The Cutting Edge of Multiple Myeloma: The Evolving Role of CD38-directed Strategies

How the Journey Might Change: Emerging Concepts, Future Directions and CD38-targeting Agents in MM

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Joshua Richter: Hello and welcome to the third and final episode of our 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. And joining me today is my esteemed colleague and friend, Dr. Andrew Yee. Andrew, please introduce yourself, sir.

Andrew Yee: Thank you, Josh, for the introduction. And I'm Andrew Yee. I focus on multiple myeloma at Mass General Hospital. I'm the Clinical Director for the Center here. And I'm also an Assistant Professor of Medicine at Harvard. Thank you, Josh, and looking forward to wrapping up our discussion about CD38.

Dr. Richter: Absolutely. So, today we're going to delve into some of the emerging concepts and future directions of CD38-based therapies in the treatment of myeloma. If you haven't seen our first two episodes, please tune in to them to gain some new perspectives on the role of CD38-directed therapy, both in the upfront setting of myeloma as well as the relapsed refractory setting. Our learning objectives in this episode are going to focus on what's next in the realm of CD38-directed therapies. What are some of the new clinical trials and strategies that will exploit this concept? How can we ensure that we have diverse inclusion and equity across the board so that all our patients are able to access these wonderful new therapies?

Let's start from there. Andrew, where do you see CD38 therapies going next?

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Dr. Yee: Right. I think it's been amazing to see, since the first CD38 antibody was approved in 2015, how it's emerged as one of the foundational drugs in myeloma therapy; they've definitely earned their chops as one of our core classes of drugs. We've talked in our earlier podcasts about newly diagnosed patients and about relapsed patients; given how core it is, I can see CD38 antibodies being a continual component of new therapies as they emerge. Since 2020, we've had five drugs which have been approved, targeting BCMA or GPRC5D. To continue extending our theme about the dance partner, CD38 antibody will continue to be a great partner with these therapies.

Dr. Richter: I think you can't talk about myeloma in 2024 without talking about T-cell redirection therapies. And you know, CAR Ts are really exciting, but to me, I'm a big fan of the bispecific antibodies. They're off the shelf, they're highly effective and they don't require a big myeloma institution like yours or mine. They can be given literally anywhere, which means they're available to anyone. I'm really excited to see some of the combinations of the bispecific antibodies and the CD38s. Do you have any particular insight or preference of combo there?

Bispecific antibodies in MM are off-the-shelf, highly effective and can be given in the community setting

Dr. Yee: Right. So, to set the stage, we've been talking about CD38 antibodies, but, along with CD38, there are other core cell surface proteins, including BCMA and GPRC.[1] Right now, we have two bispecific antibodies targeting BCMA and one bispecific antibody targeting GPRC5D,[1] with more in clinical development.

Bispecific antibodies (BsAbs) target the BCMA, GPRC5D core cell surface proteins in MM.[1]

Teclistamab, elranatamab are BsAbs targeting BCMA; talquetamab is a BsAB that targets GPRC5D.[1]

When we think about these myeloma therapies, they're often presented as if they're used as monotherapy. This is similar to how lenalidomide or bortezomib are sometimes presented as single agents combined with dexamethasone. But the reality is, as we've talked about and bantered about, these drugs are all given in combination, to ensure that we unlock their potential. CD38 is a cell surface protein on plasma cells, but it's also present in other parts of the immune environment. There is a preclinical basis where, if you target CD38, you can potentially change the immune system to augment the activity of these bispecific antibodies that target BCMA or GPRC5D. You might be a bit closer to this, Josh, but I think about the MajesTEC data, which looks at daratumumab combined with the BCMA antibody teclistamab[2] and about the TRIMM data looking at the combination of daratumumab and the GPRC5D antibody talquetamab.[3] And in those two studies, we've seen some amazing responses, especially with patients who are CD38 antibody-refractory, suggesting that there are combinations in which the CD38 antibody can augment the activity of these bispecifics.

MajesTEC-3: phase 3 trial of teclistamab + daratumumab in RRMM[2]

TRIMM-2: phase 1b trial of talquetamab + daratumumab in RRMM[2]

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Infections, severe hypogammaglobulinemia can occur in MM patients treated with anti-BCMA BsAbs.[4]

In the previous podcast, we talked about the fact that you can combine CD38 with almost everything. One point of caution, though, involves combining CD38 with BCMA antibodies, which can be immunosuppressive; an increased risk for infection with hypogammaglobulinemia is intrinsic to BCMA therapy.[4] Because of this, you have to be more thoughtful when you combine CD38 antibody with BCMA therapy, due to the potential for increased immunosuppression, risk of infection. Despite this need for caution, the fact that CD38 antibodies can have some synergy in augmenting anti-myeloma activity is very promising. Other partners, like GPRC5D, have a reduced risk of immunosuppression, just by nature of where it's expressed.[5] BCMA is expressed on plasma cells, but it's also upstream, on other immune cells as well, whereas GPRC5D is expressed more in the plasma, reducing the risk of immunosuppression. You need to consider the risk of immunosuppression, but I think that CD38 will be a part of many of these combinations in the future, primarily because of the amazing synergies we've seen in clinical trials.

Less risk of immunosuppression with anti-GPRC5D BsAbs, based on location of GPRC5D expression.[5]

MajestTEC-3, teclistamab in patients with 1-4 prior lines of therapy;[6]
MagnetisMM-5, elranatamab in patients with 1-4 prior lines of therapy;[7]
MonumenTAL-3: talquetamab in patients with ≥1 prior line of therapy[8]

That's one aspect. Ongoing clinical trials are looking at teclistamab, talquetamab and elranatamab, all of which have been approved for patients who have received at least four prior lines of therapy. But trials are ongoing, looking at using these drugs in earlier treatment settings, after one to three prior lines.[6-8] And many of the combinations being evaluated are with CD38 antibodies.

So, that data is ongoing in phase three studies; I'm excited to see how they'll read out. Moreover, we also have trials looking at combinations of BCMA and CD38 antibodies in the upfront treatment setting, in newly diagnosed patients.[9,10] Again, this just speaks to the importance and efficacy of targeting CD38.

MajestTEC-7: teclistamab in NDMM patients;[9]
MagnetisMM-7: elranatamab in NDMM patients[10]

Dr. Richter: Absolutely. There's a lot to unpack. If we look at monotherapy with the bispecifics, most of them have response rates of around 60 to 70%. When we look at some of the TRIMM data, of combos with CD38, some of those early studies have response rates of over 90%. But to your point exactly, some of the physician scientists at our institution looked at responses to COVID vaccination, and, it turns out that, the two biggest predictors of inability to mount an effective COVID antibody response were BCMA-based therapy and CD38-based therapy.[11] So, I think your

Two biggest predictors of inability to mount an effective response to COVID vaccinations were BCMA-based and CD38-based therapies[11]

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word of caution needs to be stated again, because it's one of the most important things we should be thinking about: these are both highly effective therapies, but their immune suppression is notable. I think a better combination of CD38 is with talquetamab, the approved GPRC5D bispecific; other GPRC5D bispecifics like forimtamig are in clinical trials.[12] One of the things we see there, exactly as you pointed out, is that talquetamab and other GPRC5D bispecifics don't deplete the CD19-positive B-cell population, which is probably one of the primary reasons that these drugs have fewer infectious complications.[5] You can get immunoglobulin recovery while on GPRC5D, as opposed to the BCMA backbones, which lead to persistent hypogammaglobulinemia.

Forimtamig (RG6234) is a GPRC5D x CD3 T-cell engaging BsAb[12]

GPRC5D BsAbs do not deplete CD19+ B-cell populations, supporting fewer infectious complications[5]

So, I agree, I think CD38 plus a bispecific is a great combination; I do think that I'd prefer the combination of GPRC5D and CD38. To your point, I think, with all of the T-cell redirection therapies, it's possible that we may be moving even farther away from autologous transplant. We have some wonderful studies looking at the combinations of bispecifics plus CD38s earlier in therapy; really, really exciting data.

Dr. Yee: Just from what we see in the clinic, these are amazing, exceptional responses. And I do think that we're still in the alpha stage of using these drugs, right? Maybe version 0.9, because I'm sure that, as we get more experience using them, we'll be better prepared to address the risk of possible adverse events. It's possible that making dose adjustments, in terms of frequency and schedule, may help minimize some of these potential infectious complications, as well as maximizing responses. I think once you do have a response, these responses are amazingly durable. We're all excited to see the randomized data, to see how this plays out.

Dr. Richter: I'd love to hear your thoughts about other CD38 combos with some of the up-and-coming CELMoDs (Cereblon E3 Ligase Modulators). What are your thoughts about some of that data?

Dr. Yee: Yes. We've been talking about lenalidomide and pomalidomide as the established immunomodulatory drugs, but the next exciting developments in terms of that class are drugs like iberdomide[13] and mezigdomide.[14] When you think about lenalidomide and pomalidomide, those drugs were not developed for myeloma. They were developed looking at TNF alpha inhibition, and we accidentally walked into the fact that these are amazing drugs in myeloma. It's how many of the drugs that we use, like Ozempic, are often repurposed for other uses. But now that we know the mechanism of action of these drugs, that they act through cereblon, Ikaros and Aiolos degradation,[15] I think it's possible that iberdomide and mezigdomide could potentially be the next big wave of myeloma therapy – because those drugs were specifically designed to leverage off knowledge gained

CC-220-MM-001: phase 1/2 trial of iberdomide in RRMM[13]

CC-92480-MM-001: phase 1/2 trial of mezigdomide in RRMM[14]

IMIDs bind Cereblon (CRBN), modifying its substrate specificity and mediate degradation of Ikaros (IKZF1) and Aiolos (IKZF3)[15]

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from the IMID agents. As a result, the new drugs have more activity than lenalidomide and pomalidomide, and some of the emerging data looking at combining CELMoDs with CD38 antibodies looks really promising.

And there's a part of me that says, why not combine them? There's a little bit of empiricism in this, as well. We do need to be mindful of possible adverse events with these combinations. In our last podcast, we were talking about pomalidomide and how we do see more neutropenia when a CD38 antibody is combined with pomalidomide, for example. I think we'll have to have similar considerations when CD38 antibodies are combined with the newer CELMoDs; we'll probably have to pay attention to the myelosuppression. But again, I think, with careful attention to dosing and supportive therapy, we can have amazing efficacy; if you can maintain the effort, you can have great responses.

CELMoD-CD38 mAbs combinations: monitor dosing, provide supportive therapy

Dr. Richter: Absolutely. So, if people have tuned in, not just to this podcast, but to what we talked about in the others, we'd all agree that the research world of myeloma is exploding and that we have many options, so many highly efficacious drugs in clinical trials. I can remember when I first started out in myeloma, we'd have 10 clinical trials open and if one of them kind of worked, we were excited.

Now we have 30 plus trials open with drugs we know already work. But one of the things we really want to address is how everyone can benefit from these new advances. Myeloma affects a diverse population and we need to ensure that all of our patients, regardless of any other defining factors, have access to these wonderful therapies. So, this is a bit of a tough question, but I want to throw it to you first: any thoughts about how to optimize diversity, equity, and inclusion in getting some of these amazing new therapeutic options to the widest array of patients possible?

Dr. Yee: I think it's fundamental that we're able to see how these drugs work across the broadest range of patients as possible, not just narrowly restricted to one group of patients. And I think in this way, you can have a better understanding of the efficacy of these drugs and potential side effects, right? If we only look at new agents in a certain population, we don't know about the potential range of adverse events. We really won't have a full understanding of how to best use new drugs, in terms of the dosing and potential side effects, until we've evaluated them in as diverse a range of patients as possible. It's key that, when we're enrolling patients in clinical trials, especially, we're thinking about patient diversity. As you know, multiple myeloma tends to be more common in patients with African ancestry;[16] I think that fact isn't fully appreciated. I do feel something that the multiple myeloma trial community is trying to actively address, is what steps we can take to ensure that the patients in our clinical trials accurately reflect the real-world population that this disease affects.[17]

MGUS, MM incidence is twice as high in African Americans as in Americans of European descent.[16]

Recent review of 112,293 patients recruited in 230 oncology trials: only 3.1% of patients were blacks and 6.1% were Hispanics (compared to 76.3% whites).[17]

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Some of the things that I think about involve patient support: it takes a lot of work for a patient to participate in a clinical trial. I think simple things that we could do would include coverage for transportation, for example, and support for housing –things to make the logistics of participation as easy as possible. Or, if you could arrange subsidies, such as financial assistance for housing,[18] that could go a long way to increasing patient diversity in clinical trials. You just don't want logistics to be the limiting factor, right? You don't want a situation in which only patients who have the resources to participate, can have access to these potentially amazing therapies.

Strategies addressing geographic, financial, socio-economic factors (i.e., travel subsidies, housing support) may increase racial, ethnic minority trial referrals[18]

Dr. Richter: Absolutely. You've brought up a great point, in that geographic, financial and socioeconomic reasons may provide barriers to clinical trial participation. There are a number of ways that we can attack this; one of them is absolutely providing some degree of travel assistance or subsidy; something to allow patients who may have difficulty traveling to the academic center to participate in these clinical trials.

Community oncologists, hospitals for long-term care & use of centralized CROs can support improved diversity in clinical trials.[18]

The other approach is to utilize our community oncology colleagues and satellite sites. Not every trial needs to have everything done at the main center.[18] So, shared responsibility where, perhaps for a bi-specific or CAR T, we give the initial phase at the main hub that has more research-rich facilities, and then partner with our community colleagues to continue long-term care. Using centralized CROs and data gathering allows the trials to spread out farther than just at the main hub, and can be a real way to expand access across diverse patients.

The other point that you brought up, which is a major issue, is that, we certainly notice a higher incidence of multiple myeloma-related disorders in patients of African and African-American descent. Now, we've talked about this in earlier podcasts, about the profound nature of cytopenia, specifically neutropenia that we see. We do know that patients of African and African-American descent can actually have a lower normal range of white blood count than patients of Asian or Caucasian descent.[19] This used to be called benign ethnic neutropenia, but that term has gone by the wayside now that we've found a genomic underpinning; now we call this the Duffy-Null status.

Duffy-Null status is the term for reduced neutrophil count seen in patients of African, African-American descent.[19]

The next generation of MM clinical trials will include Duffy-Null status.[20]

Because of this, we've started to incorporate Duffy-Null status testing for our patients. And in the next generation of clinical trials for myeloma, the inclusion/exclusion criteria may address this.[20] Current clinical trials may say, if you have an absolute neutrophil count (ANC) below 1,000, you're not eligible to participate. The next generation of trials will have additional criteria for patients who have a Duffy-Null status but still have no increased risk of infection; these patients may

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have ANCs down into the 800, 700, or even 500 range, but, because of definitions of Duffy-Null status, they may still be able to participate in a trial.

I think there are a broad range of approaches we can take to ensure that we're able to provide all of these great therapies with the singular focus of cure, to make sure that everyone has equal access, as much as possible.

Dr. Yee: I agree, I think the Duffy-Null status is critical because we need to focus on individualizing treatment for our patients. In terms of being able to enhance a patient's eligibility for clinical trial participation, I think it's critical.

Dr. Richter: Absolutely. Moving on, I know this is a large topic to unwrap in a short period of time, in our final few moments, but it's one of the biggest hot buttons in myeloma: I would love to get your take on MRD, minimal residual disease testing. How do you currently utilize it in your practice?

Dr. Yee: I think MRD is a big, big topic of discussion. Much of what we've been talking about in these podcasts involves adding therapies: doublets, triplets, quadruplets, adding this, trying that. But, I think that one of the next waves of myeloma therapy is to figure out how we can de-escalate therapy. How can we identify patients where you can pause treatment? Some patients may be cured, and we just don't know it; I think MRD testing may be an important tool to help us identify the patients where pausing treatment may be a viable course of action. One of the potentially exciting developments with MRD testing involves the type of MRD test. MRD is a sensitive test for underlying disease, right? Conventionally, MRD requires a bone marrow biopsy to look for $1x10^{-6}$ level of cells, and I think the next phase in MRD testing may be peripheral blood MRD. We now have a few commercial laboratories for peripheral blood MRD testing, and the results of this approach to MRD potentially rivals traditional bone marrow and next generation sequencing-based results.

For me, and for patients obviously, one of the main limitations to doing MRD testing is that you need a bone marrow biopsy. If you can get the same knowledge from peripheral blood tests, that could be a game changer. Right now, we have this tool, but we don't have the data to identify its best use, how to use it to identify in which patients we can de-escalate therapy. We briefly mentioned the PERSEUS study in the first podcast, and in that trial, they used MRD testing to guide therapy. In PERSEUS, you had the option of discontinuing daratumumab in patients who were MRD-negative after two years.[21]

The PERSEUS trial used MRD-negative status to discontinue daratumumab.[21]

But we may be able to use MRD testing in an even broader way; it may help us to identify those patients in which we can potentially discontinue all therapy, right? We need to have the test, and the data to support using the test, and then we need to decide, is it MRD at just one time point? You might need to demonstrate sustained MRD. And maybe you need to couple MRD results with imaging. Clearly, there are multiple layers of this, but I think it will be exciting to figure out, so that we can eventually say to a patient, "You know, Mrs. Jones, you can come off therapy." I think patients would love to have that opportunity.

Dr. Richter: Yes, this is one of the successes of modern-day myeloma therapy and myeloma research. You know you're doing better in a cancer where you're focusing on de-escalation. I think we've seen this in

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Hodgkin's disease, germ cell tumors, and a number of other cancers; whereas most cancers are solely focused on the need to improve because the outcomes are poor. When you get to a point where we're thinking about how we can back off treatment, that's a sign that you're making good headway. Because I completely agree with you: at the end of the day, we just want Goldilocks. We don't want the porridge too cold where the patient progresses, but we also don't want it too hot. And we all have patients who've been on maintenance therapy for a decade and we're afraid to stop it, but we also don't think they really need it.

SWOG s1803 DRAMMATIC study: Phase 3 trial of Dara-Rev vs Rev post-ASCT maintenance using MRD to direct therapy duration.[22]

One of the studies that I'm very anxiously awaiting the readout is the SWOG s1803 DRAMMATIC study being run by Amrita Krishnan where she's doing exactly what you talked about. She's looking at Rev versus Dara-Rev in the maintenance setting, with MRD stopping rules along the way.[22] And as you said, it may be that this data matures and we know that, if you have a standard-risk patient on lenalidomide who achieves sustained MRD-negativity, maybe that patient does similarly with or without continued lenalidomide. Ultimately, we can get similar outcomes but better tolerability, perhaps fewer secondary malignancies, and obviously a cost savings of not having to give continual therapy.

IMF 2009 trial: RVd + transplantation associated with significantly longer PFS than RVd alone.[23]

So, I think MRD is a wonderful tool to help us decide whether we need more treatment, or do we need less. I, for one, use it as part of a discussion with patients, pre-transplant. I think we're starting to learn from a number of trials like the IMF 2009 that, if you achieve MRD-negative with induction, in some scenarios, you may do just as well with or without a transplant.[23]

If I have a patient who is high-risk, doesn't get a great remission and they agree to a transplant, I push forward with transplant. Or, if I have a patient who tells me, "You know what, I don't want a transplant", I don't push for it; I don't force it on anyone. But we all have patients who want to make the most informed decision, based on the risks and the benefits. And for those patients, we often do a bone marrow biopsy and have a discussion that Dara-RVd is so good that if you get MRD-negative, maybe you don't need a transplant, but if you get a quad like that and you don't get rid of all of the disease, you're someone who may need a different modality, like high-dose melphalan to get that better outcome. Are there any other clinical scenarios that you're using MRD in the clinic today?

Dr. Yee: I think you've covered the key areas where it's being used, in terms of discontinuation of therapy versus escalation of therapy. Another big, big black unknown area involves patients who are on maintenance therapy: if a patient is on maintenance and they go from MRD-negative to MRD-positive, do you escalate therapy? Right now, that's uncharted territory. But we do have the AURIGA study, which is looking at escalation of therapy after daratumumab as the CD38 antibody plus lenalidomide versus lenalidomide after initial therapy in MRD-positive patients.[24] It's uncharted territory and we're really looking for more clinical trial data.

AURIGA: subQ Dara-Rev vs Rev as maintenance, escalation of therapy in MRD-positive patients.[24]

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Dr. Richter: Absolutely. So, just like we did in the last two podcasts, you have a heme/onc doc who's about to leave for the day, and you have a few minutes with them to share your immense Ivy League wisdom. What are a few main points that you'd want to get across about the future of CD38-directed therapy in myeloma?

Dr. Yee: Right. The horizon is so broad and the future is so promising for our myeloma patients. I think the way we're using CD38 antibodies is going to change in the future, thinking about the available dance partners that we have for CD38, in terms of combinations with bispecific antibodies, CELMoDs, maybe with a BCL2 inhibitor. And there are different strategies that can emerge based on these combinations. It's a rapidly changing, exciting field and I feel fortunate to be living and working in myeloma right now, where we can see so many rapid developments. That's why I feel excited talking about this, so thank you, Josh.

New combinations with CD38 and BsAbs, CELMoDs are emerging

Dr. Richter: Absolutely. I couldn't agree more. When I started treating myeloma, I used to tell people that it's not a curable disease. Now there are a handful of patients that we are curing – for lack of a better term, by accident. We give them the therapy and it turns out that we actually cured them. And the future is curing more, and eventually curing everyone deliberately. The answer in a disease that's subclonal at its fundamental level, is to use regimens that combine multiple mechanisms of action, exactly as you talked about. New agents may get approved as monotherapy, but the combinations are where it's at. And with the efficacy and tolerability profile of the CD38s, they're going to be part of treatment, either as combinations with bispecifics or trispecifics, consolidation after CAR T, induction prior to CAR T. They're certainly going to be part of the puzzle that we need to put together, to find the secret sauce for everyone.

Combinations of therapies with multiple mechanisms of action are key in a subclonal disease

And with that I would like to thank everyone for joining us for this exploration of emerging concepts in future directions of CD38-targeting therapies and multiple myeloma. We hope that you found this information informative and insightful. If you have any questions about the content or information that we've talked about today, simply scan the QR code and submit your questions. All questions will be answered in a series of e-newsletters following the podcast series. Please don't forget to complete the continuing education evaluation to claim your CE credit and be sure to download the reference resource associated with this podcast. Finally, if you've missed any of the previous episodes that are amazing with Dr. Yee and myself, please be sure to check them out for a complete picture of CD38-targeting strategies in multiple myeloma. And on behalf of Dr. Andrew Yee and myself, thank you for tuning in, and be well.

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