

Keep in mind these are still small numbers. There's only approximately 13 patients treated here, but even in these small number of patients, we saw some very impressive response rates. With overall response rates at the 30-milligram dose of 50%, with an identical clinical benefit rate. We saw this leap up to 71% at the 40-milligram dose with the clinical benefit rate, the same as well. All in, the total overall response rate was 62% with a median treatment duration of 8.7 months. Several of the patients still remain on treatment at the time of this data cutoff.

The main toxicity of this drug is heme toxicity. It's basically as if you're giving 40 milligrams a month of melphalan, so it does drop your counts. There were notable rates of a thrombocytopenia, neutropenia and anemia with the drug, the majority of which is Grade 2/Grade 3, but however, there is some Grade 3/Grade 4. As with any therapy that really hits your blood counts pretty hard, there were some notable rates of

infectious complications. Again, much of this was not serious. However, there are a few cases of neutropenic fever with pneumonia and other infections.

As we look on to the combination of melflufen with daratumumab. Again, here we compare the same relapsed/refractory patients with one to four prior lines of therapy, refractory to an IMiD and/or PI, again, the two dosing schedules of either 30 milligrams or 40 milligrams of melflufen once a month, along with daratumumab. Again, the optimal strategy for this being that once you get far out enough on your daratumumab, you're basically getting a once-a-month parenteral therapy with both the melflufen and the daratumumab.

Here, again, small numbers, but greater numbers than the bortezomib cohort. Here we see, at the 30-milligram dose, an overall response rate and clinical benefit rate of 83% when combining melflufen and daratumumab. At the 40-milligram dose, we saw a slightly lower numbers at 70% and 74% for overall response and clinical benefit rate, respectively. Overall, we're hitting overall response rates in the mid-70 percentile overall.

Looking at the swimmer's plot, the median progression-free survival coming in at around 13 months, which is pretty impressive for this group. We can see here on the swimmer's plot that some of these patients had extremely durable responses on this combination, with a median duration of response of 12.6 months. The OS data are still immature at this time, at just over 18 months of median follow-up.

In terms of tolerability, the same issues that we saw in the bortezomib arm. The main AE profile of melflufen is hematologic toxicity notable for thrombocytopenia, neutropenia, and anemia. Again, no DLTs were observed at any of the doses. However, there were some patients who did experience serious adverse events with things like pneumonitis, influenza, upper respiratory tract infections, and UTIs.

Ultimately, though, no DLTs were seen across either regimen. Both combinations were well tolerated with overall response rates in the 70 to 80 percentile, 62% for the total of 13 patient cohort with bortezomib. Median progression-free survival around 13 months. The recommended phase 2 dose of melflufen with daratumumab was 30 milligrams. Ongoing studies looking at what the final RP2D will be with bortezomib.

Ultimately, I'm really interested to hear what you guys think about where a drug like melflufen will fit into our current strategy. Is this an early drug, later drug, mid drug? Adam, where do you see the drug fitting into our paradigm?

Dr. Adam Cohen: I'm a bit intrigued by this drug, because at first glance you could ask, why do we need another melphalan or another alkylating agent when we have so many other exciting new drugs with immune mechanisms, et cetera? I have to say, and you probably have the same, there's always these patients who are rapidly proliferating. We end up admitting them for VD-PACE. They have no other options. If we had a very

active drug like this, that could be given once a month, outpatient IV and get them out of trouble, then I think that could have some appeal and could find a niche in that late line therapy. I'm thinking more of this as a late line. I think the company is also developing a similar type drug for use with high-dose for high doses with transplant. That would be interesting as well. Those are my initial thoughts about where we might use it**.**

Dr. Joshua Richter: Nina, your thoughts on the drug?

Dr. Nina Shah: Yes, I agree with Adam. This is going to be late-line. The next frontier is the post-CAR T relapses and those people are really hard to rescue. Alkylating agents work. They work great. You can never have enough drugs for myeloma. It's an incurable disease. We have no plateau. I always say there's always going to be room for a good drug and this looks like it's active. I know it's hard for us to see things combined with daratumumab and bortezomib who's going to do that? The reality is once it shows activity, then we started thinking, "Okay, maybe we could do it later-line and reuse bortezomib." Maybe the person wasn't refractory to bortezomib at first and we could combine this. The more data we have on this and the more experience we get managing the toxicities, we're able to slot it in as it's more specific for a specific patient.

Dr. Joshua Richter: Totally agree with everything. One of the things that's changing is the patient's exposure to alkylators. As there's more and more data that PI IMiD steroid is superior to PI alkylator steroid, the CyBorD patients are getting fewer and fewer, with things like CAR Ts with some of the great work you're doing, Nina. It's not unimaginable that CAR Ts do replace a high-dose therapy for patients as a consolidative measure. There are a number of patients who are getting to second-, third-, fourth-line, and even beyond with all the drugs we have, still alkylator naive. You said it perfectly, there can never be too many drugs and alkylators work, so couldn't agree more with those sentiments.

Moving on. This is over to Adam. Tell us all about the ALGONQUIN trial.

Dr. Adam Cohen: This is an investigator-initiated study, actually, led by Suzanne Trudel and multi-center in Canada looking at, combining belantamab mafodotin, the anti-BCMA antibody drug conjugate, that was approved last year, in combination with pomalidomide and dexamethasone.

This was a study looking at two different doses of belantamab mafodotin, either 1.92 or the higher doses, 2.5 or 3.4. It was given as an IV, either once every four weeks in combination with standard pomalidomide-dexamethasone, or explored at a split dose day one and day eight, every four weeks, trying to see if that might be able to mitigate toxicity. You'll remember that the drug is currently approved as monotherapy given once every three weeks IV, with a response rate of around 30% to 35% in mostly triple-class refractory patients.

They show data on 37 patients and you can see the median prior lines of therapy was three. This is not as heavily pretreated as the DREAMM-2 study that got belantamab approved. These patients had to be pomalidomide naive to get on to this study. They were largely refractory to lenalidomide as well as a proteasome inhibitor. About 40% had been exposed and were refractory to daratumumab, and about a third were triple class refractory as shown at the bottom.

Now, in terms of toxicities, the main side effect that we come to expect with belantamab is corneal toxicity or keratopathy, these microcystic-like changes that are related to very small concentrations of the free MMAF toxin that affect the corneal epithelium. In this study, that was the number one toxicity as well; 76% of patients had it, a bit higher rate of Grade 3 or higher, 51%, with the combination with Pom-Dex compared with monotherapy, and a little bit higher rate at the 2.5 dose compared to the 1.92. Importantly, this is not a permanent visual loss. This tends to be mitigated, just withholding the drug, allowing the toxicity to resolve to Grade 1 or less, and then restarting at a lower dose. You can see on the right though that at the higher 2.5 dose, they were median of five dose holds per subject compared to only one dose hold per subject at 1.92, so making me think that the 2.5 dose maybe difficult in this combo. The other side effects were as expected. Some cytopenias and some fatigue, but for the most part, there was no unexpected or unusual toxicities with the combination, and only one patient actually discontinued due to visual acuity changes.

Impressively though, there was very good activity of this combination. The overall response rate, you can see here ranging anywhere from 80% to 100% depending on the population, a large proportion of those patients, two-thirds or more getting VGPRs or better. This, again, is greater than what we might expect with either Pom-Dex alone or with belantamab alone, suggesting some possible synergy here. Many of these were actually durable. The follow up was relatively short, only seven to eight months, but you can see median PFS not reached for all patients, at least at that level of follow up, and several patients look like they were out beyond 18 months or more.

This looks clearly like an active combination, and the conclusions of the investigators were that this could be combined with a high response rate and the lower dose in particular maybe was a little bit better tolerated with lower rates of keratopathy and visual acuity changes, but they continue to investigate alternative dosing schedules to see if we can make this even more tolerable for patients. I think it's early days, but stay tuned. I think this certainly looks promising so far.

Dr. Joshua Richter: Clearly a very active drug. We've seen the approval for single agents, looking to now some of the really interesting combinations. I guess the two big questions in the top of my mind are, what again is the optimal combination, and then what's the future of a drug like this when we have some bispecifics around the corner? What are we going to do about patient selection? Who gets an ADC, who gets a BiTE? Adam, any thoughts about either of those topics?

Dr. Adam Cohen: Yes, I think it's a great question. I do like the idea of combining these monoclonal antibodies and even ADCs with IMiDs. I like the idea of pomalidomide. I like the lenalidomide combination that's being explored as well and there's combinations with monoclonal antibodies, like even this plus daratumumab. Those are the ones that I guess I would think about upfront, and then in terms of where this drug is going to fit, that's really a moving target. I really think it's almost like a jigsaw puzzle for us to figure out how we're going to place all of these new BCMA directed therapies and how we're going to sequence them. I have a feeling we're going to be using multiple BCMA directed therapies in our patients, and if they progress on one, they'll eventually get another. I just don't know quite where we're going to go yet in terms of the order.

Dr. Joshua Richter: Nina, thoughts.

Dr. Nina Shah: I also am waiting for this to have its own identity rolled out. I think part of it is trying to optimize the dose and dosing schedule. As Adam well pointed out, the lower dose had lower rates of keratopathy, which is I think probably the limiting factor for giving this drug. If that can be more optimized and there were creative ways of doing this, whether you load or give one dose and split it out, and Adam knows a lot more about that. If we can just lower the rate of keratopathy and the intensity and improve the quality of life, this drug has a lot of likes because this it's outpatient friendly, off the shelf, you can combine it with a bunch of different agents. This is the ALGONQUIN but there's DREAMM 1 through 80 being done. There's just a lot of ways to do that. I think if we can optimize the toxicity management, and we've done this with other drugs, like bortezomib and it's just a new thing, if we can do that, this drug has a lot of potential to be very useful, especially in the community.

Dr. Joshua Richter: Excellent. In interest of time, just moving along to some of the early phase trials, moving into some of the non-BCMA targets. Adam, if you can get us started off with the cevostamab data.

Dr. Adam Cohen: Absolutely. This is the start of the bispecifics, which are the new kids on the block. There was really a lot of exciting data at ASH this year. Cevostamab is the bispecific antibody that targets FcRH5. FcRH5 is a cell surface receptor, it's expressed highly on myeloma cells. It's also on a normal plasma cells and B cells, although to a bit lowered extent, but not in any other cells in the body, so it makes it an attractive target. Cevostamab is a T-cell engaging bispecific, so one end of the antibody targets the myeloma cell, the other target CD3 cells, or T-cells in the marrow, activates those cells and allows them to kill. This was a phase 1 dose escalation study of this in heavily pre-treated patients.

This is the study design. This drug is given as an IV infusion once every three weeks. It actually has a very favorable pharmacokinetics with a long half-life. This, like many bispecifics requires a step-up dose, so there's a low dose given on the first day to try to

mitigate the risk of CRS and other toxicities and then a week later, the full dose is given. Patients are hospitalized for those first two doses, and then they get the rest of the dosing outpatient once every three weeks. First, there was an escalation of the step-up, and then that was fixed at 3.6 and escalations ongoing for the target dose from 20 up to 160 and higher.

Fifty-three patients have been treated at the time of this presentation. These were heavily pretreated median six prior lines of therapy, 72% triple class refractory, 45% penta-refractory, and 20% that had a prior BCMA therapy as well, so a tough to treat population.

In terms of toxicities, the main ones include cytopenias, which were Grade 3/4, and about 15% to 25% of patients typically in the setting of CRS and that later resolved. Cytokine release syndrome was seen in 76% of patients, almost all during the first cycle. You can see in all but one patient was Grade 1 or Grade 2, and so the step-up dosing effectively mitigated that high grade CRS.

Then really minimal other high grade toxicities as shown here. There were about 15% to 20% of patients who had some neurotoxicity that wasn't shown here, all Grade 1 or Grade 2, typically during the CRS and resolved within 24 hours, either alone or with a dose of dexamethasone, and no MTD has been reached as of yet.

In terms of efficacy, overall response rate in patients getting active doses 20 milligrams above was 53% in all comers, a little bit higher at the two highest dose levels, 90 and 132 milligrams. This included responses to penta-refractory or even prior BCMA treated patients. The follow up was relatively short for this study, but several of these responses have been durable going out beyond 16 months at this point, so we're just waiting for longer follow up.

To conclude, I think this really establishes FcRH5 as a novel target, and cevostamab seems to have activity here. The CRS continues to be an issue, but its primarily within the first cycle in Grade 1 and Grade 2, and we're getting better at managing this. We're waiting to see, I think, what the optimal recommended phase 2 dose is going to be. A lot of interesting new approaches to try to mitigate that CRS with double step up dosing and starting to think about combinations as well. It's very early, but so far, this looks pretty interesting.

Dr. Joshua Richter: Really exciting drug. More targets, more targets and more targets, always amazing. Adam, just one question, is it BCMA then FcRH5, FcRH5 then BCMA? Does it matter and do we know?

Dr. Adam Cohen: We don't know. I think in the beginning I have a feeling this is going to be after BCMA, just based on approvals is my guess, but I think we'll learn soon enough as it gets moved up which way we should use it. Right now we only have the data for after.

Dr. Joshua Richter: Just to keep on track and move on to another non-BCMA targeted bispecific, talquetamab GPRC5D CB3 duo antibody presented by Dr. Chari is similar to cevostamab. This is a bispecific that includes CD3 as the T-cell target, but instead of FcRH5 or BCMA, uses GPRC5D as the target on all plasma cells. Again, my understanding is that the GPRC5D BCMA and FcRH5 expression on cells is independent of one another, so remains to be seen about how the ultimate sequence should be.

Again, just like all bispecifics, we have step-up dosing for the dose escalation part of the phase 1 design and trying to mitigate any risk of higher grade CRS or neurotoxicity.

Ultimately, there were a few DLTs seen across all doses, however, no DLTs at the recommended phase 2 dose of 405 micrograms per kilogram. Of note, the administration of talquetamab has also been tested not only intravenously, but subcutaneously, making the administration profile very favorable for patients on long-term therapy. There were some rates of CRS and neurotoxicity. The majority of this was Grade 1/Grade 2, very little Grade 3. Because GPRC5D is expressed in some of the skin cells, particularly on the hands and feet, there is almost a desquamation event that can be seen, again, mostly Grade 1/Grade 2, but akin to the hand-foot syndrome that we see in patients we used to give capecitabine to. Again, this tends to be mild and transient, but we have seen this in some patients, and there's been no Grade 5 AEs across all doses.

The overall response rate across all doses, or specifically at the RP2D was 69% with the real activity being once you get to the several hundred microgram dose, when pushed up to 800 mics per kilo, there was a slightly higher response rate, however, some AEs were noted.

Ultimately, it's a tolerable safety profile at the recommended phase 2 dose of 405 mics per kilo.

High response rates seen at around 69%, again, small numbers, but very exciting expanding out into the phase 2 data. The subcutaneous administration offers some nice advantages for patients, and again, having other targets beyond BCMA, very exciting. I just want to throw it to Nina, your thoughts on the GPRC5D talquetamab?

Dr. Nina Shah: This is one of my favorite. This, and Adam's abstract are one of my favorite extracts from ASH. They're like the new kids on the block. What I think is really important about this is that, as you mentioned, they are not mutually exclusive antigens, and so they lead the way for either serial or bispecific targeting, and I mean dual targeting for either GPRC5D, FcRH5 with, or without BCMA. Really exciting. I really think BCMA failures are the next horizon that we have to target. I'm just excited to see

that there's something else besides BCMA. I'm really looking forward to the long-term PFS data to understand how this compares.

Dr. Joshua Richter: Fantastic. With our final abstract of the day, Dr. Cohen, take us home with AMG701.

Dr. Adam Cohen: We're in the home stretch. This is one of several BCMA bispecific antibodies that had data presented at ASH this year. This one is called AMG701. This is an extended half-life BiTE, an update on the AMG420 that was previously presented, but required a continuous infusion.

This drug has a more favorable pharmacokinetics. It allows for weekly dosing. Basically, the same mechanism that was all the other bispecific, we've seen one end targeting BCMA, the other targeting the CD3 to activate T cells.

Eighty-five patients were enrolled, heavily pretreated, again, a median of around six prior lines of therapy, and almost all triple exposed and 60% triple refractory.

The toxicity of this were similar to the other bispecifics, namely cytokine release syndrome, which was seen in close to two-thirds of patients. Again, majority Grade 1/Grade 2, but about 9% did have Grade 3. Maybe a little bit higher, typically managed with tocilizumab or steroids. There were a couple other DLTs typically associated with cytokine release syndrome, but again, no unusual or unexpected toxicities. There were some infections, including a couple of cases of sepsis and a couple of cases of bleeding in the setting of cytopenias.

The overall response rate you can see here, it was 26% for all comers, but as we got into more active doses, getting up much higher, including in the most recent cohort, again, only a few patients, but over 80% of patients responded, including some CRs and stringent CRs, so showing this continuous pattern of high efficacy even in highly refractory patients with these bispecifics. Several of these patients were MRD negative as well.

The conclusions of this were that this agent has clear activity even in highly refractory patients, the worst certainly CRS and other toxicity seen, but these are manageable in experienced hands. The study is now undergoing additional evaluation at a recommended phase 2 dose. We'll see what the durability of these responses are and how it compares to some of the other bispecifics out there.

Dr. Joshua Richter: Let me just throw quickly to Dr. Shah. From all the data presented, any data that is going to change your practice, or any data that's about to come out that's going to change your practice?

Dr. Nina Shah: Actually, the data that I found very useful was the FORTE data we didn't talk about it today with the transplant. It's hard for us to know what to do with transplant with all these new things going on. The IFM data that we talked about today, that's good. I think what all the data is showing us now is that BCMA is going to very quickly go to second-line treatment, and then the question will be, what do we do after that?

Dr. Joshua Richter: Fantastic. That will actually conclude today's program. I would really like to thank all you all for tuning in to all of us, myself, Dr. Nina Shah, and Dr. Adam Cohen. Be well and be safe. Have a good one.