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Joshua Richter (JR): Welcome to the first episode of our three-part series on CD38-directed strategies in the treatment of multiple myeloma. My name is Dr. Joshua Richter. I'm an Associate Professor of Medicine at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, and the Director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mount Sinai. I'm joined today by my esteemed Ivy League colleague, Dr. Andrew Yee. Dr. Yee, I'll turn it over to you to introduce yourself, sir.

Andrew Yee (AY): Thank you, Dr. Richter. I'm the Clinical Director for the Center for Multiple Myeloma at Mass General Cancer Center and I'm an Assistant Professor of Medicine at Harvard Medical School. Thanks, Josh, and I'm looking forward to discussing all things CD38-related.

Dr. Richter: I can't wait. Dr. Yee and I have known each other for a long time and we're ready to dive into this. In today's episode, we'll be talking about the impact of CD38-targeting strategies in the frontline treatment setting. The learning objectives we'll be addressing today focus on how the upfront setting has evolved in the treatment of myeloma, specifically how the anti-CD38 antibodies, daratumumab and isatuximab, are now being incorporated into our treatment strategies to achieve the best responses for our patients. Let's kick it off by talking about a newly diagnosed patient who comes into your clinic. Our treatment strategies are evolving, Andrew; why don't you walk us through what thoughts go through your head about how to parse this out? What options have you used recently and how are they evolving?

Dr. Yee: I think the emphasis is on "evolving". As we all know, the treatment options that we have available have evolved significantly over the past several years, resulting in transformational outcomes that are now achievable for many of these patients. When we think about newly diagnosed patients in myeloma, our approaches extrapolate from oncology principles in general: we have to consider the patient's functional status and other comorbidities when we're identifying the best regimen for the individual patient. Fortunately, in myeloma, we can tailor the regimen for the patient in front of us to give the best possible response and significantly improve the patient's quality of life. And I think that the CD38 antibodies that we have available, daratumumab and isatuximab, play a fundamental role for newly diagnosed patients.

There are several things I think about when I think about newly diagnosed patients. There are some patients who have an acute urgency for treatment; for example, a patient who has acute renal failure from multiple myeloma, from cast nephropathy. Patients such as these need immediate treatment, and for these individuals, treatment with a CD38 antibody can play a key role. But, if we think about the more common, typical patients, this is the outpatient who comes in with anemia, or who presents with a backache and the primary care physician does a workup with imaging that shows a lytic bone lesion, so that there's a concern for multiple myeloma. This is a patient who needs to be evaluated, to identify if they have multiple myeloma, and if they do, if that multiple myeloma needs to be treated.

That can be one of the hardest questions to figure out: this patient has a monoclonal gammopathy, perhaps, or maybe anemia that is a little bit mild; do they have smoldering multiple myeloma? I think, for those patients, we have to watch them very closely and differentiate a patient with smoldering multiple myeloma versus a patient who should be treated. And I know, Josh, we could have another whole podcast talking about smoldering, but we'll put that aside for now.

In 2024, CD38 monoclonal antibodies (mAbs) with high tolerability are a foundation of treatment in NDMM.

But let's talk about the patient with newly diagnosed multiple myeloma who has the typical criteria for treatment, including lytic bone lesions and anemia. The way that I think about patients with newly diagnosed myeloma in 2024 is different than how I thought about them in 2014. For me, today, I think about a CD38 antibody as the foundation for treating these patients, given the tolerability of CD38 antibody. In particular, I think about daratumumab subcutaneous; of the drugs we use in oncology, it's probably one of the most well-tolerated therapies we have, in terms of efficacy and tolerability. So, for many patients, I use Dara SubQ as the underlying base that I build from. Ten years ago, I'd be thinking about either lenalidomide-based doublets or bortezomib-based doublets, but in 2024, I start with a CD38 antibody such as daratumumab. The fact that it's now available in a subcutaneous form has been transformational, since its approval in 2020. In terms of accessibility, tolerability and convenience, it really checks off a lot of boxes.

Dr. Richter: Yes, concerning the use of doublets: I think back to when we were using doublets and triplets, and many of the people listening may be very familiar with VRD or RD* as an initial doublet or triplet. And I think one of the things that you brought up, which is phenomenal and so true, is that, in other cancers, if you're going from two to three or three to four drugs with classical chemo, that's a big ask for patients. You know, if you take an 80-year-old with metastatic cancer, and you say, "oh, we can

*VRd: bortezomib - lenalidomide – dexamethasone; Rd: lenalidomide - dexamethasone

improve the outcomes by adding cisplatin or 5-FU or methotrexate", that's a big ask. In myeloma, adding a monoclonal antibody to a doublet or triplet regimen is not that big of an ask, and I think now we're really focusing on triplets and quadruplets. One of the things I'd love to hear your take on concerns the use of triplets and quadruplets, both in the transplant-eligible and the transplant-ineligible. So, is it CD38 for everyone regardless? How does that impact if you're going towards transplant or not towards transplant?

Dr. Yee: Right. So, for me, it's CD38 antibody for everybody, essentially, because of the tolerability. And, in multiple myeloma, we have regimens with two, three and four drugs. I think there's an emerging consensus that we want to give the best therapies upfront in terms of achieving the maximal, best possible response. And as you mentioned, in myeloma, we can do that without necessarily having a big ask. There are some therapies in oncology that are fairly toxic, but I think, in myeloma, you can get a nice depth of response without necessarily making any significant compromises in terms of tolerability. In myeloma, I think we're very fortunate to be in a position where we can offer patients those types of therapies.

Emerging consensus: to achieve the best possible response, use the best therapies in the upfront setting.

And there has been a traditional distinction between transplant-eligible and transplant-ineligible. In addition, like with smoldering, there's another whole discussion about whether to transplant upfront or whether to save it for later; but that's a separate discussion. For me, there's not really a critical distinction between eligible and ineligible: I think more about functional status. For patients who have reasonable functional status and not too many comorbidities, I usually do start off with the four-drug regimen.

Consider four-drug regimens in NDMM patients with reasonable functional status, fewer comorbidities.

Emerging consensus: consider a four-drug regimen for younger NDMM patients (<65 years).

In talking about the transplant-eligible, I think about the younger patient and the four-drug regimen. And I think the general emerging consensus amongst our group, and probably across the country, for the stereotypical younger patient, who's 65 and younger, I typically think of a four-drug regimen. Now, I know the other question then becomes, do you use bortezomib or do you use carfilzomib as part of your four-drug regimen? But that's a whole other discussion.

Dr. Richter: That's a whole other can of worms.

Dr. Yee: The reason why I mentioned daratumumab subcutaneously is that it is what's available, as it's approved for newly diagnosed patients. There is emerging data with isatuximab that will potentially lead to an approval in newly diagnosed myeloma, so that we'll have access to this drug for newly diagnosed patients, as well. In talking about data that's emerging for four-drug combinations, we can look at the recent ASH meeting, where we heard about the PERSEUS study, which looked at daratumumab, lenalidomide, bortezomib, dexamethasone versus lenalidomide,

Emerging data for isatuximab may support approval in NDMM patients.

bortezomib, dexamethasone.[1] This was a phase three study that helped confirm what some of us have already adopted into practice based on the GRIFFIN study,[2] which was, essentially, the phase two version of PERSEUS. And, again, you see significant improvements in progression-free survival, including in the high-risk patient population. I think that's one thing that people wonder as an open question is, in general, how effective is CD38 antibody in high-risk patient populations? What we saw in the PERSEUS study, was that for the high-risk patients who represent the most challenging treatment scenarios, we saw significant improvement in progression-free survival with the addition of daratumumab.

PERSEUS demonstrated a significant improvement in PFS with addition of Dara to VRd[1]

Dr. Richter: Absolutely. And I think you bring up some really great data. So, we talk about GRIFFIN, which is the randomized phase two trial of Dara-VRd versus VRd, and the wonderful recent ASH presentation from the PERSEUS trial. One thing that I think is worthwhile to discuss is the GMMG-HD7 study, which compared ISA-VRd versus VRd in transplant-eligible patients, and again, we saw improvements in outcomes with the quadruplet over the triplet.[3] One of the interesting aspects of the HD7 study is that it actually has more similarity to how we approach newly diagnosed myeloma in the US, as opposed to the letter of the law that was used in PERSEUS and GRIFFIN, which both utilized post-transplant consolidation. Both used induction, stem cell harvest, transplant, and then further treatment with either the triplet or the quad before moving on to maintenance. And although that practice is more common in places outside the US, like Europe, it's not really practiced as much in the US.

In the GMMG-HD7 trial of Isa-VRd vs VRd, improved outcomes were seen when Isa was added to VRd[3]

HD7 may be closer to real-world clinical practice than PERSEUS or GRIFFIN, which both used post-transplant consolidation.

For example, in my practice, I use strategies like Dara-VRd upfront, stem cell harvest, collection, and then right to maintenance. I usually don't give more Dara-VRd after transplant, but that's what PERSEUS and GRIFFIN did. HD7 with isatuximab went right on to maintenance after autologous transplant, which is more in line with what we do in the United States.

The GMMG-CONCEPT, ISKIA and MASTER trials studied quadruplet therapy with carfilzomib as the PI.[4,5,6]

You've already hinted at this, and I have to throw it back at you: there's been some wonderful data recently about quadruplet combinations with CD38, but using carfilzomib as a backbone. We've seen data from GMMG-CONCEPT,[4] data from the plenary presentation of ISKIA,[5] and data from the MASTER study.[6] I'd love to hear your thoughts on your choice of the proteasome inhibitor; while the old base was a proteasome inhibitor, we now use a CD38 as the new base. How do you decide which proteasome inhibitor to combine with the CD38?

Dr. Yee: I think this is a topic that we talk about a lot, and we know that there's a great deal of heterogeneity in practice. I want to acknowledge that, and that there can be issues related to insurance coverage. But we have to recognize that using a proteasome inhibitor can be key as part of the treatment regimen for the newly diagnosed patient. The key is to gang up. The question then is, how do you get the proteasome inhibitor in? Bortezomib was the first proteasome inhibitor we had, and we now have carfilzomib. If you look at the ENDEAVOR study, results indicate that, in the relapsed setting, carfilzomib is superior to bortezomib.[7,8] But adoption of carfilzomib in newly diagnosed patients is more complicated, because, to be fair to the randomized data, it hasn't really played out. For example, in the ENDURANCE study, which compared carfilzomib to bortezomib, there wasn't a significant improvement in PFS in the carfilzomib arm.[9] With that backdrop, why am I arguing for carfilzomib in newly diagnosed patients? That's essentially the question. For me, I tend to prefer carfilzomib as part of the four-drug regimen in younger patients, for several reasons. First, I think that the peripheral neuropathy associated with bortezomib cannot be understated. And the clinical trials that have been presented, including ENDURANCE,[9] all use twice-a-week bortezomib to achieve the responses seen in CR rate, MRD negativity, etc. And I think, with bortezomib twice-a-week, the peripheral neuropathy rate is not trivial. Because of the high risk of peripheral neuropathy, I think a lot of people in practice have moved to a once-weekly dosing of bortezomib. You also have other risks that people don't talk about as much, such as blepharitis which can be annoying, but the peripheral neuropathy rate with twice-a-week bortezomib is a major limiting factor. And, something that isn't appreciated with the ENDURANCE study is that the dropout rate for adverse events was actually higher in the bortezomib arm than in the carfilzomib arm, suggesting that the tolerability of bortezomib can be worse because of peripheral neuropathy.

Using a proteasome inhibitor in combination therapies is key to treatment in NDMM

ENDEAVOR: carfilzomib superior to bortezomib in the RRMM setting[7,8]

In clinical practice, reducing bortezomib dosing to once-weekly may reduce peripheral neuropathy

ENDURANCE used twice-weekly dosing of bortezomib; the dropout rate for adverse events was higher in the bortezomib arm than in the carfilzomib arm.[9]

So, in clinical practice, many people like to use bortezomib once-a-week, and when I use Dara-RVd, I tend to use it once-a-week also. But I think when using a drug once-a-week, once-a-week carfilzomib is probably better than once-a-week bortezomib; head-to-head, I think it's probably superior. With twice-a-week dosing of carfilzomib, many of the concerns have to do with shortness of breath and cardiac toxicity,[10] which is definitely an issue. In current clinical practice, though, using once-a-week carfilzomib and paying attention to not over-hydrating

Carfilzomib is associated with clinically significant CVAEs[10]

Recommendations for once-weekly carfilzomib: patient management to include hydration, blood pressure management to reduce cardiac toxicity.

and to blood pressure management, I think the risk of having the cardiac toxicity isn't as high as what's been previously presented.

Dara-KRd may be suboptimal in patients with cardiac-related comorbidities.

I am mindful, though, that the potential for cardiac toxicity with carfilzomib is something to think about, which is why I don't think about Dara-KRd for every patient. If somebody has comorbidities in terms of hypertension or if they have cardiac issues, I wouldn't lean towards Dara-KRd in that situation.

Dr. Richter: I think that's a great point; I want to hear from you specifically: that patient goes Dara-RVd. In your mind, which patient gets a carfilzomib quad upfront, either Isa-KRd or Dara-KRd?

Dr. Yee: In our practice, if a patient is 60 or younger without a lot of cardiac issues or hypertension and they're in reasonable functional status, I have been leaning towards those regimens. For example, I have a patient in his 50s and I just started him on Dara-KR.

Dr. Richter: There's been some wonderful data on this. In the MASTER study, Luciano Costa gave the quadruplet of Dara-KRd, and one of the wonderful things that came out of this study was that he did stop along the way when people had maintained their MRD negative status.[11] And when he looked at patients with no high-risk cytogenetic abnormalities versus one versus two or more, patients with two or more really behaved very differently.

IMROZ: Phase 3 trial, addition of isatuximab to VRd improved PFS in transplant-ineligible NDMM patients[12]

It's interesting, because the patient with one high-risk cytogenetic, such as a 17p or a 1q, tended to respond more similarly to the no-high-risk patient than those with two or more. I think one of the things we're starting to understand is that not all high-risk disease is the same; ultra-high-risk disease may warrant a more aggressive approach. We've seen a variety of quad data that involves isatuximab as well, including the IMROZ study looking at Isa-VRd in transplant-ineligible,[12] which we'll talk about in a moment. Other studies that are investigating isatuximab include the ISKIA[5] study looking at Isa-KRd and GMMG-CONCEPT[4] looking at Isa-KRd. And there's some really interesting data coming out about high-risk disease. When you subset out the ENDURANCE trial, that study didn't include high-risk. At the time, 1q-gain (+1q) was not considered a high-risk abnormality, but when data from high-risk patients was analyzed later, those patients did seem to do better with a carfilzomib base.[9] So, I tend to share your viewpoint that the younger patient, high-risk or ultra-high-risk, is probably going to benefit from a carfilzomib-based regimen like Dara-KRd or Isa-KRd. They're all wonderful options.

ENDURANCE: analysis indicated patients with high-risk MM in the carfilzomib arm had improved outcomes compared to similar patients in the bortezomib arm[9]

Younger, high-risk, ultra-high-risk patients may benefit from quadruplet therapy that includes a CD38 mAb + carfilzomib

Dr. Yee: But at the same time, if I was to push back at you a little bit, I would say that, if a regimen works well for high-risk, it should work even better for standard risk. And so, in my mind, there's no

reason why you couldn't use it for patients with standard risk disease.

Dr. Richter: I think that's extremely fair. A lot of things factor into it: in ENDURANCE, there was more neuropathy with the bortezomib-based regimens, while the KRd arm had more cardiopulmonary and renal toxicities.[9] The one benefit of using a bortezomib base, though, is that if you're giving Dara-RVd, there is no intravenous drug administered, it's all oral or subcutaneous. Using Dara-KRd, now you have an IV drug in the mix.

Dr. Yee: True, I agree. But then again, in clinical practice, I just don't see that degree of cardiac toxicity that's been described in ENDURANCE or the renal toxicity. I also think patient selection is important.

Dr. Richter: I couldn't agree more. But again, the patients we're talking about now are younger and fitter, and with these patients, you don't have to pull punches, we give full-on therapy, quads, full dose – it doesn't matter. But let's turn the page for a minute to the transplant-ineligible, or better said, the older and/or frailer patients. So, what data do you draw from when figuring out an appropriate regimen for them?

Dr. Yee: Right. So, when I think about the older patient, for me, I think about the patient who would be considered transplant-ineligible; say 65 to 70, which is a large patient cohort in myeloma because average median age at diagnosis is 69. I tend to think more about the quad for those patients as well. I think about Dara-RVd once a week, bortezomib, 28 day cycle, again emphasizing the tolerability; it's just a well-tolerated regimen. Concerning dosing, when I think about quads for the older patients, I tend not to use lenalidomide. For example, with younger patients, 65 and younger, I might try to get them to stem cell collection and transplant, and then I would use lenalidomide 25 milligrams. For the patients that I don't think are candidates for stem cell transplant, then I think about using a lower dose, lenalidomide 15 milligrams. For that patient population, let's say 65, 75 years of age.

Dara-RVd is well-tolerated in transplant-ineligible patients

Younger patients following stem cell transplant: consider lenalidomide 25 mg for maintenance

Dr. Richter: No, let's go older, because we're going to sit here and I'd fight you on the transplant in a 75-year-old. Let's go octogenarian and up. So, you have an 80-year-old walk into your office. Are you still thinking quad or are you thinking triplet and what data can you draw from?

Dr. Yee: Okay. So, with an 80-year-old, I'm not necessarily thinking quad, but then the traditional debate would be, do you do like, daratumumab, daratumumab-lenalidomide-dex, or do you do like, RVd? That's, that's sort of the bar room banter. And I guess we would talk about that at a bar, wouldn't we, Josh? We would talk about that over drinks, right?

Dr. Richter: We absolutely would.

Dr. Yee: You know, most people talk about football, but I don't really talk about football – I'm not an athletically oriented person, but I would talk about Dara-Rd versus Rd. When the MAIA data[13,14] came out, I was more of an early adopter, because again, I do think about the peripheral neuropathy rate with bortezomib and I think about the schedule with Dara-Rd. Especially since Dara is now sub-Q, it's just an

easy regimen for patients. Now, if you want to go all in on the RVd-lite regimen, the amount of patient visits is much higher than if you do the Dara-Rd regimen. So, in my mind, I tend to lean towards Dara-Rd because there's less peripheral neuropathy, and it's just an easier, more convenient regimen for patients.

Dr. Richter: Absolutely. I think we have to give credit where credit is due because I think a lot of people are using RVd-lite and this comes from a longtime colleague of yours, Betsy O'Donnell, who published that data. We can draw from not only her RVd-lite paper,[15] but the SWOG S0777 trial.[16] I think you bring up a great point: a lot of us are early adopters, and we've been using RVd for many years. The randomized phase three of RVd versus Rd wasn't initially published until 2017[16] with a final assessment in 2020[17] from Brian Durie. I agree, I think DRd is a better triplet from MAIA, but there's a big bunch of caveats. When we look at RVd the way it was given in SWOG, they only gave the bortezomib for the first six or seven cycles, and then it was lenalidomide, regardless after that;[15] whereas MAIA is the triplet, Dara-Rev-Dex throughout.[13,14] And again, you can't compare trial to trial, but when you look at VRd from the SWOG trial, it's on 43-month PFS, whereas MAIA, I think the most recent data is around 67 months. I mean, it blows it out of the water. So, I would ask you a question, because I agree: for the older patients where transplant's not even on the radar, I give virtually everyone Dara-Rev-Dex. Is there still a patient that you would use an RVd-lite approach with, as opposed to Dara-Rev where transplant's not going to be a consideration?

Dr. Yee: Not necessarily. So, the question is, where would I use the proteasome inhibitor, right? For me, I build the CD38 antibody as a base, and if their functional status is decent, I add a proteasome inhibitor. If they had really nasty, bad clinical features or high-risk FISH, or t(4;14)/1q-gain, and if they have reasonable functional status, age 75, I would potentially try to squeeze in the proteasome inhibitor. But if I'm thinking, the 80-year-old who shows up with a cane, maybe the Dara-Rd would more appropriate.

Dose reductions may be beneficial in older patients

From a practical standpoint, in MAIA, if you look at the official label, it's all lenalidomide 25 milligrams. And I think 25 can be harder for older folks. For older folks, I think dose reduction off the bat to 15 milligrams once-a-week dexamethasone; if you looked at MAIA, I think they used 40 milligrams once-a-week. But for patients 75 and older, I feel 20 milligrams is easier with rapid dose reductions. I know there's a French study where they stopped Dex after a certain number of cycles, I think three or four cycles.

Dr. Richter: Larocca et al did Rd-R versus Rd, and after nine cycles, they went from lenalidomide 25 milligrams down to 10 milligrams and they got rid of the Dex altogether.[18]

Dr. Yee: Right. So, I think the key is, start at a lower dose of Len, rapid dose reduction. And I think that helps to improve tolerability and for patients to stay on the regimen. Now, SWOG used a fixed dosing of bortezomib, right? But if patients are on Dara and we're talking about the treatment schedule, they're supposed to be on Dara every month. So, Josh, are you using a GRIFFIN-style approach, where three years out of four, patients are still on Dara or are they on Rev maintenance? Are you still continuing the CD38 antibody?

Dr. Richter: You already started to talk about the fact that one of the big things we do to optimize outcome is not just the regimen itself, but dosing. I completely agree. For older patients, 15 mg is probably better than 25 mg for lenalidomide. Dexamethasone, I personally don't give anybody 40 mg, unless I don't like them; everyone gets 20 mg, sometimes 12 mg. I think the question that you bring up is a real tough one, which is, Dara-Rev-Dex is great; two, three years into it, am I still giving Dara? And I had this conversation with a patient yesterday, someone who's been on it for two and a half years, complete remission, doing great, and they want to stop it. I don't think we have that granularity yet: all else being equal, I continue treatment. I do think that we need to be mindful of other prophylactic strategies. For example, I've had a number of patients who had hypogammaglobulinemia from the Dara that I had to start on IVIG*. They're already on HSV/VZV** prophylaxis. I have a number of patients that I always start off with a plan of continuing the Dara, but I also have a number of patients who, even despite IVIG, still get recurrent respiratory illnesses. And with those patients, we have a discussion of the risk-benefit of continuing treatment. So, I plan to continue treatment until progression, but I have stopped it because it has a more complicated schedule than just being on lenalidomide and because of the infectious complications.

No data yet to support discontinuation vs continuous CD38 mAb therapy; consider prophylactic strategies that the patient is on

Dr. Yee: From actual real-world data, I think the continuation rate of Dara isn't 100% at year three. But in my practice, I've been continuing the Dara long-term at year three/year four, because at some point, the patients have gotten so used to it and it's so well-tolerated. I haven't heard much about patients discontinuing the Dara, although I do hear a lot about some of the other side effects related to lenalidomide, especially the GI side effects. In some patients, I think, continuing the Dara is easier than continuing the lenalidomide. But I do acknowledge that we don't have overall survival benefit from Dara maintenance; the bench of data supporting lenalidomide for maintenance is a lot deeper than it is for Dara.

Dr. Richter: I completely agree. When we're deciding our upfront therapies, I would completely agree, it's a CD38 base. How does this impact thinking about relapse? In fact, should we be stopping the Dara to preserve CD38 sensitivity for second line, or is the data so compelling about keeping it going, we just keep them on the CD38? Is there anyone that you make that decision that, you've done great for so long, I want to preserve sensitivity to a CD38 in the second or third line?

Dr. Yee: I was just having this discussion within our group about this: if you discontinue the CD38 antibody, then you presumably keep treatment with CD38 available down the road. But I don't know if I completely agree with that; I think I prefer the other line of reasoning: maybe the reason why they're doing so well is that they're on the CD38 antibody. So, then the question of relapse becomes moot, because they're still on the CD38 antibody, and the fact that they're still on that treatment pushes the relapse question further down than the idea of saving the CD38 for a possible future relapse. There was a point in time where people thought, well, maybe I don't want to give a CD38 antibody upfront because I can save it for later based on the POLLUX data,[19] but I don't know if I fully embraced that strategy. I prefer to keep it going because you want to use your strongest strategy first. There are multiple layers to this, though, right? If you follow the MAIA data, if you want to be a purist, that would be to treat until

*IVIG: Intravenous immunoglobulin
**HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus

relapse. But if you follow GRIFFIN, there was a discontinuation of treatment at cycle 32 and if you were a PERSEUS aficionado, you would be doing MRD testing at two years. Josh, are you doing MRD testing PERSEUS-style to decide whether or not to continue the Dara?

Dr. Richter: No, I'm not a full buy-in on the MRD testing just yet, but at least one thing that I think about upfront is the CASSIOPEIA study. Because in CASSIOPEIA, they looked at Dara-VTd versus VTd,[20] regimens which we don't really use in the US, and they had a second randomization in the maintenance to Dara every two months versus placebo. Again, it doesn't follow what we do in the US and more follow-up is needed. So, CASSIOPEIA used four groups: (1) Dara-VTd – no maintenance; (2) Dara-VTd – Dara maintenance; (3) VTd – no maintenance; and (4) VTd – Dara maintenance. And so far, comparing patients who were in either the Dara upfront or in the Dara maintenance arms, there was no improvement if the patient got Dara in both the upfront and maintenance, but the results were poorer in those patients who didn't get Dara in either treatment phase. So, I'm still on the fence about this. I tend to give more if I'm going to put you on lenalidomide long-term, and I guarantee you get a CD38 upfront. But otherwise, CD38 on the back end long-term, to me is how I want to make sure you're getting some CD38 as part of your upfront therapy. And again, I am still a purist, so treatment until progression or intolerance.

Dr. Yee: Right. With CASSIOPEIA, people interpret the results to mean that there's no benefit if you got Dara upfront and then Dara after the stem cell. And then the question becomes, why bother giving the Dara after stem cell transplant? But I push back on that interpretation because I feel that you do get a deeper response, if I recall correctly, if you're on Dara long-term. And I also don't think the follow-up has been long enough to see the actual differences. At the initial interpretation, there's no difference, but I think it's because the follow-up hasn't been long enough. Similarly, at one point people were looking at the MAIA data and saying, "oh, with daratumumab, there's no benefit in high-risk", but that was at the initial reporting. On a more mature, longer follow-up, you actually do see the hazard ratio for high-risk improved. So, my initial take on CASSIOPEIA, is that, with longer follow-up, maybe we'll see that benefit revealed over time. But you're not convinced, Josh.

Longer-term follow up is needed to determine the impact of Dara maintenance on outcomes

Dr. Richter: I'm just not convinced that we're there yet. I'm still going to stick as a purist. But you've got two minutes for a lightning round, rapid fire your two or three main points. If you had someone in a room, you're sharing your vast knowledge on myeloma and you want to give them a couple of bullet points for their next newly diagnosed myeloma patient that walks into their office. What's going to be at the top of your list?

Use the best treatments, the CD38 mAbs, in the upfront setting; do not reserve for later lines of therapy

Dr. Yee: At top of the list is, use your best options first, use your best treatments first. I think a CD38 antibody is one of our best treatments; the time to use it is use it now. I wouldn't save it for later. And then the second point would be to think about dose modifications to suit the patient. Think about the lenalidomide dosing, the dexamethasone dosing. If you're incorporating bortezomib, pay attention to peripheral neuropathy. While the clinical trials all give

Modify treatment dosages for the individual patient

bortezomib twice a week, I think in clinical practice, once a week is easier. A lot of this is about customizing treatment to the patient in front of you.

Dr. Richter: Absolutely. The two points I would add are, in myeloma, we're still not at the exact personalized medicine level where we're giving a patient with a specific mutation, a specific drug, for the most part. But as you brought up, personalization is not just the choice of drugs, but the dosing: dose reducing lenalidomide and dexamethasone in the older patients. The other point that you brought up that I completely agree with is about the attrition rate in myeloma. We lose about 5% of patients between diagnosis and frontline, and for each subsequent line, we lose about 25 to 35% of patients. So, if you have a good drug to use, or you think a drug like a CD38 is going to be optimal, it's not a drug to save for a rainy day – because, unfortunately that rainy day doesn't always come. So, moving the most effective therapies up front.

Consider dose reduction of lenalidomide and dexamethasone in older patients

Attrition rate in MM can be high, so use the best treatment in the upfront setting

And as that is a segue, we really want to thank everyone for tuning in, and please tune into our next podcast where we'll delve into the landscape of relapsed and refractory myeloma. We want to thank you so much for joining us for our foray into CD38-targeted therapies in the frontline setting. If you have any questions concerning any of the information that we've talked about today, simply scan the QR code below and submit your questions. Questions will be answered in a series of e-newsletters following the podcast series. To claim credit, please complete the CE evaluation. By watching the other episodes in this podcast series, you'll gain a comprehensive understanding of the role of CD38-targeting agents in multiple myeloma. Thank you.

We hope you found this discussion informative and insightful. If you have any questions about the content discussed, please scan the QR code or visit https://www.surveymonkey.com/r/RZX232S to submit your questions.

Questions will be answered in a series of e-newsletters following the conclusion of the podcast series.

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