NEW HORIZONS IN MULTIPLE MYELOMA TREATMENT: THE PROMISE OF CAR-T FOR EARLY RELAPSED DISEASE

MED TABLE TALK™ SPECIAL EDITION

Saad Z. Usmani, MD, MBA, FACP: Hello and welcome to a Special Edition of *Med Table Talk* where we will discuss the latest developments for the earlier use of CAR T-cell therapy in multiple myeloma and the clinical implications of these findings to your practice.

I'm your host, Saad Usmani, from Memorial Sloan Kettering Cancer Center in New York, and I'm happy to be joined by my esteemed colleagues Dr. Melody Smith, Dr. Krina Patel, and Dr. Sanjay Sharma.

Please, Dr. Melody Smith, introduce yourself.

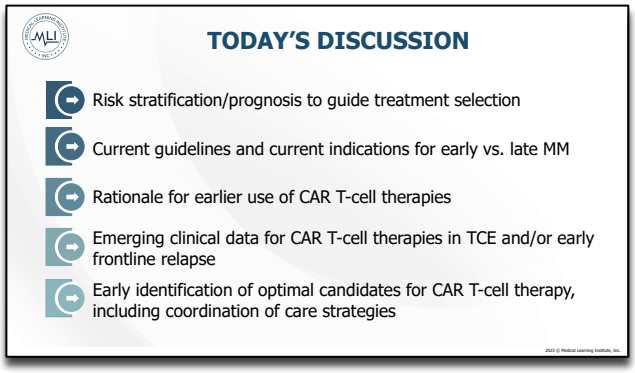
Melody Smith, MD, MS: Hi, my name is Melody Smith, and I am a Physician Scientist at Stanford University in the Division of Blood and Marrow Transplantation and Cellular Therapy.

Dr. Usmani: Dr. Patel.

Krina K. Patel, MD, MSc: Hi, I'm Krina Patel. I'm Associate Professor at MD Anderson Cancer Center in Houston and run our myeloma CAR-T program.

Dr. Usmani: Dr. Sharma.

Sanjay Sharma, MD: Hi, I'm Dr. Sanjay Sharma. I'm a Medical Oncologist and Hematologist in sunny Southern California in Orange County. Pleasure to be here.



TODAY'S DISCUSSION

Dr. Usmani: Thank you so much. In today's episode, we are going to be going over risk stratification and prognosis to guide treatment selection in multiple myeloma, we'll look over current guidelines and current indications for early and late relapsed myeloma, we will look at the rationale for early use of CAR T-cell therapies as well as emerging clinical data for CAR T-cell therapies and T-cell engagers and see whether it makes sense to move one versus the other into the frontline treatment. We'll also look at early identification of optimal candidates for CAR T-cell therapies, including coordination of care strategies between academic as well as community sites.

And in this episode, we really want to focus on, you know, each of these areas and perspectives from the community standpoint and provide, you know, input and pearls on how best to coordinate the care of myeloma patients in the context of these new immunotherapies.

Dr. Usmani: Yeah. And then, you know, we now also talk about, you know, the differences between what we consider high risk and then, you know, ultra-high-risk disease, right. So, Dr. Patel, can you, you know, tell us how to distinguish between the two?

Dr. Patel: Yeah. I think this is a great conversation and, you know, why it's so important that all our patients at diagnosis get these tests done because it really does tell us the difference between my patient that's coming to me that, you know, is going to do really well for 10 plus years versus my patient that's going to relapse in a year and I sh-, maybe should have done something differently, and I think ultra-high-risk, right, double hit. Unlike double-hit lymphoma, we talk about double-hit myeloma hasn't caught on as much, but we talk about ultra-high risk where you have more than one high-risk cytogenetic aberration, you know, 4;14; 14;16; 14;21q, and deletion 17p. And usually, we'll see 1q with 17p or 1q with 14;16, but I've had patients with 14;16 and 17p. When I see that at diagnosis, even if the patient looks really great in front of me and doesn't have a big tumor burden, that itself makes me watch that patient much closer.

And there's been retrospective studies done that have shown that patients with double hit tend to have a much shorter median progression-free survival, and overall survival, then those who have, you know, either no high-risk cytogenetic abnormalities or one.

So when we talk about patients, you know, our usual is talking about lines of therapy. I think that's going to change, especially with data like the MAMMOTH study, which is looking at patients who've had either, you know, all three PI, IMiDs, and CD38, exposed or refractory, versus even penta-refractory with, you know, both PIs and both IMiDs and CD38. Usually these are standard risk patients that are exposed and either refractory to all these drugs; they have the worst outcomes in terms of overall survival and median progression-free survival. And I think we use this as our landmark, right, for our studies now in the relapsed/refractory setting that if we can beat this with new therapies, then those are really drugs that we should be looking into further for our patients.

Dr. Usmani: You know, I agree, Krina. I think, you know, we must consider both the drug exposure and the impact of disease biology and, again, recognizing that myeloma is not one disease and there is continual disease evolution, you know, over time as well in these patients because we're selecting out the more difficult to get rid of clones in our patients by giving them therapies.

So open kind of question to all my colleagues, I can start with Dr. Sharma, you know, how we can address some of these challenges as we see patients in the clinic.

Dr. Sharma: Yeah. So, Saad, yeah. So you're bringing up excellent questions, and I'll say the way that I approach all oncology I call it the pillars of oncology how I, how I explain it to my patients, and it's based on two questions. The first question is, "How dangerous is the cancer?" – I'll keep referring to this – "And how do you manage a cancer?" And that, and that's kind of the pillar holding up the cancer.

So the discussion that we're h-, we're having here right now is a discussion amongst oncologists on how we study the disease defining the danger of the disease, okay. So let's think about it when we're in a patient room. The more esoteric thing, like Krina was talking about, well, shoot, when you're diagnosed with cancer, you don't look at your own body. Your fatigue is not telling you you have a 17p deletion or, you know, you've got 11;14 and you're going to do great on the venetoclax, or whatever it may be. And that's where we come in and try to recognize all of this.

And then, then when we got to the pillar of the danger of the cancer, to the extent of how I understand it as an oncologist, how scientists and researchers identify it in terms of getting research trials and how we interpret it to the patients, we then move into how you treat this. And now we're going to talk about, "Well, shoot, what can we do with modifying the B-cells? How do we introduce CAR-T? What else can we do to fit this

management, how to treat this cancer in regard to now that we're smarter and recognizing how dangerous it is."

Dr. Usmani: No, very well said, you know, Sanjay, and, you know, I, I'm going to, you know, ask Melody and Krina if they want to, you know, add their own experience of how they, you know, approach these conversations with patients. But you're absolutely right, you know, there is a lot of information out there as well, so, you know, there are patients that they've heard about different things, and they're getting worried about what does this deletion 17p thing really mean? And, you know, many times it's, you know, it's that role that we have in helping alleviate, you know, provide measured hope and information about what they've really got.

Dr. Smith: Right. You know, I would just dovetail on what Sanjay mentioned in terms of, you know, thinking about how some of this understanding of triple versus quad, penta-refractory exposure has on the long-term response and overall survival of the patients. I think that also comes into play with the discussion, as he was mentioning, about the sequence of the therapies and some of the cellular therapies or even bispecific therapies that can be offered to patients.

And, you know, thinking about the time that it takes to manufacture, for example, CAR T-cell therapy, you know, I think a strong consideration is bringing those, you know, not necessarily just to the penta-refractory which their survival is limited because of their exposure to all these prior lines of therapy, but trying to make sure that we're choosing the patients in terms of what we know about how that, their prior exposure can impact their long-term survival and doing it in a time frame where the product can be manufactured and the patient can get it and actually, hopefully, benefit from it. So, I think that's something that this type of data really helps us to understand and incorporate.

Dr. Patel: Yeah. And I completely agree with everybody so far. And I think that the biomarkers that we have are great, but I also tell my patients that just because I'm putting you in this box doesn't mean your outcome's going to be bad, right? I think that's just as important to talk to our patients about that the whole point of this is that we can get you, as Melody said, some of these novel therapies earlier that we might be able to change your outcomes from what's, you know, in the last 5, 10 years. And that's what the history of myeloma has been that our high-risk patients if we can do better for them, we know our standard-risk patients are going to do better. They always do better, but how do we really help our most vulnerable group? And I think that's sort of what we're going to talk about in, you know, there, the next few studies that we discuss too. It's just putting that in perspective that this, these guidelines are really to help us figure out how to do better for them.

Dr. Usmani: Then I want to pivot back to Sanjay for a bit because, you know, I think it's very important to appreciate that there is a lot of value in this, you know, in the community academia partnership in taking care of patients, especially as they get into the later lines of treatment. It's important to have that, you know, comfort in the back of the mind, you know, for our community colleagues that they have, you know, folks, you know, on standby to help them, you know, in terms of caring for their patients. So any thoughts there, Sanjay?

Dr. Sharma: Yeah. So, from the patient perspective, again, they don't necessarily need to see what's going on in the background. They should have one focus and one focus only, which is themselves, which is their family, and what their vision is, and what their goals are. And you're right, it, it's a team sport for us. I mean we'd be foolish. We'd be, none of us live in a kind of a silo of, you know, individualism. That doesn't exist. That's not how oncology works. It's work in a partnership.

And Melody correctly and so hit on how important it is nowadays in oncology of logistics, not just in myeloma but it's in every disease class because we have novel agents. So, Melody said, "Well you got to make the darn drug. You know, you got to teach the cell on what to do and how for it to work." Okay, fine, I get the technology. Okay, fine. Now I got to, you guys got to pherese the person. You got to give the lymphocyte depleting stuff. That's time.

And, Saad, what you're talking about is well logistics. How am I going to get my patient to, you know, the Saad in my local area, the Melody in my local area, the Krina in my local area? We're all practice in different parts of the country. And that's an added thing. How do you get the insurance approval? Can you get it going? And, also, quite realistically is educating the staff on what it means.

So, we are used to forever doing second consults to tertiary care centers. We are used to having conversations texting our colleagues, but now there literally must be a means where we're saying, "Hey, you know what, this patient is going. Now we can carry the same route that we've created with transplants in terms of how we have the relationships and we're going to cellular therapy now that this is, there's another therapy." So going to your point, Saad, yeah, we are all in this together and it'd be foolish for us not to have a fantastic relationship to help our patients.

Dr. Usmani: Thanks for a very, you know, eloquent, elaborate response, Sanjay. As we think about the different treatment options our patients have at the time of early relapse, you know, we have come a long way in the field. So there is a lot of hope for that early relapsed setting, you know, there are many different things that we can try. But as we get into later relapses, you know, I think that's where the challenge, you know, becomes of, you know, what options to give to our patients. And this is where I think the B-cell maturation antigen or BCMA-directed strategies have really come into play in the past two and a half, three years but, you know, now we have these two CAR T-cell therapy products, ide-cel and cilta-cel or idecabtagene vicleucel and ciltacabtagene autoleucel. Yes, it took me a long time to actually practice, you know, churning out these names. And we now also have, you know, more recently as of October of 2022 teclistamab, which is our first BCMA-directed bispecific antibody.

Each of these therapies, you know, are currently approved for patients who've had four or more prior lines of treatment and have had an immunomodulatory drug proteasome inhibitor and anti-CD38. You know, and at many forums, you know, we have, you know, these conversations and debates, "Okay, which patients are better for one therapy versus the other? Will we ever overcome the logistic issues? How best can we partner with our community colleagues?" because more than 80% of the myeloma care is being given by our colleagues. You know, it's not at academic centers, so how do we make this worthwhile for our patients?

You know, I think it's a very, you know, interesting challenge that's posed to us, but, you know, also lot of opportunities to work closer together. So, you know, any thoughts from my colleagues, you know, with regards to this before we re-, really dive into the data?

Dr. Patel: I agree. I think it's fantastic that we've, you know, come such a long way. And when fellows come into my clinic to see patients with me and someone needs new therapy, we literally are like, "Okay, which one shall we pick?" It's really nice to be able to sort of personalize treatment right now. And I think, you know, CAR T-cells will be really personalized 'cause we're taking your own T-cells in doing this.

Yeah, I think that that partnership with community is so important that when my patients, you know, they want to be able to live where they live where their family is. And the only way we can do that to make sure their outcomes are good in terms of quality of life, quantity of life, and getting the treatments they need is really that

partnership. And I think CAR T-cells has really taught us that that if we can do CAR T-cell successfully, you can do all the other stuff. So, I think it's been a really exciting time to actually work with my colleagues down here in Texas and in the south and getting to meet people where maybe it was silos before. And this has helped me, you know, work with my community colleagues as well. It's been great.

Dr. Usmani: So, Melody, you know, what has your experience been with the two commercial CAR-T products so far?

Dr. Smith: You know, in taking care of these patients, there have definitely been some challenges but certainly also successes. I think that there's a lot of ways that we are as a field going to grow in terms of how we try to incorporate or think about the logistics in terms of the timing and lines of therapies and making sure that our patients can have an optimized response.

Dr. Usmani: One of the challenges we had when our first CAR T-cell products were getting approved, we were super excited, but we were still in the middle of the pandemic. There were capacity concerns on the sponsors then to make enough product for patients. And that posed challenges for our interactions with our, you know, community colleagues who had patients, you know, who did not have any other options and wanted to offer CAR T-cell therapies, but most sites were getting maybe one or two initial slots and then, yes, you know, things got a little better. Maybe we would get three or four for a product. And that probably influenced the perception that our community colleagues, you know, had and I wanted to get Sanjay's, you know, comments around that because, you know, now capacity is really opening up in 2023. So, Sanjay, you know, how was your experience, you know, early on?

Dr. Sharma: Yeah. So I mean you brought up an, a great point in terms of oncology in terms of all the medicines in two ways: (a) regarding our experience during COVID and how that alters our perception on the drug and how it works and our experience and logistics, etc., and, two, for in general, we talk about, you know, drug shortages and how it's affecting how we treat our patients, even our curable patients.

So, but specifically in terms of CAR T-cells, it added a, an additional complexity. So, this is kind of new in the sense of its cellular treatment. When Krina was talking about earlier when she's talking to her fellows and they go through what are the regimens that you can offer, in terms of the world of myeloma, it is so incredibly refreshing with, as opposed to in the last few years, you're like, "Wow, which anti-CD38 do I use?" We have new treatments which force us to go back and recognize the danger of the patients and start talking about double hit or triple hit, lymphoma terms. You know, start putting our clinical, you know, observations in play, you know, penta-refractory, triple refractory, something refreshing with the discussion and now we don't have the drug.

Okay, so why don't we have a drug? Okay, (a) COVID makes sense. (b) maybe this is some kind of crazy complicated thing where it's hard to, you know, make these drugs and there is, you know, some sort of contamination. We've seen this in other fields of oncology. So, Saad, there, there's no question that we now have to define what actually happened regarding why it's not available to saying, "Hey, it's here. Come get it."

Dr. Smith: I would also want to mention in terms of the community colleagues, I think that that line of communication, you know, reaching out to them when you see the patient when you see that, okay, we're going to manufacture the CAR T-cells but we need something to bridge until they come, like those lines of dialogue are very much open. And I think that these types of novel therapies are compelling us to do that in ways that we may not have done before, but I think is also very beneficial for the patients, particularly when patients are being referred.

And, also, you know, if a patient's being referred to a tertiary center just making it clear and having those established relationships with the community colleagues such that they know you're going to take care of the patients for this realm of your expertise but you're not trying to supplant them or take the patient from them. I think that's something that's also important for breaking down the barriers between communication between academia and the community.

Dr. Sharma: Melody, I should make a comment about that. So, you said that it's not a risk that you guys are going to take the patient away. I hope in our world that we don't practice with that ownership of a patient.

Dr. Smith: Correct.

Dr. Sharma: I mean this is nature. Nature created this cancer. I have no power over this cancer and what's going to happen. So, I really, really hope that all oncologists who are listening here recognize that we're all in this together, that there is no ego. You know, you're here for the patient and that's it.

Dr. Smith: Yeah. And that, I agree, that collegiality makes such a big difference. Yeah.

Dr. Usmani: Absolutely. And it's becoming, you know, more needed now because we can't do this alone for our patients, you know, and the wealth of n-, knowledge is swelling. There is so much subspecialty here that I think it's so important to lean on each other. And, you know, I think, you know, the stronger this partnership the better outcomes for our patients. You know, and, you know, accessibility for each other as well is important as well.

With all that being said, I do want to, you know, pivot to the more recent data with CAR T-cell therapies that we're seeing in the earlier lines of treatment now. And, in fact, you know, we just had, you know, a Phase III study in early lines of treatment readout, a study that was led by, you know, several women in myeloma, including our very own Dr. Krina Patel, you know, who was on that paper. And the study was KarMMa-3. And I would love to get, you know, Dr. Patel's take on this, so, Krina, please tell us—

Dr. Patel: Yeah.

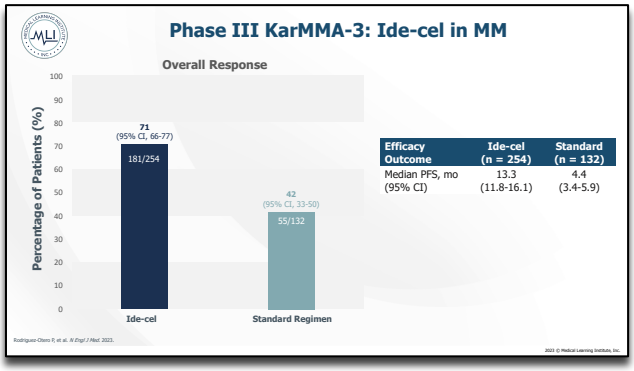
Dr. Usmani: - a bit about this trial.

Dr. Patel: No, thank you. It was really exciting cause, again, it was during the pandemic partly and so we learned a lot. But we were able to put quite a few patients on here, and it really was looking at earlier lines. The first CAR T-trial that's randomized, which was exciting, and it was looking at earlier line therapy, so lines two, so you had to have two to four prior regimens, so lines three to five. And remember, standard of care right now is approved after four prior lines of therapy. So especially for my high-risk patients, this was something that I was able to offer on a clinical trial to get them something novel, you know, and, again, in hopes that we would change their outcomes.

It was randomized 2:1, so two-thirds of the patients actually got CAR-T and one-third got standard regimen. And I just want to say one thing on the trial when we were putting patients on, I think we got 19 patients on during that period, which was amazing. But every time my patient would get randomized, they get CAR-T my entire team actually did a CAR-T dance. It was so awesome. So, I love this trial for lots of different reasons. It made my team much closer during the pandemic as well.

But what you can see, you know, is that in terms of the different patient populations, the standard regimens versus ide-cel, they're all very, very similar in terms of age and prior lines of therapy – average is three – their

performance status, ISS Stage III disease, high risk – about a quarter of patients had this – high tumor burden about a quarter of patients. But we talked about high-risk cytogenetics, you know, we did see about 42% of patients with high-risk cytogenetics on the ide-cel arm, 46 on the standard regimens, mostly the classical. But when you look at 1q and, you know, 1p deletion that are newer, all of a sudden, it was almost 49% of patients on the ide-cel arm had these aberrations and 39% standard regimen. And we just said that these are earlier line patients now yet we're seeing these patients with really, you know, kind of high-risk aggressive myeloma.



PHASE III KARMMA-3: IDE-CEL IN MULTIPLE MYELOMA

But what it really did show was that the overall response was still fantastic. The patients who got ide-cel was 71% response rate and standard regimens 42% but the bigger difference was the PFS and ide-cel at 13.3 months versus standard regimens at 4.4 months. So, and so it still tells that this is amazing therapy and, again, are higher risk patients.

And then, of course, talking about toxicity, we always want to make sure any of our new therapies don't have higher treatment-related mortality or anything that long term is going to cause problems for our patients if we're going to move it earlier. And, again, we do see the cytopenias, which is the main thing that improves over, you know, a few weeks to months from all our patients. Infections, you know, again, during COVID, we saw some patients with COVID but grade 3/4 was pretty low.

And then, you know, the other big thing CRS. Thankfully, we don't see very much high-grade CRS with this product where they need really CAR-T for myeloma, so it was all mostly while they're in the hospital, at the academic centers; and we don't really see delay till they go back to the community. Really what you're dealing with is the cytopenias and potential infection, so that's where I still talk to my colleagues about patients that might still be lymphopenic or prolonged neutropenic and what to do with that.

And then neurotoxic events, you know, ICANS like in lymphoma we don't really see very much thankfully, at least high grade, but there is this phenomenon of a delayed neurotoxicity. We haven't seen it much with ide-cel, so definitely different than the other CAR-Ts that we have to monitor for, but, you know, with cilta-cel we see that too. So, again, when I send my patients home with papers that say exactly what happened in the hospital and what are the things to look out for and our phone numbers, it really is to make sure that we're looking at all of these things that if patients are having trouble that we're talking to them.

And so, then what we're excited about at ASCO is CARTITIDE-4. So, we don't have the data yet. We're almost there; couple weeks. But, again, they were looking at even earlier line. So, this is patients who could have been just len refractory after their induction treatment and maintenance and they had to have one to three prior lines, and they were randomized to either two standard of care options, so PBd versus DPd, or cilta-cel.

So, I really do think that, you know, I'm hopeful. I'm a CAR-T enthusiast; that's my COI and this is the research I do. It's come around such a long way, and I'm really excited and, you know, I'm hoping that this will go earlier.

But, you know, Saad, I kind of wanted to get your thoughts about these data and where you think it's going to go and then maybe even the logistics of, you know, now there's even more patients that we might have to, you know, get these therapies to.

Dr. Usmani: Yeah. I think, you know, I agree with you, Krina, and, you know, wonderful job in summarizing the data. I think this really supports the utilization of CAR T-cell therapy in earlier lines of treatment.

W-, one of the key issues, you know, I think, you know, we talked about early on is drug exposure. Now we have, you know, patients who will be getting quadruplet, you know, induction therapies. You know, our patients will likely be getting two-drug maintenance strategies for high-risk patients. You know whether it's a PI with IMiD or an anti-CD38 with an IMiD, you know, that still remains to be seen. But, you know, we were kind of moving away from just, you know, having the same strategy for all patients and then modifying induction and maintenance from between a standard and high-risk patient. So, we are going to have patients who get to that penta drug exposure or refractoriness within three lines of treatment. So, I think having the, these kind of options in earlier lines kind of makes sense.

So, there're a lot of these, you know, considerations that come to mind, you know, as I see this whole landscape evolving. Melody, what do you think?

Dr. Smith: Yeah. I think the data that shows that in those patients who are able to get the CAR-T that their progression-free survival and median overall response was much improved. And, you know, looking at that shape of the curve how different it is it caused me to think about just because we see these patients that progression-free survival difference means so much. It means that the patient's quality of life during that time where the disease is under better control and they're not needing therapy is just better. They can enjoy their family. They can go back to work.

So, I think that that's really exciting to see this data and, hopefully, like you said, we can start using these therapies in earlier lines. And, you know, especially also with novel therapies that are being developed, I think it's important to also think about, you know, the studies and trying to design randomized control trials where we can in a fair and balanced way look at these cell therapies at earlier time points. I think that'll be really important moving forward.

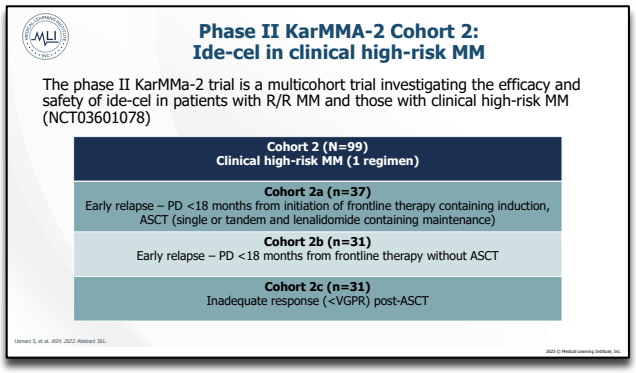
Dr. Patel: Yeah. And I was going to bring Sanjay into this too. You know, I think when I only see myeloma in clinic and my patients are relapsing every three to four months on a therapy, I, it's so hard for me to keep up, right, and I only do myeloma. So, I always wonder like for my colleagues if really by third line your triplets are only going to give you three/four months, right, as the standard of care here showed. What does that do in terms of be able to give your patients, you know, treatments and then how you can actually do that and in a real-time fashion cause I can't in my clinic. It's so hard.

Dr. Sharma: Yeah. So, Krina, the question you're asking is actually twofold is you mentioned that all you see is myeloma whereas we see everything, right. I do benign hem, I do malignant hem, I do oncology. So, you know, how do we kind of (a) keep up on the data and know what to do with our patients, but (b) how does it relate to our other patient population? And that's actually a huge benefit to us whereas I can relate what I do in solid oncology to hem oncology to inducing someone in with acute leukemia to, you know, treating someone with CLL. And there's tons of overlap.

First, and probably most important, is recognizing patient symptoms and recognizing the course in which a patient is going through. Secondly is the, some of the pearls that you're talking about is kind of like bread and butter stuff to us. I mean you made the data so easy to understand and listening to the backstory is also super cool. So, you clearly simplified it for any sort of oncologist, which was great.

And then in terms of understanding the data, this is kind of what we do. Like it would be harder for me, I think, to be so super subspecialized in something as opposed to seeing everything, whereas I feel that with that breadth of knowledge, I can handle numerous complexities.

Dr. Usmani: No, I think Krina also brought up a very important point. You know, many times, you know, we are seeing those kinds of patients relapsing within the first two years of their initial therapy. And when we go back to their data, you know, there isn't really a high risk that was found at the time of diagnosis. Those patients we start calling them functional high risk.

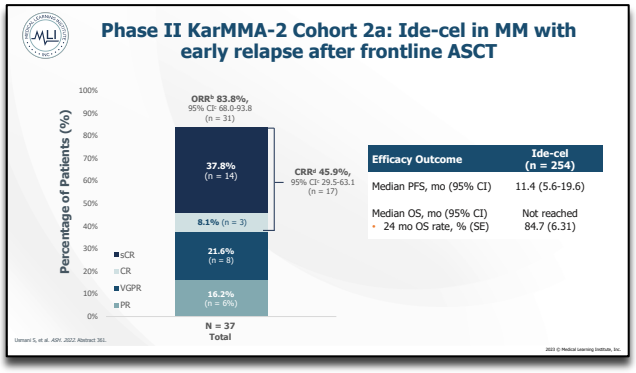


PHASE II KARMMA-2 COHORT 2: IDE-CEL IN CLINICAL HIGH RISK MULTIPLE MYELOMA

And, again, you know, Dr. Patel and I have been part of, you know, this study of looking at clinical high-risk patients. So there were different cohorts, you know, in frontline treatment patients who are progressing within, you know, 18 months of initial therapy, you know, with or without stem cell transplant or those who are not getting an adequate response to treatment, not getting to even up to VGPR post transplantation, so there were, you know, many different cohorts that were examined in this KarMMa-2 trial.

The study design was fairly similar to what, you know, how the ide-cel construct has been studied, you know, very similar to what Krina just presented. These patients who had early relapse after frontline autologous stem cell transplant, so within 18 months of starting their initial therapy; but they had to have at least a len-containing maintenance strategy. So primary endpoint for this particular study was just looking at complete response rates because one key observation that we see in these, you know, early relapse patients is they're not getting to optimal responses with their first-line treatment.

There were 37 patients that were enrolled on this study, and they are enriched for high-risk karyotypic abnormalities. Only 24% got to a complete response into their first-line treatment. This included a triplet induction transplant and then going onto maintenance. And so, you know, and then look at the refractory status IMiD and PI, so many of these patients were actually on a PI/IMiD maintenance.



PHASE II KARMMA-2 COHORT 2A: IDE-CEL IN MULTIPLE MYELOMA WITH EARLY RELAPSE AFTER FRONTLINE ASCT

So if we look at the responses, almost 84% response rates, and it's good to see that the complete response rate here is almost double of what was seen with their first-line treatment. So, 46% of the patients had a complete response in this experience. And looking at the median PFS, you know, and the duration of response for these patients, you know, it's something that, you know, was better than what we see for these patients because it ends up being a downward spiral for patients.

So, you know, looking at these data is single intervention and then patients are on nothing and getting, you know, a really good mileage out of it. So, what really excites me is seeing these kinds of responses in patients.

The safety profile we don't find anything different that we haven't seen. If anything, you know, the tolerability, you know, of these therapies is better in earlier lines of treatment. The picture was very similar to what has been observed, you know, with the early KarMMa trials, with KarMMa-3, etc.

CRS is very manageable. That was another, you know, important observation in this experience. And, you know, we have learned to use tocilizumab quite early on. You know, as soon as we see the first signs of CRS not getting better, you know, if it's persistent fevers, boom, you know, you go ahead and give toci. Make sure your patients actually have dexamethasone handy at home, you know, if, if you're going to be monitoring, you know, them during the CRS periods at home.

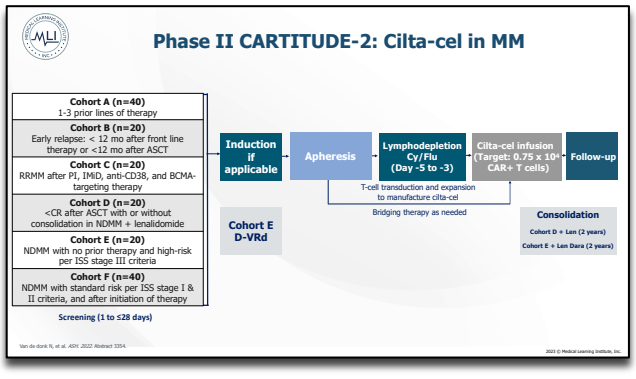
And then neurotoxicity signal is typically less than grade 2. Most of the events were grade 1 or 2. There weren't, you know, any major grade 3 or 4 events seen here. So, tolerability appears to be better, Krina, actually, you know, in this earlier lines of treatment, even better than KarMMa-3. The deeper the response, the better the progression-free survival, the better the durability or duration of response for patients. So, you know, looking at patients who are two years post therapy, seeing a durability or duration of response of, you know, or rate of more than 90%, you know, is, it's pretty cool, you know. And then none of these patients have passed away from myeloma at the 24-month mark. So that's also, you know, quite impressive for this patient population.

Dr. Patel: Yeah. I'll just say that I have a couple patients on here. One of my patients three and a half years out on nothing and I just see her, you know, every couple months, and she's doing amazingly and went back to work. I mean she was not working anymore and went back to work because she feels so great.

And to me that's the biggest part of all of this is that she feels like I can do everything again rather than when I first saw her that, you know, within a year of transplant relapsing, my heart sank. I was like, "Oh, I already know what's going to happen no matter what I do." So that, I think, is the biggest hope that this is really for my team and me pr-, you know, selfishly that gets me to work every day, right, because of that.

Dr. Smith: Also, as you mentioned, these patients who we are designating it as high risk because of their lack of a long-term response I'll say seeing this data and the CR rate really approaching 50% of the patients and really shrunk overall response rates in general I would say this data is really encouraging.

Dr. Usmani: So, throwing it back to you, Melody, you know, what about the other CAR-T construct that we have available commercially?



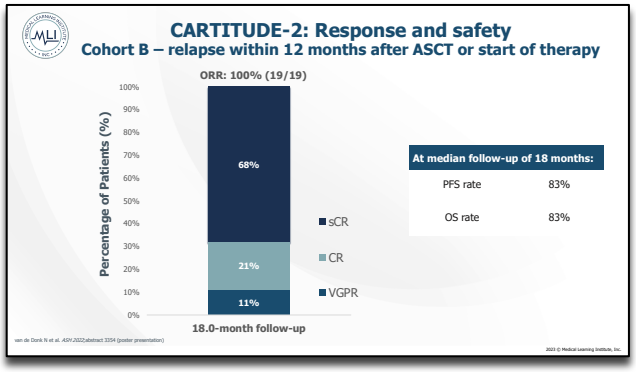
PHASE II CARTITUDE-2: CILTA-CEL IN MULTIPLE MYELOMA

Dr. Smith: Yeah. So, the other construct we have is cilta-cel, as was mentioned earlier, and so I'll talk a little bit about the Phase II CARTITUDE study for patients with refractory multiple myeloma. And this study, similar to the prior one, had several cohorts, cohorts A through F. These cohorts were delineated by exposure to various prior therapies or staging or ISS risk classification, so let's say either cytogenetic or clinical risk features.

And the cohort, though, that we'll focus on though is cohort B, which was the cohort with early relapse. So, these are patients who either relapsed less than 12 months after their front-line therapy or less than 12 months

after an autologous transplant. So, these patients across all cohorts went on the study. They got Flu/Cy lymphodepletion and then were evaluated for follow-up. And so, the data that we see in terms of the patient characteristics included 20 patients had high-risk cytogenetics and 15 out of the 20 had a prior autologous transplant.

The other important thing to note is that these patients were primarily either triple class exposed or triple class refractory, again, because they had relapsed to after prior frontline therapy or prior auto. And so that percentage ranged around 16 to 21% in terms of the triple class exposed or the triple class refractory.



CARTITUDE-2: RESPONE AND SAFETY COHORT B

And then when we look at the outcomes for those patients, 100% of them had an overall response with about 89% having a CR, which is really impressive data.

When we look at some of the long-term survival with the median 18-month follow-up and the median duration of response at 18 months for progression-free survival and overall survival was 83%, so also very encouraging for these patients.

And then in terms of side effect profile looking at really higher-grade toxicities, neutropenia as has been alluded to which we not uncommonly see because of the conditioning as well as CAR T-cell-related cytopenias but really the CRS and neurotoxicity was very low at high grades, only 5%. So, one patient having CRS, one patient having ICANS, and so that's also really encouraging just looking at the side effect profile from the CAR-mediated toxicity perspective. So, I think in terms of managing the patients, as we know across CAR T-cell therapies, it's really important to be very early and aggressive with identifying clinical symptoms and treating them.

So, Sanjay, so based upon what we discussed with these CAR T-cell-related clinical trials, do you believe that future treatment sequencing will focus on refractoriness to drug class rather than the number of prior lines of therapy? And what do you think are the implications for your clinical practice?

Dr. Sharma: Yes. So, Melody, so that, what you're alluding to is kind of the points that are made by these trials. Of course, this data makes me change the way, it makes us all change the way we think in oncology, and it goes along with how patients are thinking that there is something else out there. And not only is there something else out there, you're talking about a one-time treatment where then a patient could be done, hopefully, for a heck of a long time. So absolutely. I mean, Saad, do you agree?

Dr. Usmani: No. It certainly does. What we struggle with, Sanjay, is, you know, we cycled through different lines of treatment and ran out of options for those patients very quickly. You know, going back to the original discussion around, you know, what kind of disease we're dealing with, what kind of drug exposures patients have had, you know, and bringing in a treatment like CAR T-cell therapies for those vulnerable patients where we know what's coming down the pike, you know, I think is so important.

And, you know, this is where I think, you know, we need to do a better job I feel in educating both patients as well as building better community, you know, partnerships, you know, to highlight the fact, hey, you know, yes, you know, we have this data, but, you know, these are the patients who may benefit the most from the

intervention early on. So just let me know when we have such a patient. Just reach out to me and, you know, we can try to get this patient the best option they need.

That's where we need to head, you know, towards, you know, having a very direct two-way conversation between a-, all the, you know, for the lack of better word, stakeholders involved here. So, you know, I, I'd love to, you know, get an opinion from Melody because the challenges for folks in California are going to be very different than folks in Kansas or Texas or in the New York/New Jersey area or in the Carolinas. So, I think building those strong community partnerships to care for our patients.

Dr. Smith: I agree. Yeah. The coordination of care with community partners and having them engaged on like the deeper conversations in terms of sequencing and planning that out I think is really important.

You know, to the question about the prior lines of therapy versus drug refractoriness potentially dictating future treatment logistics and plans, I think that the data that I just shared about cilta-cel was really encouraging in the sense that their analysis of cohort B did show that all of those patients responded. To note, the majority, or about I think 15 of those 20 patients, did have an, a prior auto, so they were, you know, after three lines. So, I think that this data is encouraging that maybe we will move more to be able to even not only incorporate the refractoriness but consider moving CAR T-cell up earlier. But it's a small study, and I think additional studies will be needed to validate these findings, you know, maybe in a larger cohort. So that would be really nice. And this is just like interim analysis, so they're still enrolling that data.

As we think about these clinical trials, we know that clinical trials are set up in an idealized way, controlled environment; and so, you know, what have you been seeing from real-world studies, Krina?

Dr. Patel: Yeah. I think that's so important, right, because, again, these are at institutions that do, you know, stem cell transplant, so it's a bubble of sorts and then taking patients who are not eligible for trials, you know, how do we deal with that? Can we do these crazy things in patients who have heart issues or kidney issues? And we did it, right.

So actually the first ide-cel patients in the last two years 77% of them this consortium that we did it was 11 centers that saw about 200 patients or so. 160 got, that got cells 77% of those patients were not eligible for KarMMa, right, because of cytopenias, because of renal insufficiency, which is so big for our patients in myeloma that get excluded all the time for trials and all these other things, you know, prior history, strokes, etc. And we saw similar response rate, so it was still 86% for the majority of patients. PFS was about 8.8 months. Again, a little bit shorter than what we saw for 450 million cells on the KarMMa study. So, you know, not perfect but still pretty impressive compared to anything else we have out there for our patients.

And I think the biggest things they've shown is it's really safe for the real-world population. Of course, there's lots of issues with retrospective trials and looking at data this way, but, again, we're sort of seeing similar, you know, things that we were seeing in the trials for these really relapsed/refractory patients, and I'm excited to see when we go earlier what happens.

Dr. Smith: Yeah. You know, thinking about another aspect of the real-world data, it'll be nice to see that the more landscape ethnic and racial diversity in the real-world data that has been lacking in many of the clinical trials that have led to these drugs' approvals. And so that real-world data I think is also very powerful to think about how outcomes may potentially vary based upon various racial and ethnic factors or socioeconomic and ge-, geographic factors because there's so much that's required of patients and their family socially in order to receive a CAR T-cell product to be near the treating center. So I think the real-world data helps us to really look

in and take the blinders off just outside of our institutions but look more largely how does this type of an introduction of therapy that is so different from any of the other chemotherapies patients may receive locally how does that impact the outcomes that we see long term.

Dr. Patel: Yeah. You're 100% right. We have a paper coming out soon but really looking at Black patients and Hispanic patients and their outcomes; and outcomes are very similar, but toxicity may be different. But I agree with you, I think this is such a huge effort for us.

Dr. Smith: As a pivot, Sanjay, I'd love to ask you so, you know, as an academic clinician working in that environment, I don't really have a full scope as to what constraints or considerations that you have as you consider CAR T-cell therapy for your patients or interacting with academia. And so I'd just love to hear your perspective as to any other things that you really keep in mind as you're considering one of your patients for this type of therapy and working with a nearby academic center.

Dr. Sharma: Yeah. So, Melody, that, I mean that, that's so important to the viewers of this program understand. So it's been clear, right, in terms of the benefits of this treatment. We've shown that (a) you know, it's super darn effective, (b) that using it earlier and earlier is showing benefits and future trials will come about, and (c) it's a new paradigm and new treatment regimen in terms of refreshing to think about multiple myeloma we're just not moving around in anti-CD38 and IMiD and a proteasome inhibitor. But now you're kind of talking about and asking the questions, "Well how do we do it?" The viewers, hopefully, will look at this, "Okay, fine, I get it. I believe you. And now how do you make it work?"

So then a few things. So, one, you have the intellectual conversations between oncologists, right. I can text you, you can call me, whatever, "Hey, you know what, this is what I want to do." But now you need an institution to give you that portal to get that patient to you guys. And that's possibly more involved. And so, for example, in my center, okay, so fine all the doctors are on board, but that also means that we're educating.

So I'll give you a great example. The other day, you know, I was rounding in the hospital and one of my nurses they're like, "Oh we're going to a presentation." I was like, "Where do you go to a presentation on at 7 in the morning?" They're like, "Oh we're learning about cytokine release syndrome." I was like, "Oh, okay."

So that's an institutional approach. You know, so my institution has decided that they're going to teach the nurses and the, and inpatient nurses on what to possibly see if these patients are landing up in our ER, okay. So there's the education part.

Two, at an administration level, our administrations have to recognize that this is another treatment pathway for our patients that is necessary that we strongly believe in that has a benefit, so what are the portals that they can create to make it easy? All right.

Next, let's think about a real practical world. Where do I spend most of my time on? I'm on my darn computer in the world of Epic. So how does that get coordinated where I kind of hit, whatever, SmartPhrase to go set up a consult and get into that portal to the tertiary center?

So it's really like, okay, fine we all have the intellectual knowledge. (b) we all know each other. We all went to med school with each other at one time or another. (c) explaining to the administration to give us a way to do this mechanistically. And then (d) how does it get done through the IPA, are they accepting of such treatments? And then, lastly, depending on what type of center you are. For me in Orange County we're a very, very big group. We have a big, big population. So we as an institution in this partnering, we have to be

educated regarding my entire staff – my navigators, my nurses, the ER doctors – regarding how to manage these patients in terms of side effects.

Melanie Smith: Yeah. No, I think that's a really important perspective and thank you for sharing that.

Dr. Sharma: Oh, and the last thing I'm going to say, and it's totally doable. I mean this is stuff—

Melanie Smith: Yeah.

Dr. Sharma: -we do it at my institution. This is totally doable. It's really not that complicated, and it's totally manageable.

So let me ask you guys, all right, so then I just created that discussion in terms of the portal of getting the patient to you. I told you that we get it, you get it. So let me ask you, when do you guys want to see the patients? When do you want that patient record in your Epic chart? You know, when does the call need to be made? Saad.

Dr. Patel: Sanjay, that's a great question, and I think what I really try to tell my colleagues, 'cause it's a moving target, right. So as CAR-T gets approved earlier and earlier, my goal is if I can get to see that patient one line before CAR-T, because, again, we talked a little bit about it before the logistics for us are really involved too. We have to work on making sure the patient's there at the right time, the insurance approvals, then making sure we have a slot for them. The slot part, hopefully, is, it is getting better and, hopefully, by the time this goes earlier, we'll have even more slots. And then really being able to say, "What is that prior line?" because this is a T-cell. You know, we need these T-cells to be in the best shape possible. So we try to avoid alkylators right before. We try to, you know, bendamustine, especially if anybody was getting that for whatever reason. But even cyclophosphamide now if they've been on it weekly even the outpatient does for a long time it affects the T-cells.

And then bispecifics I think our patients need everything, but if you do that right before CAR-T, we actually have manufacturing failures. And so it's that timing piece that, you know, we have a little bit more insight to that I can help my colleagues with. And really, so if it's approved in fifth line, if I can get to see them by fourth line, that helps us a lot to get them at the right time to optimize everything versus if it gets approved in second/third line, you know, I want to see them early, you know, as possible. So if they're slowly biochemically relapsing, I want to see them then so I still have time by the time they officially need something to be able to do something.

Dr. Usmani: That's a great response and a perfect segue to wrap things up. This has been a wonderful episode. Let's end with what we'd like to see in the perfect world. You know, I know what Dr. Patel is going to say already. She kind of, you know, called me out on that too. But we've had an amazing, you know, informative conversation. You know, I truly enjoyed everyone's insights. It was a, you know, pleasure to have, you know, Sanjay join us and this was, you know, a very insightful discussion, you know, all around.

So starting with Dr. Smith, what would you like to see in a perfect world?

Dr. Smith: In a perfect world, I would really like to see clinical trials for the next phase of CAR T-cell therapies and newer CAR T-cell therapies be more representative of the community of patients that's impacted by this disease and patients who we know not only have higher incidence but worse responses. So I think that that is going to be really important so that we can see the clinical trial data as well as the real-world data be more reflective of these varied populations.

Dr. Usmani: So, Dr. Patel, what about you?

Dr. Patel: So in a perfect world, I would love to see our patients getting these bigger breaks that they are from their treatments, right. The fact that patients who are getting treatment from the day they're diagnosed until they unfortunately pass from it to now where we have CAR-T and we've seen this glimmer of I can be off therapy and have this great quality of life. So in a perfect world, I'd see patients that got bispecifics but then got CAR-T, then got to be off therapy, then maybe got CAR-T of a different type later down the road, then got off therapy again. And so and one day cure it. But that, that's my answer. I'm sticking to it.

Dr. Usmani: And, Dr. Sharma, what about you?

Dr. Sharma: So in a perfect world, I want clarity. So I'll tell you a story. So when I first started practicing, we bought a house. And we moved into the house, and the previous family they left things and left a crystal ball, like a real crystal ball. So I keep that in my office and when patients ask, "What do you see in your crystal ball?" It's like, "Well I have a crystal ball."

So I want clarity in what's that crystal ball. And that's what's been happening year after year and decade after decade in multiple myeloma. We are increasing survival. The crystal ball is now teaching us through discussions that we talked about how dangerous is your cancer? How do I define that cancer? That crystal ball is now getting more clear because we're now having treatments that are saying, "I can give you treatment breaks. I can give you remissions. I can get you back to work." That crystal ball, hopefully and more importantly, is going to be clear for the patient. What's going on with the patients? What are they doing when they get home and they say, "What did the doctor say?" and they said, "Everything's fine"?

I want them to be educated. I want them to, I want cancer to be less complex for the patient out there. I want their crystal ball to be clear.

And you, Saad?

Dr. Usmani: So in a perfect world, I would like for us to cure all myeloma utilizing these immunotherapies, giving therapy for no longer than a year regardless of whether they have standard or high-risk disease. I think we'll get there. That's, you know, my hope that I get to see this in my career, you know, and, hopefully, retire and be out of a job.

I think we can do this together for our patients. I truly appreciate everyone's input. This was a very organic kind of a discussion that I had with all of you.

Thank you for participating in today's Special Edition *Med Table Talk*. You know, for our audience, there are several resources you can download from the activity website. We do full hope that you enjoyed this discussion as much as we did. Now that you have completed this activity, you may get credit for this activity by completing the post-test and evaluation.