Managing Myeloma

Recent Advances Made in Myeloma Treatment

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Dr. Richter: Hi. Welcome to *Managing Myeloma*. My name is Dr. Joshua Richter and I'm joined today by my colleague, Dr. Ajai Chari. We both work at the Tisch Cancer Institute at the Mount Sinai Hospital, and today we're going to discuss the most exciting and impactful news from the International Myeloma Working Group meeting held in September 2019, as well as the American Society of Hematology meeting in December 2019.

When patients do truly have symptomatic disease, I think it's been an argument for many years, what is the optimal upfront therapy? Do you move everything upfront? Do you sequence it out? There's a lot of new interesting studies between ALCYONE, GRIFFIN, and CASSIOPEIA about using four-drug regimens in the upfront setting, and I would ask you, where do you think these fit in today and in the future, and would it change if you're transplant eligible or not?

Dr. Chari: Great questions. I think part of the discussion about the number of drugs, the granularity matters which is, which four drugs are we talking about? For example, we know that the EVOLUTION study, which showed that VRd plus cyclophosphamide did not add anything and it hurt patients, so we can't just have a blanket statement that four is better than three. Then the second question is, if you are going to do four drugs, what is the duration of therapy and what will patients end up becoming resistant to? So with that setup, probably the study and then the drug that has moved the fastest from relapsed/refractory MM into newly diagnosed is daratumumab. Because of its safety profile and easy combinability, basically dara has been approved with practically every other backbone agent at this point, and so the question is, what does it add to for newly diagnosed populations? If we start with the transplant ineligible population, we know that dara has already been approved with Rd-based on the MAIA study and also the ALCYONE study, dara with VMP. Regarding dara/VMP, while more of an ex-US regimen, I think the most interesting update from Maria Victoria Mateos was that both PFS2 and OS are improved, and this is really important. People might think, oh we're so used to seeing this in randomized clinical trials, but this is very important because one of the push-backs to frontline dara is that, well I'm going to use up all my drugs early and patients are going to be resistant and then I'm going to have more complicated relapses. And I think what this tells us is what many of us have assumed, and this has been shown very beautifully by Dr. Yong in *British Journal of Hematology*, that we have issues of attrition and

diminishing returns. Our best chance of getting a deep durable response is that first response. And so not everybody makes it to the second relapse (attrition). So what do you save that drug for, if the patient is not even going to be alive? And then the response duration also shortens with successive relapses (diminishing returns). I think dara/VMP confirms that if you get a better PFS, it can translate into an OS, and there is no evidence that development of dara resistant relapses compromises those initial benefits. So, I thought that was a very important presentation. What do you think about the transplant ineligible population?

Dr. Richter: I agree. I think because OS takes so long to read out, any study that demonstrates OS is something we should really lock on two very big and even VMP, the comparator, that showed OS from way back when from the VISTA studies, so adding daratumumab here I think is a really important study, although as you pointed out, I think ALCYONE is more of a regimen ex-U.S. That being said, I think the MAIA study, dara/Rd, it really has the potential to move upfront in the U.S. as a very big regimen for the transplant ineligible.

Dr. Chari: And I think we heard that the control arm, Rd in that study, is now 33 months, which is amazing because if the median PFS has not been reached for dara/Rd and the control arm of Rd is already associated with an impressive 33 months, that's amazing. For transplant ineligible population, that's a game-changer. We're saying that our newly diagnosed older population is on a frontline therapy for more than three years, right?

Dr. Richter: It's amazing, and we don't know yet where DRd is going to read out. The last I heard was if you kind of look at the curves, we're probably looking at maybe 50 to 60 months for the DRd. I don't know if you've heard anything different.

Dr. Chari: Yes, I know. I think we will have to see, but also what's good about the DRd is that you're actually continuing the Rd backbone in both arms of the study, not terminating it after a fixed number of cycles, which is a criticism of a lot of the bortezomib based regimens.

Dr. Richter: Absolutely, and I think that's something that's a very important point is that many of the triplet trials, both upfront and relapse, at some point stopped the third drug, and when you drop the third drug and went to a doublet, that's a criticism. It's not able to control the disease as well using multiple mechanisms of action. So, the CASTOR study and ALCYONE had to stop the bortezomib to compare it to registration. I do agree that if we're able to continue, we probably would have had better outcomes, whereas MAIA absolutely exceeds.

Dr. Chari: Right, so then moving to the transplant eligible population, we heard basically three major regimens. We have dara/VTd from the CASSIOPEIA, dara/VRd from GRIFFIN, and then dara/KRd from two U.S. studies that were single arm. So, I think the one with the longest follow up was probably the one to start with, which is CASSIOPEIA, dara/VTd showed not only better response rates, depth of response, but also what I find very surprising, given that this was dara/VTd with

transplant, and outcomes discussed are even prior to the maintenance therapy starting. The addition of dara at 18-month follow up already led to a PFS benefit, which I was actually surprised by because if we just talked about how good the MAIA patients are doing, here at 18 months with the addition of dara, we're already seeing a PFS improvement. And so that I think sets up the GRIFFIN study which, of course, the American criticism to all European things is that we don't use VTd, what if you use RVd, and so GRIFFIN is showing similar deepening of responses with more stringent CRs after induction, transplant, and consolidation. I think we have two studies now showing that these quads are definitely adding to the depth of response.

We have to keep in mind toxicity and I think one of the things to be mindful of all of the frontline studies and even relapse, the addition of dara does increase the rate of infections, typically grade 1 and 2, not grade 3 and 4. And then the other thing that came up with GRIFFIN, which is different from CASSIOPEIA a little bit, is the collection. We know that in in CASSIOPEIA there was really no difference in the stem cell yield but there it was with thalidomide, which is not myelosuppressive, and in Europe, cyclophosphamide (Cy) mobilization is used. In GRIFFIN, in the U.S. study, there was no Cy mobilization permitted unless patients failed growth factor collection. So it's primarily plerixafor or G-CSF and we did see a hint of lower stem cell yield, and perhaps more need for extra collections. I think that's something we have to keep in mind.

I guess I will just close, for the folks listening with DKRd. The key message if you're going to use DKRd, I think, for community folks is carfilzomib with lenalidomide, or any IMiD for that matter, we have to pay attention to the dosing schedule. Carfilzomib is approved in basically a gazillion different doses and schedules, but for the sake of simplicity, if you're going to do it with an IMiD, I don't think it's prudent to go more than 56 mg/m^2 weekly, and that's what both of these studies did. They did weekly dara/carfilzomib 20/56 with lenalidomide and dex. I think that's an important message if you're going to use DKRd, and I'll just say that these responses are great, but with the Costa study, it was interesting, they have potentially, if you have two consecutive MRD negative timepoints, you can discontinue that treatment and monitor these patients. We can talk more about that, but I guess the first question is, are you going to use quads in your clinic these days?

Dr. Richter: So interesting thought, I have not yet completely embraced quads upfront for a number of reasons. First of all, as you pointed out, dara may affect collection. We thought when dara was approved that this is rituximab, we're just going to add it to everything. But it turns out that as opposed to rituximab, which is CD20, CD38 is on almost everything. It's on a lot more than just plasma cells. So it does affect other things, may affect stem cells at some level, NK cells clearly. The other issue is it probably does matter how you achieve your deep remission, that if you get there with VRd is that the same then if you needed dara/VRd to get there? And I'm not quite sure that's the case. Some of the interesting subgroup analysis of CASSIOPEIA was that the addition didn't seem to help the high-risk patients. So for those people that are high risk and transplant eligible, at least for me, I

don't see dara as the vehicle to overcome the high-risk nature of their disease. How do I overcome that? I looked to the FORTE trial, for whatever that's worth, where it seems that both KRd arms did better than KCyd. But those who went on to stem cell transplant probably did better if they had high-risk disease than if they continued with just the 12 cycles of KRd.

Dr. Chari: Yes, I think you bring up some very important points with the high-risk study. When we talk about high risk, putting aside the definitions because that in itself is complicated, but regarding a drug's utility in a particular risk patient population, the ideal way to do it is you need four arms in the study: you need standard risk with standard therapy; standard risk with novel therapy; high risk with standard therapy; and high risk with novel therapy. And I think study after study is showing, and this isn't true just for dara, but no drug truly has overcome high risk, with perhaps the only exception of proteasome inhibitors and translocation 4;14. Everybody does better with the novel agents (ie improve), but high-risk patients are still having a lower survival curve than the standard-risk (ie not overcome), and even with the novel therapy.

I think that is an important point; however, no study, other than perhaps two, has actually shown that the high-risk patients are being hurt by the novel therapy. The two examples I'm getting at are thalidomide with 17p deletion actually does worse, and we've heard recently the venetoclax treated patients in the BELLINI study, high-risk patients did worse. So I think that goes back to the ALCYONE study where there was no decrease in overall survival, and that's the other point of the overall survivals' endpoint. Yes, we want early readouts, we want to use MRD in a clinical trial, maybe for regulatory purposes. Then yes, we want to use PFS, but we can't forget that the OS still needs to be looked at because if you're compromising your OS outcomes then it should give us pause. And so that's why I think ALCYONE doesn't show it would hurt high-risk patients. And I think the FORTE study is very important, but one of the challenges that we really do, and this occurred at one of the ASH oral presentations, I'm sure you heard him say is that we're not supposed to do cross-trial for comparisons. Such comparisons are so dangerous, is that doses, schedules, and durations of chemo matter and, for example, in the FORTE study, if you're not getting a transplant, it was 12 cycles of KRd. Who's getting 12 cycles of KRd in the real world?

Dr. Richter: Very few people.

Dr. Chari: Right, and so, it's very important that when community doctors look at these studies, for example, even KRd versus VRd. Guess what? The VRd schedules are all 21 days, the KRd schedules are 28 days. So four cycles of each is actually more chemo with KRd. So you can't even compare KRd four cycles to VRd 4 cycles. All of these cross-study comparisons are really fraught with issues and I think it's difficult to know what to do with that. I personally think as long as you're not using all four drugs to progression, I'm in favor of it, and I think CASSIOPEIA is showing a PFS benefit. I don't think patients or the healthcare system can tolerate quads for everyone forever.

Dr. Richter: Completely agree. I think for a lot of these patients, we're going to start off with quads and then if we achieve sustained MRD negativity for some will stop; others we'll likely to continue them on something like dara and REVLIMID® (lenalidomide) long term. Interesting, and I'll ask you this, mostly because you have an investigator-initiated trial looking at this is, is there a role for quadruplets in the older or for frailer patients?

Dr. Chari: Yes, I think we're obviously investigating that because, again, going back to I don't think it's a number of drugs, it's the doses and schedules, right? So, for example, I would bet money that Rd full dose with lenalidomide 25 mg and dex 40 would be much more poorly tolerated than lower dose of len with weekly bortezomib and lower dex, and there's an example of two versus three drugs. So you really have to be careful, because we know that newly diagnosed patients have a significantly impaired quality of life from the disease itself, and I would submit that older patients, just like amyloid patients, are just as deserving of a rapid and deep response. But we have to not end up treating and getting them in the hospital. And so I think the key is picking the doses and schedules, but I think right now, we need to be careful, because we unfortunately don't have a lot of prospective studies about the frailty index. We know that the frailty has been shown to be an independent predictor in myeloma outcomes, but we don't have prospective risk-adapted treatment yet. So I think our gut would tell us that the truly frail patient, we may not necessarily want to do quads for everyone, especially when you have a triplet, like DRd, which is doing so well. I mean, if your PFS hasn't been reached, it's going to be very hard to beat that, right? But I think again, maybe for those high-risk, those fitter older patients, there may be role. What do you think about quads?

Dr. Richter: No, I completely agree. I think that from Betsy O'Donnell's RVd lite, which a lot of people use as a management for the older patients where we dose-reduce the len down to say, 15, we give the bortezomib weekly instead of twice-weekly, I would completely agree that I would rather give that type of approach than full-dose len/dex in the same patient. And I believe you're absolutely correct that there are patients where we could add the dara to the RVd lite backbone, and if we do our due diligence in the clinic to do the frailty indices, like Charlson and things of that nature, Freiburg, we may be able to find the patients who can withstand this and will ultimately benefit from it.

Looking at the treatment landscape for what we've seen now in upfront, and now we have so many drugs to choose from the relapsed/refractory setting, we're ushering in a new age where there is so many treatments available for relapsed and refractory patients, and we've seen some updates from IMW and from ASH with drugs such as venetoclax, isatuximab, melflufen, and a variety of others. Venetoclax is obviously a very well-known drug to a lot of our partners who treat other hematologic malignancies as it's already approved in myeloid leukemia and non-Hodgkin lymphoma. It has been studied in the BELLINI study, which was the registration study looking at venetoclax, bortezomib, and dexamethasone versus bortezomib/dexamethasone. Unfortunately, that trial was put on hold by the FDA due to increased AEs and deaths in that arm. However, venetoclax has really

shown excellent responses in two types of myeloma, both the translocation 11;14 as well as those who overexpress BCL2, which makes a lot of sense as it's an oral BCL2 inhibitor. The hope is that the lift comes off and that we're able to move forward with this drug in myeloma. I'm curious to hear your thoughts, where do you think venetoclax is going to fit into the landscape?

Dr. Chari: We keep talking about personalizing medicine and not treating everybody the same, and I think this is our first genomically kind of targeted therapy, if you will. So, I think the 11;14 is really promising. One of the challenges to the high BCL2 is whenever you link a drug approval to a diagnostic test, it becomes the question of how is that diagnostic test being done? What is a high BCL2? What's the cutoff? I think that will take a little bit more work. But I think the data that we heard at ASH, a couple of presentations, showed that not only there was the use of venetoclax in heavily treated patients showing very encouraging response rates and durability, I think the response rates were 40% to 50%, and very encouraging durability compared to other regimens. And this is in a median of five lines of prior therapy. So for venetoclax and dexamethasone, that's very encouraging. And then we also heard about the addition of daratumumab, which was associated with very good responses as well. Of course, as we alluded to earlier, that this is a good example of toxicity needs to be thought of as well, but clearly, very promising for 11;14 patients.

Dr. Richter: Absolutely. So this really broadens our horizons, especially as I think we're all very comfortable giving the combinations of IMiDs and proteasome inhibitors early on, now monoclonals early on, and unfortunately, despite these amazing outcomes, people do eventually relapse. So having new classes of agents in myeloma doesn't give us one new therapy, but ultimately gives us many new therapies as venetoclax appears to be able to be combined with both the proteasome inhibitors, given a single agent combined with monoclonal, so it really does open it up for the relapsed and refractory patients.

Another drug that I'm very excited to see the approval of is melflufen, also called Ygalo. The updates from OCEAN and HORIZON were discussed. This is a really interesting drug, as it's basically the newfangled version of melphalan as a peptidase approach and from my standpoint, the wonders of it is that as a monthly infusion, it's very convenient for patients potentially. Also, as patients are getting deeper and deeper remissions upfront, we may see patients fewer and fewer that potentially go on to high-dose melphalan with transplant and inside the U.S. not getting much melphalan as part of their upfront therapy. So, we're going to be seeing more and more patients who become dual refractory, quad refractory, penta-refractory, and are still alkylator naive. So I think this may represent a new great option for our patients. Any idea where melflufen may fit in?

Dr. Chari: Melflufen is very promising data. We're seeing that response rate of the sweet spot of 30% PFS of three-and-a-half months. That seems to be where you need to be for a novel agent in the heavily treated population, especially for an accelerated approval. I guess the challenge I'm always wondering is, we always

want to think about novel mechanisms of action and yes, myeloma cells have increased aminopeptidase making them more vulnerable to this target, but we did a study, for example, with a salvage transplant, melphalan resulted in six-month PFS in the median of four lines of prior therapy. So my question is always, if you're going to give this monthly drug of melflufen, how would it compare against mel-140 at one-time intervention, right? And again, we don't have that data, but I think they're going to be certainly patients who either may not have stem cells or are not candidates for myeloablative-type of therapy where this might be a great agent for patients like that. One of the other differences between U.S. and Europe is, of course, in Europe they use a lot more alkylators, both melphalan and cyclophosphamide. But so far, I haven't seen that there's been a major difference in prior alkylator or not, so we'll have to see more data.

Dr. Richter: Absolutely, and one of the things you pointed out earlier about something we see with daratumumab infusions, that although it's controlling disease very well, we are seeing a higher risk of infections from hypogammaglobulinemia, one of the toxicities of chronic alkylator therapy of melflufen is the cytopenias have been a bit of an issue. So patients who are a little more pretreated may not have the same marrow reserve, may not do as well with chronic alkylator exposure such as this, so definitely has to be balanced.

On July 3, 2019, we saw the FDA's first approval of selinexor. A lot of this is based off of your *New England Journal of Medicine* article from the STORM study, ushering in a new class of agents, the selective inhibitors of nuclear export, and some of the updates that we saw at IMW and ASH relate to the STOMP trial, using selinexor as a backbone, combining it with all of the other classically used agents in myeloma, the proteasome inhibitors, the IMiDs, and the monoclonal antibodies. Some of the very interesting data was the combinations with the IMiDs and the wonders of combining aside with IMiDs and steroids as now we have a highly effective all-oral regimen to potentially offer patients. Your thoughts on optimal combinations of selinexor as we move into 2020?

Dr. Chari: Yes, one of the challenges with selinexor that we also had is the toxicity management and I think there's a learning curve, but when you learn how to use it, it's a very effective drug and as a co-author on the paper, you know very well the risk-benefit balance of this drug. I think one of the important things is that the STORM study that was published in the *New England Journal of Medicine*, the intent of that was really to show, does this have single-agent activity and can this get accelerated approval? In a heavily treated population, it showed that response rate of in the mid-20s percent PFS at three-and-a-half months, and while that may not seem that encouraging, we have to remember who these people were, and they were heavily pretreated, over 95% were carfilzomib, pomalidomide, and daratumumab refractory, and there was 22% increase in their paraprotein from the daily signed consent to 12 days later. So these are not patients that could wait the months for CAR T slot. But why I'm bringing that up in the context of what you're saying is, you need that STORM study to show that this has single-agent activity, is this drug in the category of carfilzomib,

pomalidomide, and dara, or is this in the category of ixazomib, elotuzumab, panobinostat which are approved but in combination because of lack of single-agent activity or lack of approval. So this puts this into the single-agent category, but myeloma is too genetically complicated to be treating with single agents and none of those drugs (car, pom or dara) are typically being used as a doublet therapy. The purpose of the STOMP is to show that you can combine it and the key is again, going back to doses and schedule. If you're giving selinexor as a single agent with dex, it's twice weekly, but when you throw in a third drug, you can give it weekly and depending on an IMiD or versus a PI or monoclonal, the dose goes up and down because of the myelosuppression. SPDs is another great option, completely oral. So hopefully more patients will benefit.

Dr. Richter: Absolutely, SPD. We received a lot of excitement on Twitter that some very prominent myeloma physicians were very excited about the data. Also anticipating the results of the BOSTON study combining weekly selinexor with bortezomib, another very potent regimen. Something you pointed out, which I think is really important to share, is the management of the toxicity, that the drug is highly active. But one of the things that we do here in our institution is prophylactically go about preventing as much of the GI side effect as possible by giving multi-agents including things like rolapitant (VARUBI®), things like olanzapine, which is Zyprexa, 5HT3, steroids. We really have a whole protocol. As many of you all know that once a patient develops nausea and vomiting, you're already behind the eight ball, it's much harder to deal with. So being upfront about the side effects of being aggressive about controlling them, you're able to weather that beginning of the storm, no pun intended, and get them through and allow them to continue on their regimens with the appropriate dosing. The other thing that we've also seen is the potential need to include things such as TPO mimetics, like Nplate® (romiplostim), eltrombopag (PROMACTA®). These are agents that at least in the myeloma world, we don't use very often, but they may be needed here to support the patient, at least in the beginning of therapy to help clear out the marrow.

Dr. Chari: And the other thing worth mentioning in toxicity management is the drug has a very short half-life, so worst case scenario, you try all these things, but if you're having problems, you hold the drug, side effects clear, and then you restart at a dose level lower. So I think those are the tricks that people need to be aware of to help get patients through this drug.

Dr. Richter: Absolutely. Really excited to see some of the upcoming data and accommodation studies with BOSTON and STOMP.

Switching gears for a moment, one of the big excitements that we've seen a lot of updates, especially at ASH, from the CAR T studies, of which now there are quite a number of them, including the Legend CAR T, which we're doing many of the studies here. Very exciting new data with the possibility of a different CAR T bb2121 ISOCELL being approved next year, in 2020. Some of this data was presented by our very own Deepu Madduri. Very exciting new data from the CARTITUDE study, looking at the Legend J&J CAR T, the fully humanized CAR

T in patients who are heavily pretreated with some very, very impressive results. For those of you who may not be as familiar with this technology, CAR T is chimeric antigen receptor T cells. Essentially, we take patients in the study who are heavily pretreated, we first lympho pheresis them to collect their T cells in the lab. They are engineered to target BCMA, a B-cell maturation antigen, which is located on all myeloma cells. The patient then has to undergo bridging therapy while this process is going through to keep them in remission or to hold their disease at bay. At which point, we need to create immunologic space. We give lympho-depleting chemotherapy with cyclophosphamide and fludarabine, after which we re-infuse the CAR T cells. The patients typically stay in the hospital for approximately 14 days, but the big issue is monitoring for CRS or cytokine release syndrome, which is a sign of activation of the immune system that goes along with the infusion of the CAR T, which has its own issues with managing with a variety of different drugs such as tocilizumab and anakinra, even steroids or chemotherapy if needed. We're all really excited to see drugs like this or therapies like this enter the clinic. What are your thoughts on the CAR Ts?

Dr. Chari: From a patient perspective, to have a single intervention from the bb2121, a PFS of around a year, is amazing because we've talked about all these other therapies in the relapsed/refractory segment that typically lasts for three-and-a-half month duration for PFS median and require ongoing therapies. From a patient perspective to be penta-refractory or triple-class refractory, seven lines of prior therapy, and get one treatment and be free of any therapies for a year is amazing. The caveats, of course, are the CRS management, the tremendous patient selection that's going on because there are limited slots. There's also the manufacturing process, which you'll have attrition, the bridging chemo and the impact of that on PFS. This will primarily now be applied to the transplant eligible population. I think that's the second issue, and then the third issue I would say is the cytopenias and management of supportive care. So yes, it's a one-time intervention. But a substantial number of patients will require ongoing blood count support or IVIG, etc. So I think those are some of the things to think about. But clearly very exciting for patients and I think we're very early in the side effect management and perhaps we'll get to more sick patients, more fragile patients if we get better at that CRS prophylaxis, because it would be like giving melphalan transplant but not yet knowing the antiemetics and diarrheal and growth factor support.

Dr. Richter: Absolutely, and one of the things you alluded to earlier was this, the difficulty of comparing trial to trial/study to study. You mentioned that with bb2121 we've seen the heavily refractory patient's median outcomes of around 12 months, and one of the abstracts they looked at the Chinese Legend CAR T and patients in China achieving a median PFS of 28 months for people who achieved MRD negativity. Now, because different drugs are available in different parts of the world, heavily pretreated in one country is going to differ from another country. So, there's less exposure to drugs like pomalidomide or even daratumumab, but one of the things that this brings encouragement is, as the studies move these therapies further and further up, at least in the U.S., the possibility of having

extremely long durations of remission, and I don't know dare I say the word cure, potentially, if we use it in the right patient in the right way?

Dr. Chari: Absolutely. What I'm also very interested to see is how this might do for the high-risk patients, right? Because that is truly an unmet need. None of the drugs have overcome high risk. And it'll be very interesting those studies are already open and so for early relapses of high-risk patients rather than blowing through the usual cocktail of drugs, one after another with diminishing returns, can we do something more innovative, like CAR T? So it'll be very exciting to see those results.

Dr. Richter: Absolutely. Your thoughts on, because you mentioned earlier, I guess a lot of us are kind of considering are you CAR T eligible in the same way of are you transplant eligible? Do you see CAR T as a substitute for transplant for some patients?

Dr. Chari: I mean, definitely for those high-risk patients who are not doing as well and it may not be even an either/or and we could do both, right? Because perhaps that if you take a patient who gets melphalan transplant, and you've debulked them significantly, and you have these rich, juicy T cells left from a relatively newly diagnosed patient that are going to be more engageable in the control disease, can you use the CAR T as a consolidation? All of these needs to be investigated, and then, of course, we haven't talked about the long term. We know that transplant will increase the risk of secondary malignancies with len maintenance, we might not see that with CAR T, so the long-term data we have for CAR T is very limited, but I think that'll be really exciting to see.

Dr. Richter: You used the term engage. So, I'm going to use that as a segue to the bispecific T-cell engagers. Over the last year, we've seen a lot of interesting data about using off-the-shelf products that target BCMA, both from the data presented about belantamab mafodotin, AMG 701, and most recently at ASH - some interesting findings from the Celgene product, the off-the-shelf product. These have a number of distinct advantages over the CAR Ts in that they're off the shelf. There's no reason for bridging therapy. They are titratable, if someone's in the back having a problem, you can turn it off. If you give a CAR T and someone has horrible CRS that is a little more complicated to manage, cost is definitely something to consider across all of this. And the other thing is access, we have the luxury of having access to many things at our center. Many patients don't have the access now to even things such as transplant. So access to CAR Ts may become a very big issue following approval. The ability to give off-the-shelf BCMA products is something to overcome that. Your thoughts on the landscape of BCMA?

Dr. Chari: This new unanswered question is the sequencing. And so we have these three different approaches, the BiTES, the ADCs, and the CAR T, but what if you get one? Can you not get the other? Obviously that gets to the biology of relapse and resistance. But again, we don't have any cross-trial comparisons, but if I were to think in my mind, we take a patient below the age of 70 because they would be

potentially CAR T eligible, and you said okay, I'm going to randomize them to either CAR T, bispecific, or the ADC, what would you pick? And I think the ADC strength is really the ease of infusion, 30-minute, no CRS, super convenient, but those ocular issues that require monitoring or limitation, and the PFS, we don't have long-term data yet, whereas the CAR T we know that single intervention gives you that year. But the bispecifics have a real potential. I mean, the Celgene data were quite impressive, very high response rates, durable remission so far, even the deep ones. And so if you can get that PFS of CAR T without bridging chemo because remember, CAR T some of that PFS may be lost if the manufacturing period was shorter, and you didn't get bridging chemo. So I think that's the key question and we know that in lymphoma, there's about a 20% attrition from the day you sign consent who actually gets the CAR T and I don't think you have that attrition with bispecific and ADC because they're off-the-shelf. What do you think?

Dr. Richter: Absolutely. No, I completely agree. As you talked about with the STORM study, the patients who were heavily pretreated may have kinetically very aggressive disease that either doesn't have time to wait or in the period while waiting, they have some sentinel event preventing them from getting other CAR Ts and we're seeing this in the myeloma space, in the lymphoma space. Some studies showing 10% to 15% and even 20% of people queued up to get CAR T, never get it because of disease progression, infectious complication or some other adverse events. So, off-the-shelf products are absolutely going to help for people who need therapy immediately. The high kinetic plasma cell leukemics may be able to treat very quickly. I do share your concern about the complexity of dealing with the ocular toxicity of belantamab, the Celgene data was quite impressive for their off-the-shelf product. Very interested to see what the long-term data is. Because as you pointed out earlier, early data we get very excited, but this needs to stand up under higher rigor with phase 2 and phase 3 studies.

Turning to a slightly different area and this is a study that you have a very close connection to, the CANDOR study, looking at the combination of carfilzomib, daratumumab, and dexamethasone in relapsed/refractory myeloma, compared with carfilzomib and dexamethasone alone. This study was presented recently and very exciting new data. There's two very important parts about this study that really bring it to light; one is the triplet was continued, and as compared to the CASTOR study where the proteasome inhibitor was stopped. The notion of continuing triplet therapy to intolerable toxicity or progression is in my mind the correct way to approach, especially heavily relapsed and refractory patients. The other notion is over the last decade, we have had a large number of studies looking at lenalidomide-based triplets in the early relapse. We've had ASPIRE, POLLUX. But we've had a number of these studies with len/dex as a backbone. The difficulty is nowadays with the modern-day approach, if you're transplant ineligible, you remain on lenalidomide until progression. And if you're transplant eligible, you remain on lenalidomide until progression. So ultimately looking at early relapse in a len refractory patient group hasn't really been done as robustly until this study. So those old data as impressive and informative as they were, doesn't have the same impact now when everyone's progressing on len, and

about a third of the patients in CANDOR were len refractory by the time they entered. So, to me the applicability to the bedside is enormous in this study. And I think this may have a big impact, obviously, excited to hear your thoughts.

Dr. Chari: I completely agree. People always want to pit the PI versus IMiDs against each other with dara, and is not a fair comparison. Now we have a more fair comparison. But one of the questions people ask is this hazard ratio of the 0.6 range. Doesn't that seem worse than the other studies with the DRd, for example 0.3 and even bortezomib 0.3? But the key here is we have to think about the patient population. What is the control arm? We're not using a historic old-school control arm, right? This is not a Vd, this is a K56 twice weekly. And that's important, because ENDEAVOR showed that 56 twice weekly is better than Vd. So this is actually a next-generation study trying to build on what we've already learned not going backward and comparing DKd to Vd, right? So, when the control arm does better, it gets even harder for the experimental arm to do better. I'm very curious to see more detail, the high-risk outcomes, because again, we haven't overcome high risk. But I really echo your point about if you look at those three Vd-controlled backbone studies with prior len exposure/len refractory, the outcomes of that subgroup are much worse. I mean, at best, we're looking at 8 to 11 months, whether even with the novel agent, and here with DKd we've already surpassed that. I think that's a real important real-world message that if your patient is len refractory, make sure that your salvage treatment will be giving them the maximal benefit.

Dr. Richter: Absolutely, and, again, one of the points you brought up earlier is making sure that you're aware of the dosage of carfilzomib that you're using when you start mixing it. There've been a lot of studies with carfilzomib over the past year including ARROW which has shown the ability to dose the drug safely at 70 mg/m^2 weekly, however, to your point, that was as the doublet with dexamethasone, when combining it with daratumumab or combining with an IMiD, it's really important to go back to the studies to see how it was dosed to avoid any over toxicity.

Dr. Chari: An important distinction between the CANDOR and the DKd study that we did in 1001 is the dosing of carfilzomib. So, this CANDOR is ENDEAVOR dosing 56 twice-weekly, but the one we did was K70, weekly. So with daratumumab, you can give it weekly. It's the IMiD where you worry about the thrombotic cardiac profile, but I think in the real world, it may be hard to do 56 twice-weekly to progression. So I'm thinking that people, if they start with this 56 twice-weekly, they can always go to then later, 70 weekly again off-label but at least you're treating to progression, because the reality is as you alluded to treating to progressions, the most important thing, and if the patient and physician and treatment team are getting tired of the twice-weekly schedule, we need to have a practical weekly dosing.

Dr. Richter: Absolutely. So in the final moments, just want to hear your general thoughts on data that was presented this year or data you're anticipating in the coming year,

in terms of what are you seeing as the immediate next-steps in terms of our understanding of myeloma and how we're going to treat it?

Dr. Chari: I guess I would integrate it with where are the needs, right? I think, starting with the newly diagnosed, we have the high-risk frail elderly. If those patients don't make it to line two, we're not going to have them around; high-risk, we have done a terrible job; central nervous system myeloma; plasma cell leukemia; and probably the last would be the multi-drug refractory patient. And I would now put into that category. We've already talked about triple-class refractory, we're going have BCMA refractory patients. So to me, those are the areas of unmet need, and we're starting to see some glimmers of activity, for example, we did see selinexor can work in post CAR T failures. So that's exciting, but that's going to be the next generation of studies that I'm interested in. What did you think or what are you looking for?

Dr. Richter: I think 2020 is going to be very, very exciting. There's a lot of new drugs that are probably going to come into our hands, so we have the potential for isatuximab to come into our hands, the PDUFA date, I believe, is April 30th. So from the ICARIA study isa/pom/dex versus pom/dex, the data is very exciting. Again, hard to compare with the EQUULEUS study, the DPd comparator because the ICARIA patients were not as heavily pretreated. That being said, the infusional nature of isatuximab is so much shorter than daratumumab. So this may provide some of the community centers that have difficulty with that first dose dara to give an anti CD38 without the long infusion. However, as we're hoping for the subcutaneous dara is not far behind. Melflufen, belantamab, mafodotin, venetoclax, all potential exciting approvals for next year, as well as bb2121. Something you alluded to earlier, which is the most complex question is sequencing, which is now that we have all these tools on our plate, how do you sequence? At the moment, BCMA-based therapy is placed after PIs, IMiDs, monoclonals. But should that be the case? Is it the case that BCMA should come earlier and to your notion, I completely agree, the efficacy of selinexor shown in patients who have gone through prior CAR T is something we're all going to need to remember that as soon as CAR T enters the field, unfortunately, it's not yet a cure, people are going to relapse from it. And so far the only real data we've seen of how to treat post CAR T is coming from the STORM study with selinexor, so selinexor combinations potentially post CAR T may be very exciting. I'm really hoping we get some new clarity about the sequencing of these different therapies, and especially for the BCMA, who should get an ADC, who should get a BiTE, and who she get a CAR T?

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