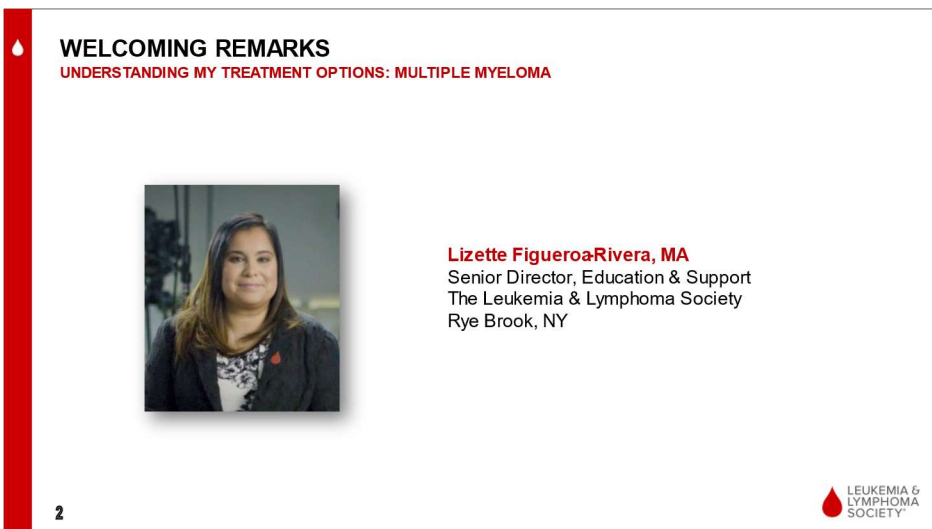


## WELCOME AND INTRODUCTION



### ***Lizette Figueroa-Rivera, MA***

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you.



Special thanks to Dr. Sagar Lonial for volunteering his time and expertise with us today. We have over 2,400 people participating in today's program from across the United States, as well as other countries, including Canada, Colombia, Egypt, France, Indonesia, Ireland, and the United Kingdom.

# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

TRANSCRIPT



## WELCOMING REMARKS

UNDERSTANDING MY TREATMENT OPTIONS: MULTIPLE MYELOMA

This program is supported by



3



We would like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GSK, Janssen Oncology & Legend Biotech, and Karyopharm Therapeutics for their support for today's program.

Following the presentation, we will take questions from the audience. We are also taping and transcribing this program for future posting on our website.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. To advance this mission, LLS's Office of Public Policy supports a policy agenda aimed at accelerating the development of new treatments for cancer and breaking down the barriers to care that patients often encounter.

You may want to become active in LLS's advocacy efforts to ensure that myeloma patients get the access to quality, affordable, and coordinated care or to share your story to inspire a legislator and help them understand your experience by visiting [LLS.org/Advocacy](https://LLS.org/Advocacy).

## PRESENTATION

*Lizette Figueroa-Rivera, MA*



**PRESENTATION**  
UNDERSTANDING MY TREATMENT OPTIONS: MULTIPLE MYELOMA



**Sagar Lonial, MD, FACP**  
Professor and Chair  
Department of Hematology and Medical Oncology  
Chief Medical Officer  
Winship Cancer Institute of Emory University  
Anne and Bernard Gray Family Chair in Cancer  
Emory University School of Medicine


4



I'm now pleased to introduce Dr. Sagar Lonial, Professor and Chair in the Department of Hematology and Medical Oncology, Chief Medical Officer at the Winship Cancer Institute of Emory University, as well as the Anne and Bernard Gray Family Chair in Cancer at Emory University School of Medicine.

Dr. Lonial, I'm now privileged to turn the program over to you.

***Sagar Lonial, MD, FACP***



**DISCLOSURES**  
UNDERSTANDING MY TREATMENT OPTIONS: MULTIPLE MYELOMA


**Sagar Lonial, MD, FACP**

**Consultant/advisor/speaker:** AbbVie, Amgen, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Novartis, Takeda, Pfizer

**Researcher:** Bristol-Myers Squibb, Janssen, Novartis, Takeda

**Board member with stock:** TG Therapeutics.

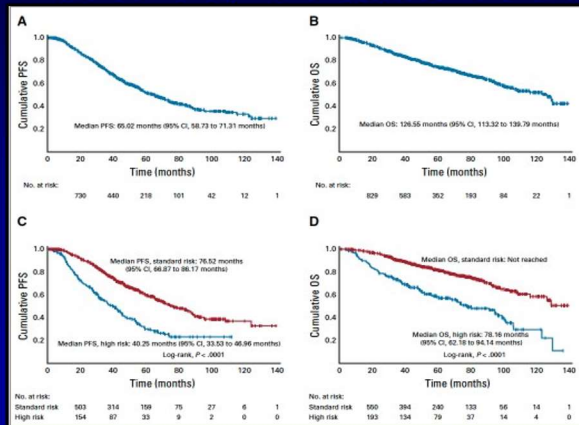
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Thank you very much, and I appreciate everybody taking time out of their day to join us today for this, what I hope will be a very informational session for you all; and really what I wanted to do with the next 30 or 40 minutes was give you an insight into some of the really exciting areas of development of myeloma. I know many of you all are aware of the new drug that just received accelerated approval

yesterday, teclistamab (teclistamab-cqyv/Tecvayli™). I've got just a couple slides on that already built into the program, potentially anticipating that approval, but also wanted to show you the breadth and depth of what we're doing in myeloma research that really has changed the natural history of this disease over time.

### What is the current state of the art?



Joseph et al, JCO 2020

And so, to get started, what I really want to begin with is an idea for hopefully all of you about where we are in 2022. And while I will often talk about this slide, this is the RVd 1000 Series (lenalidomide/Revlimid®, bortezomib/Velcade®, and dexamethasone therapy) that was published by our group. The reality is that while this is an expectation for where we hope our patients will be in 2022, the reality is that it's probably even better. And the reason I say that is these are progression-free and overall survival curves for 1,000 consecutively treated patients at Emory. It goes back to about 2009, 2010. And what you'll see is that the median duration of first remission for those patients is five and a half years, and the median overall survival is over ten years.

Now we did update this data more recently at ASCO (American Society of Clinical Oncology), and the median survival has gotten better. The median progression-free survival has improved with longer follow-up as well. But I think it really sets a benchmark for what the expectations, both from physicians and patients, should be for what a myeloma patient's journey should be using drugs that were available ten years ago, recognizing that we now have drugs like anti-CD38 antibodies, we have second- and third-generation immunomodulatory drugs, we now have CAR Ts (chimeric antigen receptor T cells) and bispecifics, and that likely these curves are even better today than they were based on patients' treatment from eight to ten years ago. And so, I am hopeful that the next time we update this data in the next five years, the curves will continue to improve, demonstrating that, hopefully, there is an even larger fraction of patients that are potentially cured of their disease with the kinds of drugs that we have available in 2022 and beyond.

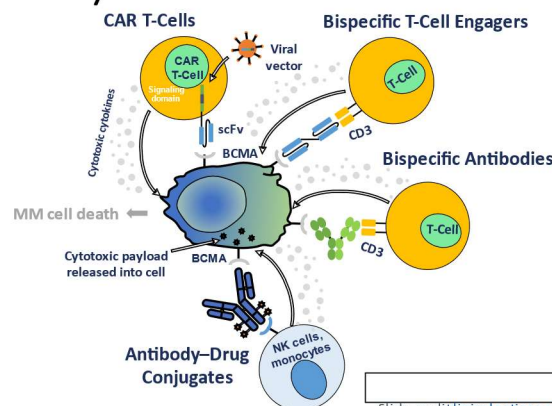
### Topics to Cover

- Immune therapy and targets
- Precision Medicine and MM
- New versions of existing agents

So, I'm going to really cover three topics in the talk. I'm going to talk about immune therapy and targets, and we'll focus a little bit on antibodies, bispecifics, and CAR T cells. I then want to tell a story in precision medicine and myeloma because that's something that I think has spread beyond. In all of cancer, precision medicine is a big buzzword that people are using; and it's been much more limited in its efficacy in myeloma. And then finally, talk about new versions of existing agents that are likely even better than the current compounds that we have and how they may make an impact on the treatment paradigm as well.

### BCMA in Multiple Myeloma

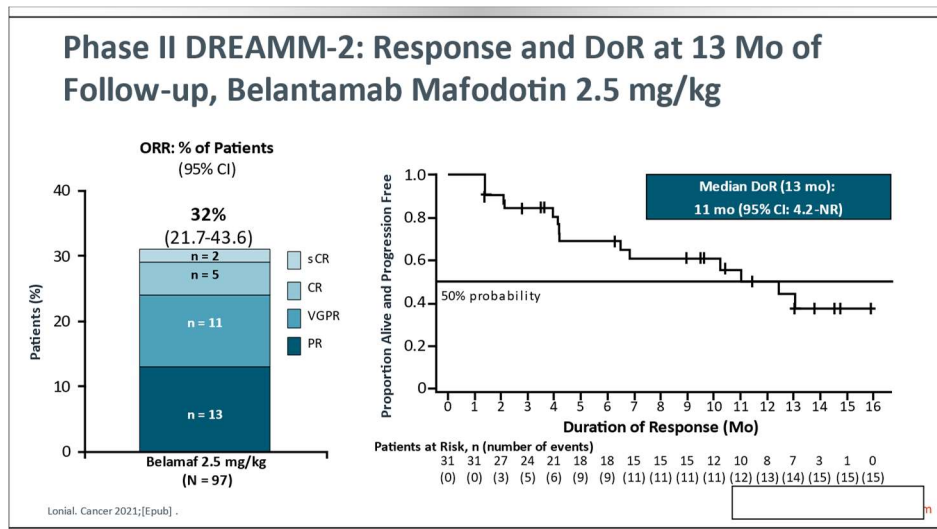
- Expressed on late memory B-cells committed to PC differentiation and PCs
- BCMA plays a role in survival of longlived PCs
- $\gamma$ -secretase cleaves BCMA from the cell surface, yielding soluble BCMA



So, let's start off talking about what I guess you could argue in 2020 or 2021 was the molecule of the year in myeloma, and that's BCMA. And we know that BCMA, also known as B-cell maturation antigen, or BCMA for short, is a really important receptor on the surface of myeloma cells. And so not only does it serve as an important target for things like CAR T cells at the top of the cartoon or bispecific antibodies in the middle right of the cartoon or antibody drug conjugates that you'll see at the bottom, and we're going to talk about each of those briefly, but BCMA also is responsible for many of the important things that malignant plasma cells do to stay alive. And so, by blocking signaling through BCMA, you may ultimately make it harder for that myeloma cell to stay alive. That

ultimately will make it more susceptible to the therapy that we're using. So BCMA is an important therapeutic target because we have antibodies and things to go after it, but it's also an important drug resistance and myeloma cell proliferation target; and so, we sort of get a two for one in many ways if we target BCMA.

It's also important to recognize that there are, and we're going to talk about this later on, there are enzymes that cleave and remove BCMA from the surface of the myeloma cell and release it into the plasma. And there are, in fact, strategies now trying to prevent that cleavage that may actually make the treatments more effective.

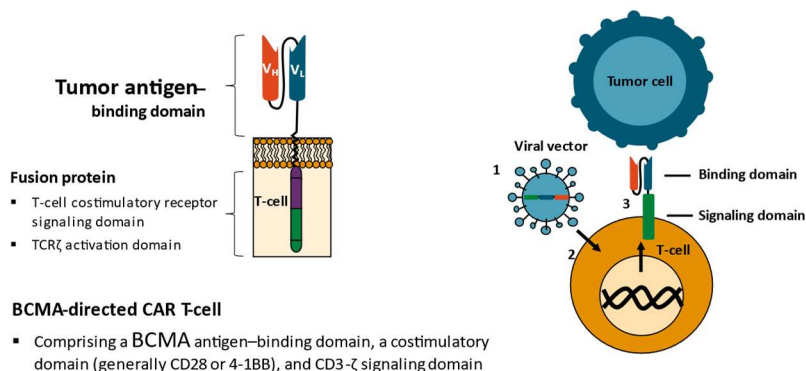


So, the first drug that was approved targeting BCMA is an antibody drug conjugate. This is belantamab mafodotin (Blenrep), also known as belamaf. Belamaf is an antibody drug conjugate, meaning that there's a piece of chemotherapy hooked onto the back of that antibody so when it binds BCMA, that piece of chemotherapy then gets internalized; and in the context of refractory myeloma, about one in three patients will have a response. And, for the patients who do respond, that response can often last up to a year.

Now there are some unique adverse events associated with belamaf, the most important being ocular toxicity or keratopathy. There are some very practical things that one can do to try and minimize that, and this does require a partnership and team approach, not just on the oncology side, but also partnering closely with ophthalmology. And most of the large practices have set this up where we are set up to partner with an eye doctor or an eye care specialist to help deliver this drug when it is the right treatment for a given patient.



### CAR T-Cell Structure

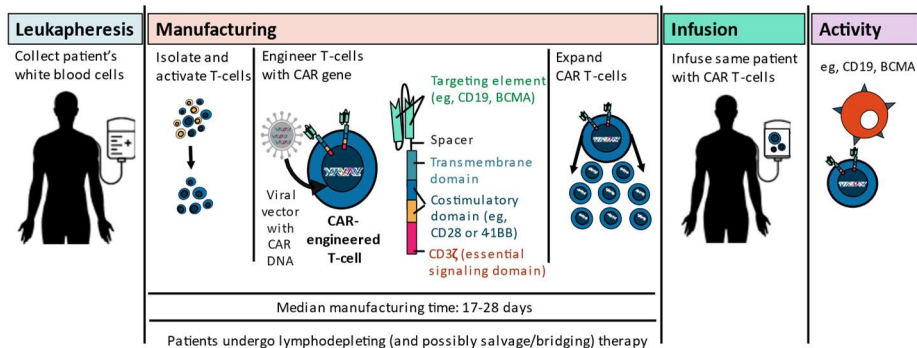


Bruno. Haematologica. 2021;106: 2054. Morgan. Biomedicine. 2016;4:9.

Now the other thing that we have that targets BCMA that everybody's very excited about are CAR T cells. And just to give you a little bit of a primer in basic biology, what a CAR T cell really does is it has a binding domain. On the inside of a T cell, there's also what's called the co-stimulatory domain. And CAR T cells have been used with great success in diseases like ALL (acute lymphocytic leukemia) or in large cell lymphoma or even in CLL (chronic lymphocytic leukemia) and are now being tested in a number of different blood cancers, with the idea that you can change this tumor antigen binding domain at the top to whatever you want.

And so, what ends up happening is you create a T cell that has that specific binding domain, and in the case of myeloma right now, it's BCMA. You then engineer those cells and give it back to the patient, and then the T cells that have been engineered to target BCMA go after any cell that expresses BCMA. So that is, right now, the two FDA (U.S. Food and Drug Administration) approved treatments that are CAR T cells in myeloma really target BCMA through this binding domain that is induced by a viral vector against a patient's own T cells. So, it's using their own T cells to do this.

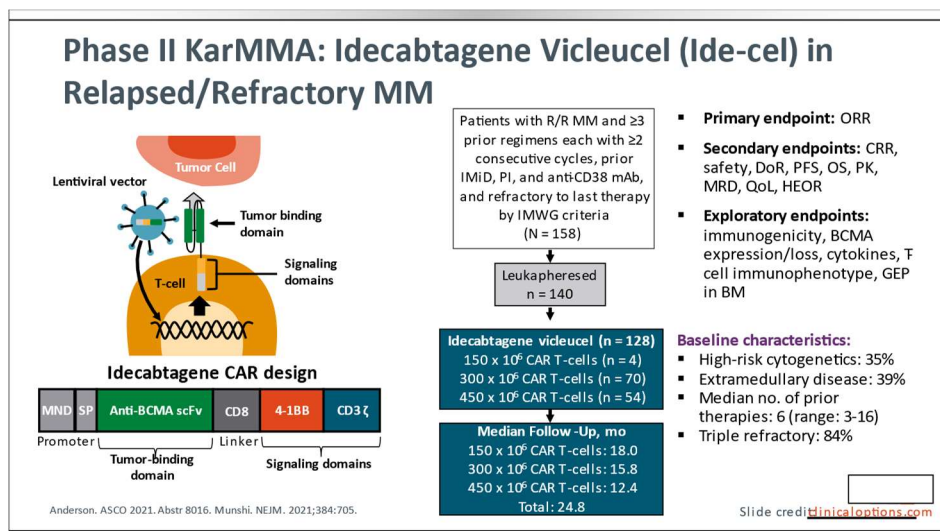
### Autologous CAR T-Cell Therapy: Underlying Principles



Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35. Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

And so, the process from a logistics perspective is that a patient undergoes leukapheresis, and leukapheresis is a fancy way of saying, "We filter out the blood to collect the T cells." Now those of you who have had apheresis to collect a stem cell graft, this is the same concept only there is no growth factor administration. We just want whatever's in the blood, and then we use that, those cells are then isolated at the manufacturing site. They are then transduced with a viral vector that then causes those T cells that came from the patient – so this is a patient-specific treatment – to express a binding domain that targets in this case BCMA.

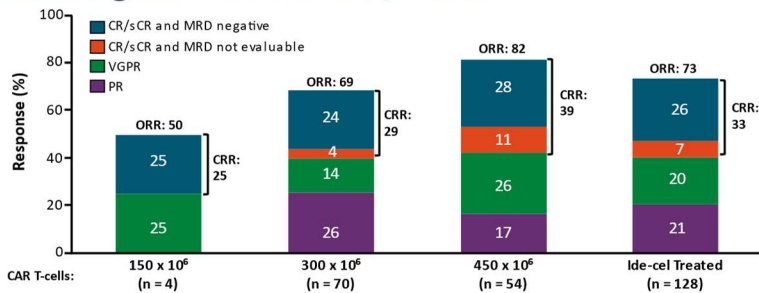
You then expand those CAR T cells in vitro, and then you give it back to the patient. So, you give them back their own T cells after they've received a little bit of chemotherapy to allow that T cell to be accepted. And then you wait for the activity. So, we'll talk about that as we go forward as well, but this is sort of the CliffsNotes, if you will, on CAR T-cell manufacturing and administration for a given patient with multiple myeloma.



Now the first trial that led to the FDA approval of a CAR T cell in myeloma was the KarMMA trial, and the KarMMA trial used a product or a vector that we now call ide-cel (idecabtagene vicleucel/Abecma®). And ide-cel is just a binding domain and a vector that was used here again that binds BCMA. Again, the co-stimulatory domains are listed here. These are not huge important details from a patient perspective. What's really important is that the target of those CAR T cells was BCMA.



## Phase II KarMMa Update: Clinical Response of Idecabtagene Vicleucel in R/R MM



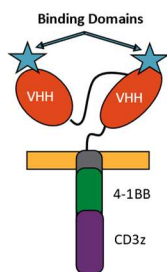
- Median time to first response: 1.0 mo (range: 0.5 -8.8); median time to CR: 2.8 mo (range: 1.0 -11.8)
- Median follow-up of 13.3 mo across target dose levels
- MRD-negative (<10<sup>-5</sup>) in all treated patients (n = 128) was 26% and 79% in evaluable patients with ≥CR (n = 42)

Anderson. ASCO 2021. Abstr 8016. Munshi. NEJM. 2021;384:705.

Slide credit: [clinicaloptions.com](https://clinicaloptions.com)

And one of the things that we know about this early phase trial is that we gave different doses of the CAR. In some patients we gave 150 million, in some patients we gave 300 million, and in other patients we gave 450 million cells. And if you begin to look at the overall response rate, remember, this is a median of five to six prior lines of therapy, so very heavily pretreated patients. And what you'll see here is that the overall response rate does vary based on the dose; and on average, it was about 73% across the board. And this really was unprecedented when we talk about response rates in the context of triple class and generally refractory myeloma in general. So very encouraging data across the board.

## CARTITUDE-1: Ciltacabtagene Autoleucel for R/R MM



- Contains 2 BCMA-targeting single-chain antibody designed to confer avidity
- Identical to the CAR construct used in the LEGEND-2 study

Berdeja. Lancet. 2021;398:314. Martin. JCO. 2022;[Epub]

- Single-arm, open-label phase Ib/II trial
- Patients with R/R MM per IMWG and ≥3 prior regimens or double refractory to IMiD and PI and had received IMiD, PI, and anti-CD38 mAb (N = 113)

Lymphodepletion  
n = 101

Ciltacabtagene autoleucel (n = 97)

Target 0.75 x 10<sup>6</sup> CAR T-cells (range 0.51 x 10<sup>6</sup>)

Median administered dose:

0.71 x 10<sup>6</sup> (0.51 – 0.95 x 10<sup>6</sup>) CAR+ viable T cells/kg

- Primary endpoints: Phase Ib: AEs; phase II: ORR

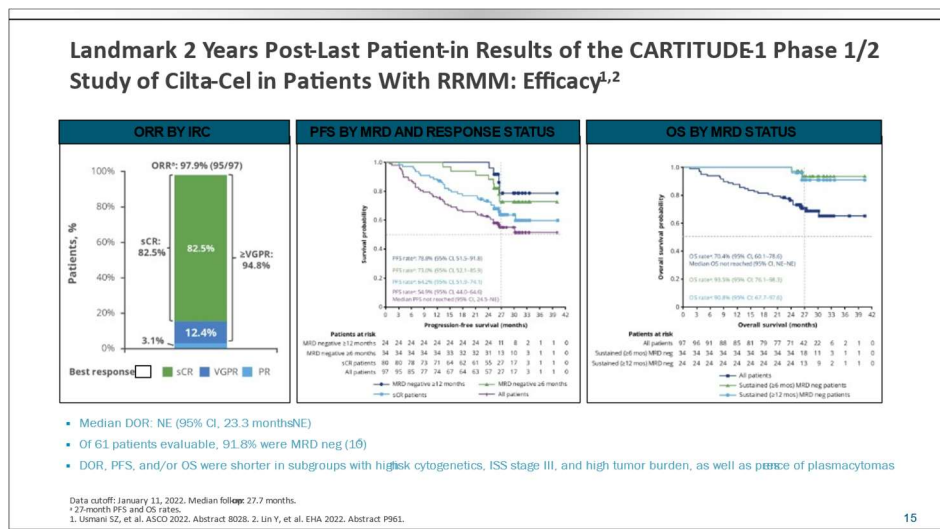
### Baseline characteristics:

- High-risk cytogenetics: 23.7%
- Extramedullary disease: 13.4%
- Median no. of prior therapies: 6 (range: 3-18)
- Triple refractory: 87.6%

Slide credit: [clinicaloptions.com](https://clinicaloptions.com)

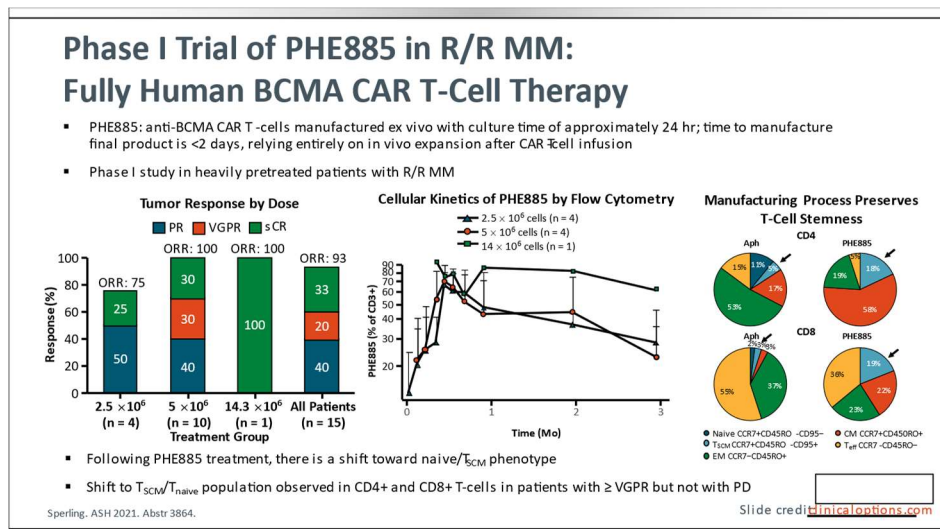
Now the other CAR T-cell product that was out there is cilta-cel (ciltacabtagene autoleucel/Carvykti™), which is a different product. It's got a different vector. It actually binds BCMA in two different places, so structurally it's a little bit different. And the dosing of cilta-cel was different. They got doses as low as 0.51 million cells all the way up to almost one million cells. And so based on those differences in dosing, what we see is a slight difference in side effects. The cytokine release syndrome that one is going to see occurs sooner with ide-cel than it does with cilta-cel. With ide-cel, it tends to occur within the first 24 to 48 hours after infusion. With cilta-cel, it tends to occur about a

week after infusion because those cells are growing in vivo. In the patient those cells are continuing to grow up.



And just as an example, the overall response rate for cilta-cel was almost 98%; and if you look at remission duration, it's over two and a half years here. And again, the remission duration varies based on how deep the response was. The deeper the response, the longer the remission duration appears to be.

Now this in cilta-cel is to be contrasted in ide-cel with a median remission duration of about a year. Although, again, whether these products are appreciably different I think is currently an area for some discussion and debate. But certainly, on the surface, it appears that the cilta-cel remission duration appears to be longer than what we see with ide-cel overall.

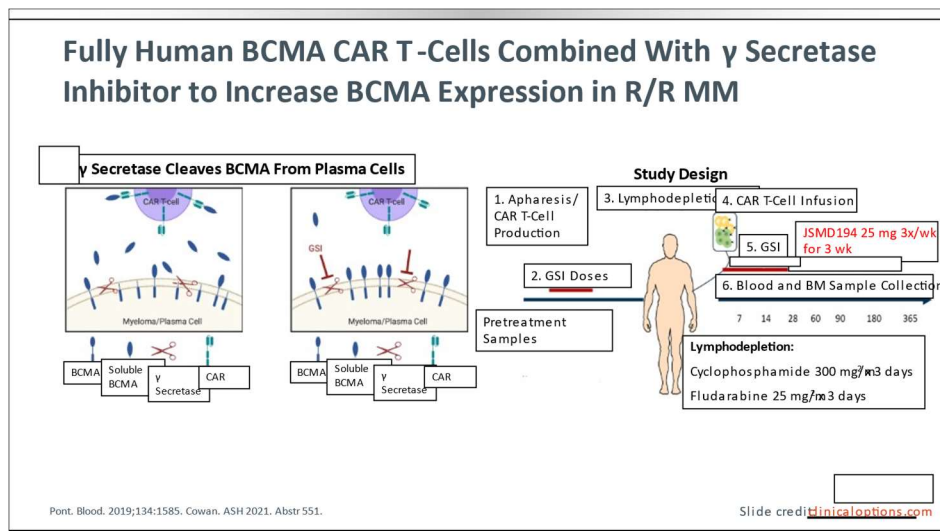


Now as good as those two products are, and I think we're certainly happy with the response rates, what we have not seen is a plateau on a curve that suggests that some patients are ultimately cured of their myeloma. And that may be a function of the fact that we're treating very, very late and

resistant patients; but it also may be a function of the fact that many of these patients that we're treating, the CAR T cells don't last long enough or there are residual cells that somehow escape the treatment and death induced by a CAR T cell.

And so, we're trying to make CAR T cells better, and this is an example of a trial that's being run through Novartis using a product where instead of three to four weeks for manufacturing, which is what both ide-cel and cilta-cel require, with this compound, it's 48 hours. So, you don't have to worry about what's happening to the myeloma after you collect those T cells; 48 hours later you're ready to give the CAR T cell product back.

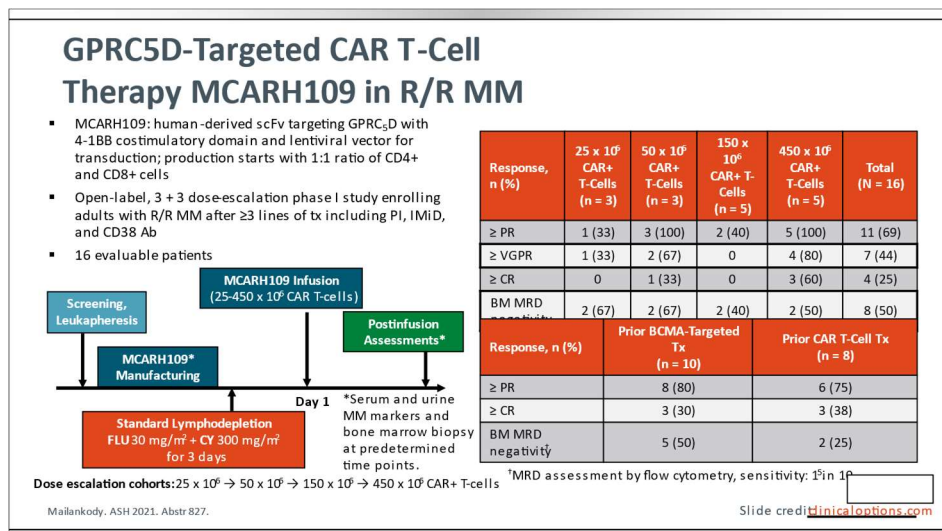
And what we've seen in very early preliminary data is that the response rates are equally as high. What we don't know right now is whether the duration of response will be longer. But certainly, it appears on the surface that we're getting a slightly different T cell population that may portend for a better long-term remission, at least using in vitro studies. So, this is one way where we're trying to improve on the efficacy of a CAR T cell to really get to that plateau phase and ultimately tell patients they are, in fact, cured of their myeloma and don't require additional therapy.



Now another way to try and enhance the efficacy of a CAR T cell is to use something called a gamma secretase inhibitor. And a gamma secretase, as you recall from a few slides ago, is the scissors here. It's the enzyme that removes BCMA from the surface of plasma cells and puts it into the serum. And when it's in the serum, it can sort of distract, if you will, from whatever strategy you're using to target a BCMA by binding up, whether it's a CAR T cell or an antibody drug conjugate or a bispecific antibody. It serves as a sink, if you will, to take away effective drug from the tumor cell and allow it to just float freely in the serum because it's bound to that serum or soluble BCMA.

Now as you can imagine, that is suboptimal; and so, there are actually studies, one done by our colleagues out on the West Coast at the Hutch (Fred Hutchinson Cancer Center, Seattle, WA), giving a CAR T cell where they use a gamma secretase inhibitor to try and increase expression of BCMA and see whether they can overcome resistance or get better responses. And at least in early preliminary data, the answer may, in fact, be yes to that question. It's also being combined with belamaf or belantamab mafodotin to also reduce the amount of belamaf you need, perhaps reducing that ocular toxicity, but maintaining the same level of efficacy by giving a lower dose of belamaf. So,

this is something you're going to see in the future as well to generally improve the efficacy of anything that targets BCMA.

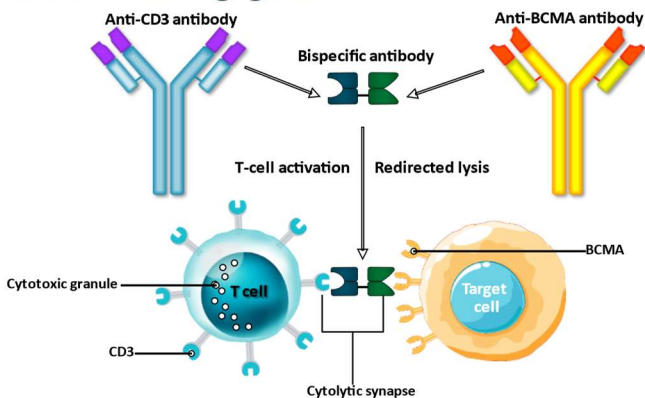


Now again, we talked about BCMA; and this is really important data from a CAR T cell perspective looking at another target for CAR T cells; and these are CAR T cells that target GPRC5D (G protein-coupled receptor, class C, group 5, member D). And if that's a mouthful for you to say, the actual name is even much longer than that. So just focus on GPRC5D. And the reality is that GPRC5D is yet another target on the surface of myeloma cells, and so the group at Memorial Sloan Kettering actually did a phase I study of a CAR T-cell targeting GPRC5D. This was actually very recently published in *The New England Journal* just in the last month, and what they demonstrated was very encouraging activity in that phase I trial, and the safety appeared to be similar to what we see for a BCMA-directed CAR T cell.

So, one of the questions that I'm sure is going to come up in the discussion today is, "Well, I've had a BCMA-directed CAR T and my myeloma came back. What else can I do?" This is one potential option that you could do is have another CAR T or potentially another treatment that targets this different antigen called GPRC5D, if BCMA targeting is no longer an option for you as a patient. So just trying to show you some of the really exciting data and opportunities that we have coming in the near future.



## Bispecific T Cell Engagers



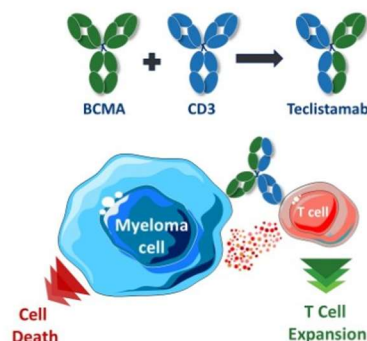
Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944.

Now we've talked about CAR T cells and antibody drug conjugates. I also want to talk about what is probably the biggest news in the myeloma world in the last 48 hours and that's bispecific T cell engagers. And this is basically like giving a monoclonal antibody, except that it makes the antibody look different. So, if you'll see the blue antibody on the left has two portions, the left and the right portion of the Y, both bind CD3. That's a T-cell antibody. On the right side, you'll see that orange and yellow one where both sides bind BCMA. That's a typical monoclonal antibody.

What we do in a bispecific is take one part of the antibody and have it bind CD3, which binds T cells, and the other half binds BCMA. So, you're basically bringing the two antibodies together into a new bispecific antibody, and what that does then is bring a T cell right next to a cell that expresses, in this case, BCMA. And what that does is activate that T cell and bring it physically close to the myeloma cell so that it can then kill the myeloma cell by activation. So, in many ways, this is like having a CAR T cell without having to take the cells out of the body. You basically use an antibody to activate and bring that T cell next to the myeloma cell.

## Teclistamab: BCMA x CD3 Bispecific DuoBody® Antibody

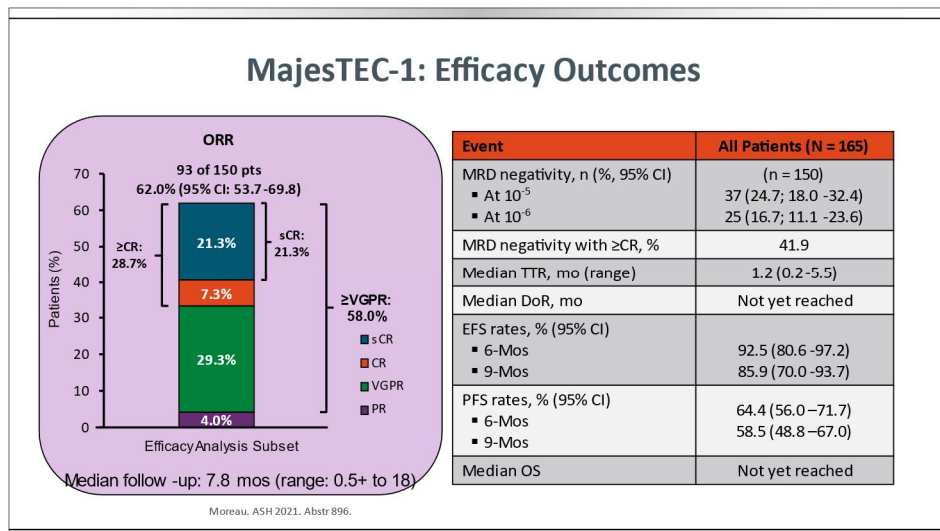
- Teclistamab (JNJ-64007957) is a humanized IgG-4 bispecific DuoBody® antibody that binds to BCMA and CD3
- Teclistamab redirects CD3<sup>+</sup> T cells to BCMA-expressing myeloma cells to induce cytotoxicity of the targeted cells in preclinical studies<sup>1,2</sup>
- Teclistamab potentially kills myeloma cell lines and primary myeloma cells from heavily pretreated patients<sup>2</sup>
- A Phase 1 first-in-human study is underway to evaluate safety and antitumor activity of teclistamab in patients with RRMM (NCT03145181)



Teclistamab includes technology licensed from GenMab. Labrin A et al. *Proc Natl Acad Sci USA*. 2013;110:5145. <sup>1</sup>Frerichs KA et al. *Clin Cancer Res*. 2020; doi: 10.1158/1078-0432.CCR-19-2299. BCMA-B-cell maturation antigen; MM-multiple myeloma; RR-relapsed or refractory

56th ASCO Annual Meeting 2020, Usmani SZ, et al. Abstract #100 3

And the antibody or the bispecific, that was approved yesterday, is teclistamab. This is a BCMA CD3 bispecific antibody. Again, it's got a portion of a BCMA, a portion of a CD3, and you put it together and you get this part that the blue part binds the T cell, the green part binds a myeloma cell, and together it induces cell death. And so, you can see that very nicely illustrated in the cartoon here in terms of its potential. And what I think is really quite exciting and, as you saw from the FDA approval yesterday, is that it can be highly effective.



And in fact, if you begin to look at overall responses with this target – this is the MajesTEC-1 trial looking at teclistamab – it's over 60%. If you look at responses, even among patients who had prior BCMA-directed therapy, whether it's a CAR T cell or an antibody drug conjugate, the response rate is over 50%; and it looks like the remission duration in all patients lasts about a year. And again, that's in a very heavily pretreated group of patients. That data was published in *The New England Journal* earlier in the summer and I think is very encouraging data and ultimately led to the FDA approval of teclistamab in myeloma.

## BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response	DOR/PFS
Teclistamab <sup>1</sup>	<ul style="list-style-type: none"> <li>Bispecific</li> <li>IV/SC (RP2D: 1500µg/kg SC)</li> <li>Weekly and every other week in f/u</li> </ul>	157	<ul style="list-style-type: none"> <li>At SC cohorts:</li> <li>Median of 5PL</li> <li>79% triple refractory</li> <li>38% penta refractory</li> </ul>	<ul style="list-style-type: none"> <li>At RP2D:</li> <li>CRS 70% G1-2</li> <li>Neurotoxic 1% (G1)</li> <li>Infections 50%</li> </ul>	At RP2D, ORR: 65% with 40% sCR/CR	No mature data
AMG701 <sup>2</sup>	<ul style="list-style-type: none"> <li>BITE modified</li> <li>IV</li> <li>Weekly</li> </ul>	82	<ul style="list-style-type: none"> <li>Median of 6PL</li> <li>62% triple refractory</li> </ul>	<ul style="list-style-type: none"> <li>CRS 55%, G3-4: 9%</li> <li>No ICANS</li> <li>20% cytopenias</li> </ul>	83% ORR at the top dose level and 50% VGPR	No mature data
REGN5458 <sup>3</sup>	<ul style="list-style-type: none"> <li>Bispecific</li> <li>IV</li> <li>Weekly and every other week C4-&gt;</li> </ul>	49	<ul style="list-style-type: none"> <li>Median of 5PL</li> <li>100% triple refractory</li> <li>57% penta refractory</li> </ul>	<ul style="list-style-type: none"> <li>CRS 39%, no G3-4</li> <li>ICANS 12%</li> <li>cytopenias 47% and infections 18%</li> </ul>	62.5% at 96 mg and 95% of responders were VGPR. Some CR in lower dose levels	Preliminary median DOR: 6m
TN3-3838 <sup>4</sup>	<ul style="list-style-type: none"> <li>Triple chain anti-BCMA bispecific</li> <li>IV fixed doses</li> <li>Every 3 weeks</li> </ul>	58	<ul style="list-style-type: none"> <li>Median of 6PL</li> <li>64% triple refractory</li> <li>34% penta refractory</li> </ul>	<ul style="list-style-type: none"> <li>CRS 45% and no G3-4</li> <li>No ICANS</li> <li>Cytopenias 21% and infections 14%</li> </ul>	80% (13% CR) at the dose levels 40-60 mg	No mature data
PF-3135 <sup>5</sup>	<ul style="list-style-type: none"> <li>Bispecific</li> <li>SC and weekly</li> <li>RP2D: 1000 µg/kg</li> </ul>	30	<ul style="list-style-type: none"> <li>Median of 8PL</li> <li>87% triple refractory</li> <li>23% prior BCMA-based therapy</li> </ul>	<ul style="list-style-type: none"> <li>CRS 73% and no G3-4</li> <li>ICANS 20%</li> <li>ISR 50%</li> </ul>	83% ORR at RP2D	No mature data

1. Usmani SZ et al. Lancet 2021. 2. Harrison SJ, et al. Presented at ASH 2020. Abstract 181. Madduri D, et al. Presented at ASH 2020. Abstract 291. 4. Rodriguez C, et al. Presented at ASH 2020. Abstract 293. 5. Bahlis NJ, et al. Presented at ASCO 2021. Abstract 8006.



Now not to be left out, there are probably five or six other BCMA-directed bispecifics that are in middle- to late-stage development. Some of these include agents like elranatamab from Pfizer down here at the bottom, again showing an overall response rate of about 80%. There's another one, the TNB-383B that shows a response rate of about 80%. There's a Regeneron® compound that's got a response rate of about 62% and others that are in the development and in the works right now as well.

And this to me is a really exciting avenue of investigation because each of these bispecifics is slightly different. Some are IV (intravenous), some are subcutaneous, some are dosed once a week, some are dosed every other week, some are dosed every three weeks. They're all slightly different, subtle differences between these that I think will ultimately help us to identify what's the best approach for targeting BCMA with a bispecific in the context of a patient with multiple myeloma.

Updated Results From the MonumentAL-1 Phase 1 Study of Talquetamab in Patients With RRMM: Study Design and Patients <sup>1,2</sup>			
<b>Key Eligibility Criteria</b> <ul style="list-style-type: none"> <li>• RR or intolerant to established MM therapies</li> <li>• Prior BCMA-targeted therapy was permitted</li> </ul>		<b>Patient Characteristics</b>	
<b>Dosing Schedule at RP2D</b> <ul style="list-style-type: none"> <li>• Required premedications * were limited to step-up doses and 1st full dose</li> <li>• MTD was not reached</li> <li>• Collective data supported 2 RP2Ds for talquetamab</li> </ul>		<b>405 µg/kg QW (n=30)</b>	<b>800 µg/kg Q2W (n=44)</b>
<b>PHASE 1 (N=130)</b>	<b>SUBQ Talquetamab (n=30)</b> 405 µg/kg SUBQ QW for ≥2-3 step-up doses given prior to 1st full dose (21-day cycles)	Median age, years (range)	61.5 (46-80)
	<b>SUBQ Talquetamab (n=44)</b> 800 µg/kg SUBQ Q2W for ≥2-3 step-up doses given prior to 1st full dose (28-day cycles)	BM plasma cells ≥60%, n (%)	6 (20.7)
		Extramedullary plasmacytoma <sup>‡</sup> , n (%)	11 (36.7)
		High-risk cytogenetics <sup>§</sup> , n (%)	3 (11.1)
		ISS stage, n (%)	12 (41.4)
		II	13 (44.8)
		III	4 (13.8)
		Median years since diagnosis (range)	5.6 (1.7-19.6)
		Median prior lines of therapy (range)	6 (2-14)
		Prior SCT, n (%)	27 (90.0)
		Exposure status, n (%)	30 (100)
		Tripleclass	24 (80.0)
		Pentadrug	30 (68.2)
		BCMA	9 (30.0)
		Refractory status, n (%)	23 (76.7)
		Tripleclass	34 (77.3)
		Pentadrug	6 (20.0)
			12 (27.3)
<b>Key Objectives:</b> RP2D (Part 1), RP2D safety/tolerability (Part 2), antitumor activity, PK, PD			

Data cutoff: April 6, 2022.

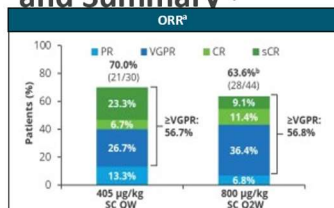
\* Glucocorticoid, antihistamine, antipyretic, and steroid(s) (17p), (14:14), and/or (1:14:14); calculated from n=27 for 405 µg/kg SUBQ QW and n=40 for 800 µg/kg SUBQ Q2W.

1. Minnema MC, et al. ASCO 2022. Abstract 8015. 2. Minnema MC, et al. EHA 2022. Abstract S182.

23

Now there are other targets, however, that I think are extremely important in myeloma; and we've talked about one of them already. That's GPRC5D. This is data from the MonumentAL trial using talquetamab. This is another bispecific. This bispecific targets GPRC5D. So, the CAR T cell that I showed you earlier, this one targets the same target, GPRC5D. And as you can see, this agent is given subcutaneously. There are some specifics about these bispecifics that I think are really important, and we can talk about them in the Q&A. But I think in general what you're seeing here is an idea that these bispecific antibodies are being tested in a very resistant patient population.

## Updated Results From the MonumentAL-1 Phase 1 Study of Talquetamab in Patients With RRMM: Efficacy and Summary<sup>1,2</sup>



Response	405 µg/kg QW (n=30)	800 µg/kg Q2W (n=44)
Median follow-up, months (range)	13.2 (1.124.0)	7.7 (0.716.0)
ORR, n (%)	21 (70.0)	28 (63.6)
Triple-class refractory, n/N (%)	15/23 (65.2)	23/34 (67.6)
Penta-drug refractory, n/N (%)	5/6 (83.3)	9/12 (75.0)
Median time to first confirmed response, months, (range)	0.9 (0.23.8)	1.2 (0.36.8)
Median DOR, months (95% CI)	10.2 (3.0NE)	13.0 (5.3NE)

### PK and PD Summary

- For both regimens, PK and PD profiles were comparable
- 17.6% of patients (13/74) had low titer antidrug Ab, which did not impact safety, efficacy, or PK
- Both regimens were associated with peripheral induction of PD+T cells and consistent induction of cytokines

### Authors' Conclusions

- Both doses of talquetamab had comparable safety, efficacy, and PK/PD profiles in patients with RRMM
- Longer followup ORR results (64% to 70%) across triples and pentadrug-refractory patients confirm the efficacy of QW or Q2W schedules
- A phase 2 expansion study of both RP2Ds and phase 1 studies evaluating talquetamab combination therapy are ongoing

Data cutoff: April 6, 2022.

<sup>1</sup>Investigator assessment of evaluable patients per 2011 IMWG response criteria; includes unconfirmed responses.

<sup>2</sup>Due to rounding, individual response rates do not sum to the ORR.

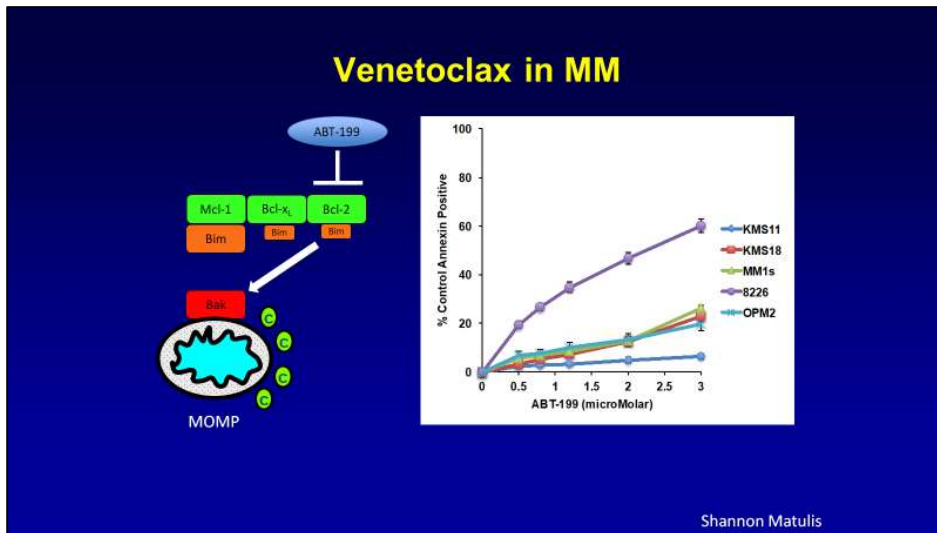
1. Minnema MC, et al. ASCO 2022, Abstract 8015. 2. Minnema MC, et al. EHA 2022, Abstract 5182.

24

And if you begin to look at response rates, what you'll see here is 70 and 63% overall response rate in refractory myeloma, so median again of five to six prior lines of therapy and that this is yet another new immune target that we have to go after in the context of multiple myeloma.

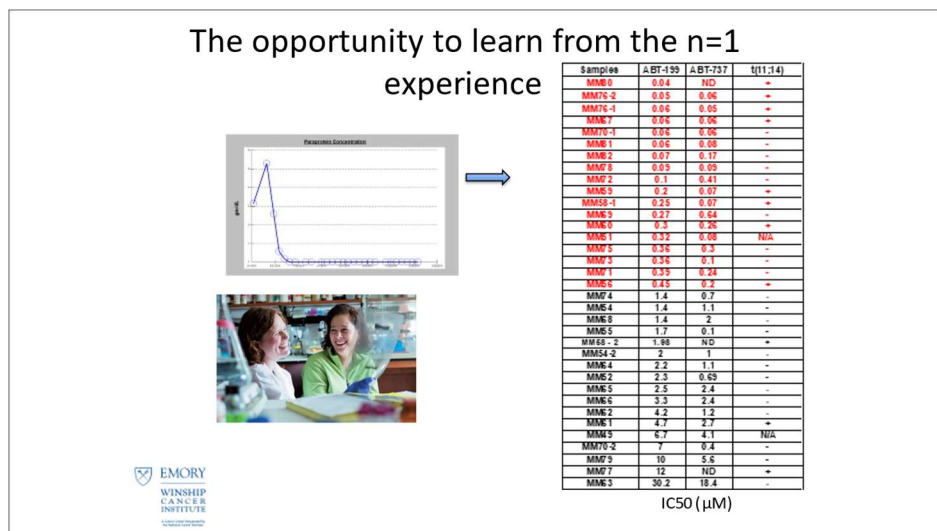
Now I'm going to confuse you [no slide for this section] even further by showing you yet another immune target that has a bispecific that's targeting it, and this is an agent called cevostamab. Cevostamab binds a protein called FcRH5. And FcRH5 is also present on all plasma cells. So, we've talk about BCMA. We've talked about GPRC5D. This is FcRH5, and this is also a bispecific T-cell engager. It binds both CD3 on a T cell and FcRH5 on a plasma cell. And this, again, was a very resistant patient population. Their myeloma was very resistant, a median of six prior lines of therapy. Almost all were resistant to their most recent treatment. And what you're seeing here is an overall response rate of almost 60% at the higher dose level, and again the adverse events are really no different than what we've seen with BCMA or GPRC5D targeting.

GPRC5D may have a slightly different adverse event profile that is worth us probably talking about in Q&A; but, in general, the main adverse events are cytokine release syndrome and neurologic toxicity and happy to talk through that again during the Q&A that's going to follow this session. So lots of immune targets, lots of immune therapies. This to me is an incredibly exciting era and area in the context of myeloma research.



Now I'm going to spend a little time talking about precision medicine in myeloma, and I want to talk about this because this is an emerging area, particularly in a genetic subset of patients. And the subset I'm going to really focus on is the 11;14 translocated myeloma patients. And I'm going to really make a pitch that that is our first example of precision medicine in myeloma.

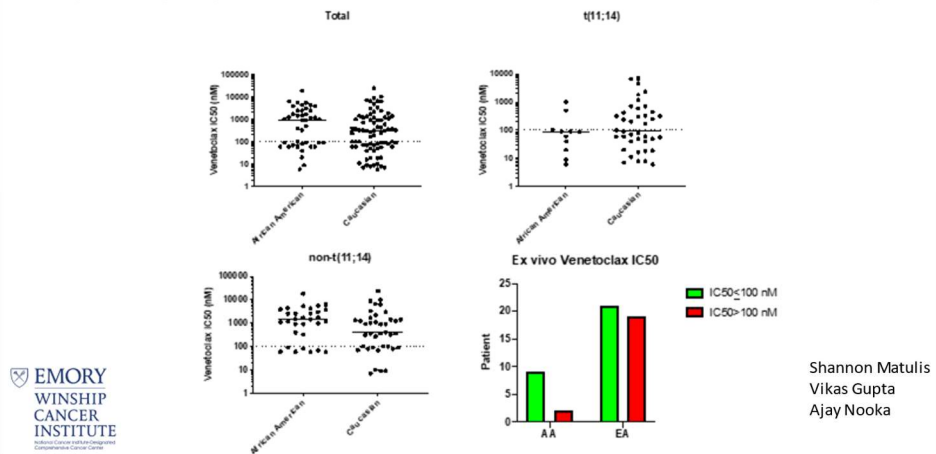
And what you see here on the right side of this screen is a series of myeloma cell lines, and other than the purple one, you don't see much cell death with a drug called ABT-199, which is also known as venetoclax (Venclexta®). You can see it in the title of the slide. Venetoclax doesn't work in most myeloma cell lines. It does, however, work in a few; and those few are what we call BCL-2-dependent or have the 11;14 translocation.



And what we showed in a series of in vitro studies was that there are, in fact, some patients who were exquisitely sensitive to venetoclax in myeloma. And what was most common about those patients on the right side is that they expressed the 11;14 translocation. And in fact, the second most sensitive patient that we've ever treated is this patient that you see here in the right with the M protein very rapidly going to zero. This was a patient that had over a five-year remission with single-agent

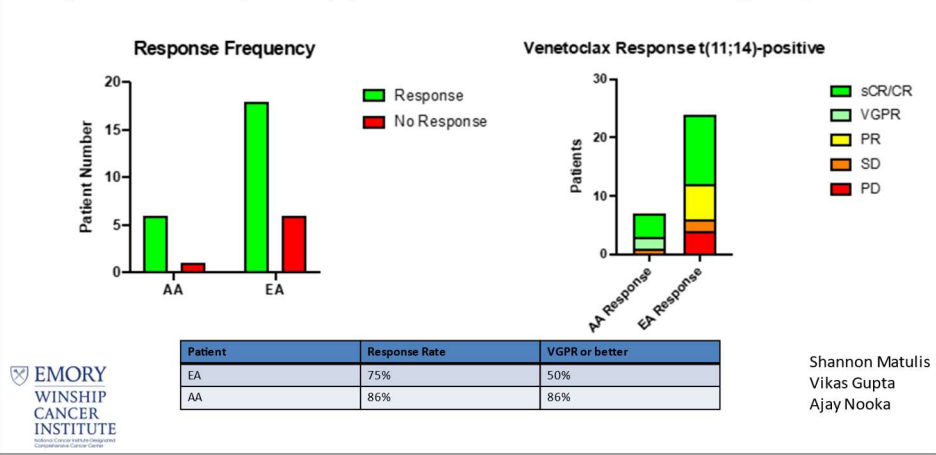
venetoclax after being told that they had refractory myeloma and didn't have other treatment options, really, to manage. So, this can be a highly effective treatment in the right patients.

AA t(11;14) myeloma trend towards Venetoclax sensitivity



And, in fact, what we're also beginning to understand from a biologic perspective is that African American patients who have the 11;14 translocation may actually be more sensitive to venetoclax than their Caucasian counterparts who also harbor the 11;14 translocation. And what you're seeing here is that the IC50, meaning that the sensitivity of the drug, is actually better for the African American patients than it is for the non-African American patients, suggesting that they may actually be more sensitive.

Responses of t(11;14) patients to Ven-containing regimens

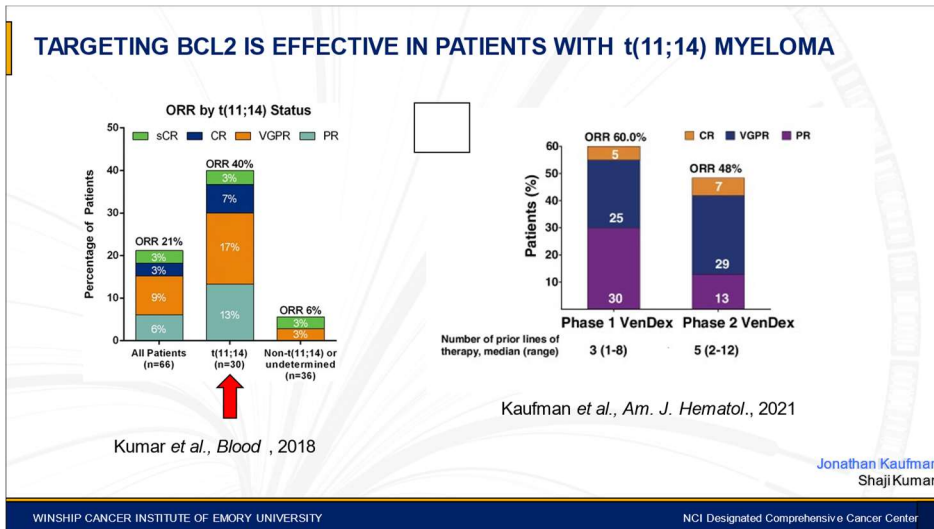


This is work that we're doing at our center. This is preliminary data, but we are actually hoping that this will be tested in a clinical trial that we're doing at our center, testing a combination of venetoclax with another drug in this patient population.

# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

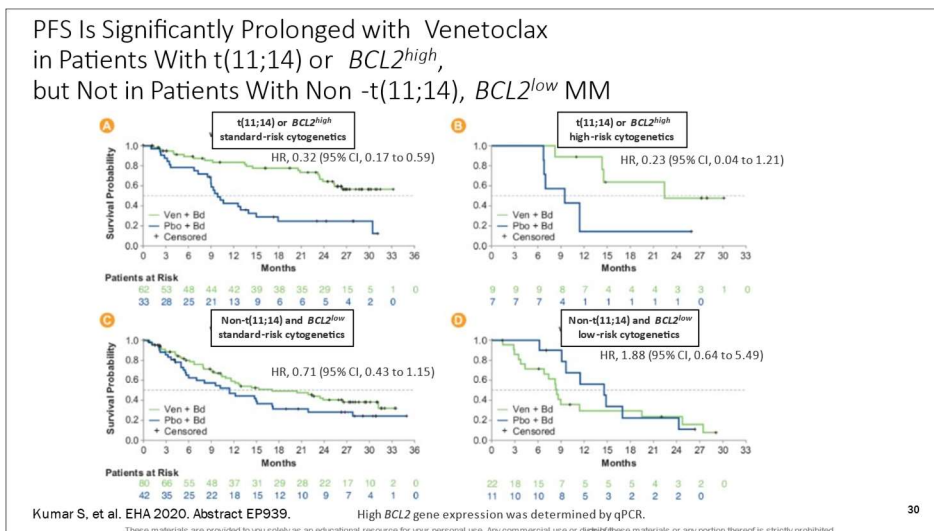
TRANSCRIPT



Now even more importantly, when you start to treat myeloma patients with venetoclax, what you begin to see is that if you look at patients who are not 11;14-positive, you see a very low overall response rate. When you look only at the 11;14 in a phase I study, you see about a 40% response rate. And in fact, when you look at all patients in aggregate, both the positive and the negative, the response rate is about 21%. But this led our group to say maybe we should be treating more people with 11;14 translocation.

And so, we did that, and what we actually demonstrated was that if you use venetoclax and dexamethasone only in 11;14, the response rate is 60% in the Phase I portion; and it was 50% in the Phase II portion. Now, remember, these are resistant myeloma patients, median of five prior lines of therapy, 50% overall response rate with venetoclax and dexamethasone only in the 11;14 subset.

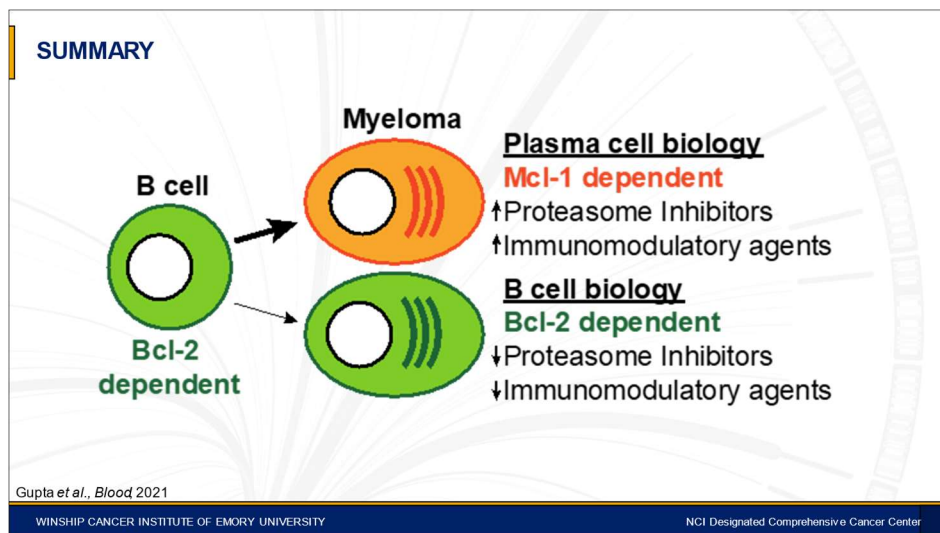
Now, if you take this one step further and say, well, let's do a larger randomized, Phase III trial to understand whether or not this can be effective, that's a good idea only if you believe in precision medicine.





And as an example, there was a trial done in the US and around the world called the BELLINI trial that suggested that if you use venetoclax in all patients, that you do see an improvement in remission duration; but you actually see a worsening in overall survival. The reason this was not using the biomarker, the precision medicine approach, that we recommended.

If you look at the 11;14 in the top curves here, you see a huge difference in remission duration and, in fact, no decrement in overall survival. And so, this to me is an important lesson that if you're going to believe in precision medicine, test your trials in precision medicine. Because if you test it in everybody, you may not see that biomarker driving responses and to me the 11;14 subset is a perfect biomarker for identifying who are going to be most sensitive to venetoclax-based therapy.



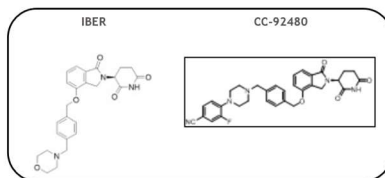
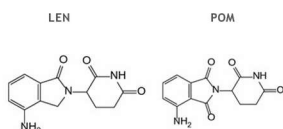
And so Vikas Gupta from our group actually published, a year or so ago, sort of a model saying that most myelomas are Mcl-1-dependent, they are very proteasome- and IMiD-sensitive (immunomodulatory drugs), but there are a subset of patients that are more BCL-2-dependent. They are less sensitive to proteasome inhibitors and IMiDs and very sensitive, for the most part, to venetoclax-based therapy. And this to me is the lesson of precision medicine.

### New CELMoD® agents in development

- LEN and POM (a subgroup of CELMoD® agents) helped to transform therapy and drive survival in MM 1-3
- Rational selection of molecules based on **deep scientific understanding of CRBN and MM biology: IBER and CC-92480**4-6

2019 and 2020:

First clinical data for new CELMoD® agents (IBER and CC-92480) in MM



IBER (CG220) and CC92480 are investigational products, currently not approved by any regulatory agency. CELMoD®, cereblon E3 ligase modulator; CRBN, cereblon; IBER, iberdomide; LEN, lenalidomide; MM, multiple myeloma; POM, pomalidomide.

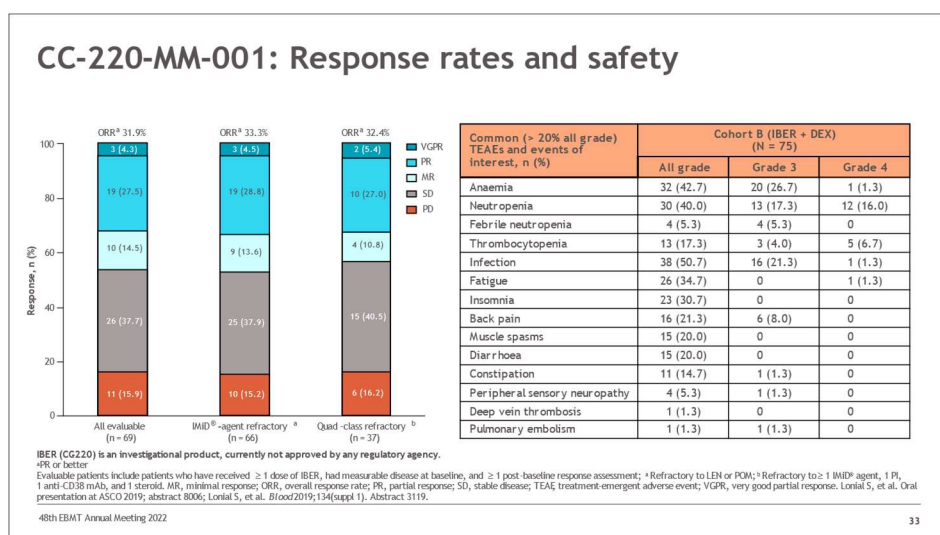
1. Rajkumar SV, et al. Lancet Oncol 2010;11:293-7; 2. Facon T, et al. Blood 2010;113:301-310; 3. Durie BGA, et al. Blood Cancer J 2020;10:53; 4. Ito T, Handa H. Int J Hematol 2016;104:293-299; 5. Matyskiela ME, et al. J Med Chem 2016;59:335-342; 6. Hansen JB, et al. J Med Chem 2020;63:6648-6676.

48th EBMT Annual Meeting 2022

32



Now the last story I'm going to tell is about taking old targets and making them better. We know that the IMiDs, lenalidomide (Revlimid®) and pomalidomide (Pomalyst®), and previous to that thalidomide (Thalomid®) were highly effective drugs in the management of patients with relapsed and refractory myeloma and are so effective that they got moved all the way to earlier lines of therapy because they really did work quite well. But what we learned most recently is that you could further engineer the structures of lenalidomide and pomalidomide to really try and take advantage of their immune side effects, not side effects, but immune properties. And that led to the two new drugs that we're going to talk about which are called CELMoDs (Cereblon E3 Ligase Modulating Drugs) – CELMoDs because they really do modulate cellular immunity probably more effectively than lenalidomide or pomalidomide did. And the first drug we're going to talk about is iberdomide, also known as CC-220. And the second is a drug called CC-92480, now known as mezigdomide or MEZI. So IBER and MEZI are the two newest CELMoDs on the block.



And I presented this data, and we actually recently published data on iberdomide in relapsed and refractory myeloma; and what we showed is that when you combine it with dexamethasone, you get about a 30% response rate in heavily resistant multiple myeloma. But for a patient, the reason that I have this table listed here is if you look at the grade three, grade four, nonblood-related adverse events, what you'll see here is that there are lots of zeros and ones. And what that tells me, and what my patients who've received this drug tell me, is that this drug is much better tolerated than lenalidomide or pomalidomide, which were the precursors of these drugs in the IMiD class.

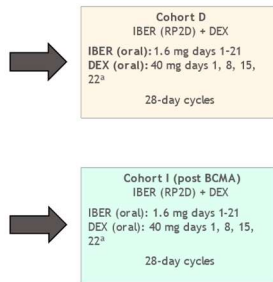
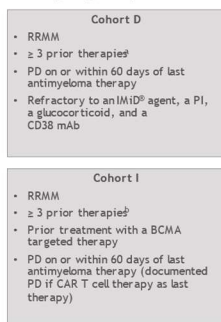
And in fact, I've had a couple of patients now that have said to me, "You told me I wasn't on a placebo. I was getting the drug, and yet I can't tell that I'm on the drug. Are you sure that I'm really getting something that's active?" And I think this reduction in grade three, grade four adverse events really speaks to the efficacy of this drug and the safety of this drug overall.

# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

## CC-220-MM-001: dose-expansion phase; Cohorts D and I

### Key eligibility criteria



### Endpoints

- Primary: efficacy (ORR)
  - Secondary: safety and additional efficacy parameters (including DOR, PFS, OS)
- Primary: preliminary efficacy and safety

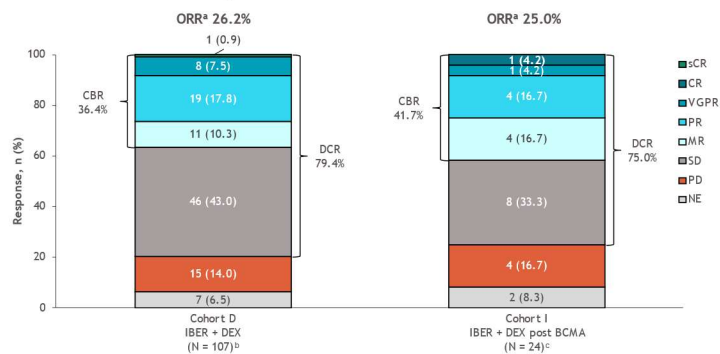
IBER (CG220) is an investigational product, currently not approved by any regulatory agency.  
<sup>a</sup> Including LEN, POM, a PI, a glucocorticoid, and an anti-CD38 mAb; including LEN or POM, a PI, a glucocorticoid, and a BCMA therapy.  
<sup>b</sup> CAR, chimeric antigen receptor; DOR, duration of response; OS, overall survival; PFS, progression-free survival.  
 Loria et al. Oral presentation at ASH 2021; abstract 162.

48th EBMT Annual Meeting 2022

34

Now what we published most recently in *Lancet Haematology* was this Cohort D of patients. These are over 100 patients who received iberdomide at the normal dose as well as dexamethasone with a median of at least five prior lines of therapy.

## CC-220-MM-001: response



IBER (CG220) is an investigational product, currently not approved by any regulatory agency.  
<sup>a</sup> PR or better; <sup>b</sup> 2 patients in SD and MR discontinued treatment because of death due to COVID-19; <sup>c</sup> includes all treated patients who have post-baseline efficacy assessment or have discontinued treatment before any post-baseline efficacy assessment (2 patients were in C1 with no post-baseline efficacy assessments so were excluded from analysis).  
 C, cycle; CBR, clinical benefit rate; COVID, coronavirus disease; CR, complete response; DCR, disease control rate; NE, not evaluable; sCR, stringent complete response.  
 Loria et al. Oral presentation at ASH 2021; abstract 162.

48th EBMT Annual Meeting 2022

35

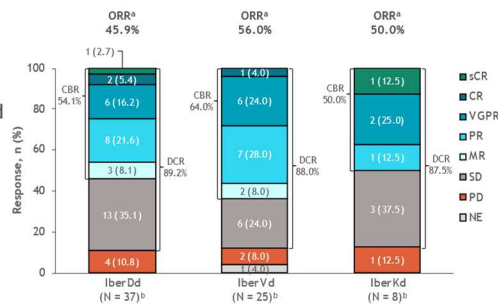
And what we showed was that it had about a 26% response rate. But even more interestingly, if we look at patients that were BCMA-treated, so the newest class of drugs in the refractory setting, these patients had all seen BCMA-directed therapy, the overall response rate for IBER-dex was about 25%. So, we had clear activity even in patients who were resistant to BCMA-directed therapy. So, that to me is very encouraging data.

# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

## CC-220-MM-001: IBER in combination with DEX and DARA, BORT, or CFZ (Cohorts E, F and G) in patients with RRMM

- IBER + DEX in combination with DARA or BORT or CFZ showed a favourable safety profile in patients with heavily pretreated RRMM; TEAEs were mainly hematologic and well manageable
- The RP2D was determined at 1.6 mg in the IberDd cohort, while dose evaluation continues in the IberVd and IberKd cohorts
- Promising efficacy was observed even among patients refractory to IMiD agents, DARA, and Pls



IBER (CC220) is an investigational product, currently not approved by any regulatory agency.  
<sup>a</sup> PR or better; <sup>b</sup> Excludes treated patients who did not reach any post-baseline efficacy assessment and were still on treatment at time of data cut-off.  
 Lonial S, et al. Oral presentation at EHA 2021; abstract S187.

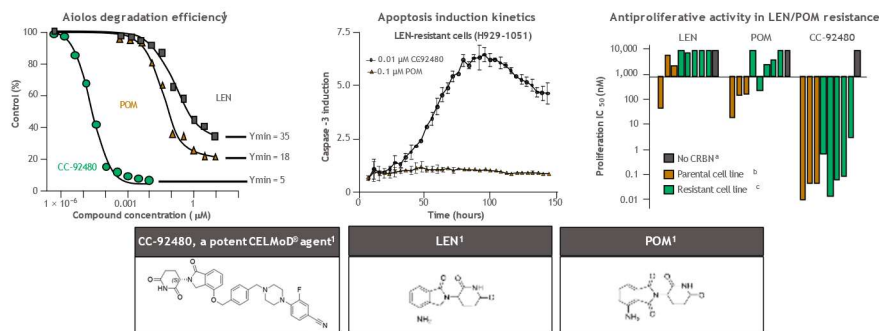
48th EBMT Annual Meeting 2022

36

And of course, when it works alone in myeloma, our job is to put it together with all the other commonly used myeloma drugs; and so, we combined it with daratumumab (Darzalex®), we combined it with bortezomib (Velcade®), and we combined it with carfilzomib (Kyprolis®). And what I think you're seeing here are very encouraging response rates in a Phase I study, suggesting that iberdomide is very easy to combine with other commonly used myeloma agents. And because it's more potent and it has a better adverse event profile, meaning fewer side effects, it might make a better partner drug than either lenalidomide or pomalidomide in earlier lines of therapy.

## CC-92480 is a novel CELMoD® agent<sup>1,2</sup>

Efficient substrate degradation leading to apoptosis and potent antiproliferative activity in LEN and POM resistance<sup>3</sup>



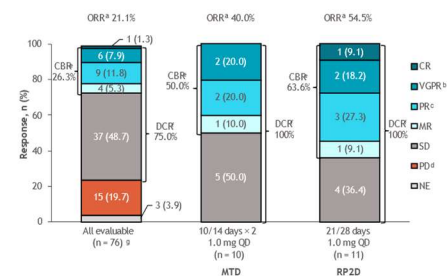
CC-92480 is an investigational product, currently not approved by any regulatory agency.  
<sup>1</sup> DF15R; <sup>2</sup> DF15, H929, and OPA-2; <sup>3</sup> H929R1, H929R2, OPA2R1, OPA2R2, and OPA2R3. IC<sub>50</sub> 50% inhibitory concentration; Y<sub>min</sub>, maximum degradation point.  
 1. Hansen JD, et al. *J Med Chem* 2020;63:66-6676; 2. Wong L, et al. *Blood* 2019;134(suppl 1). Abstract 1815; 3. Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

48th EBMT Annual Meeting 2022

37

Now the last new drug that I'm going to talk about is CC-92480, also known as mezigdomide, again structurally very different from lenalidomide and pomalidomide; and, in fact, what we know is that both IBER and MEZI are able to activate T cells and activate NK cells much more effectively than lenalidomide or pomalidomide. So, these drugs, in my mind, make perfect partners with many of the immune therapies that we've already talked about today.

## CC-92480-MM-001: efficacy and safety in patients with heavily pretreated RRMM



Common (> 20% all grade) TEAEs and events of interest, n (%)	All doses (N = 76)	
	Grade 3	Grade 4
Neutropenia	23 (30.3)	26 (34.2)
Febrile neutropenia	4 (5.3)	1 (1.3)
Anaemia	24 (31.6)	-
Thrombocytopenia	5 (6.6)	7 (9.2)
Fatigue	7 (9.2)	-
Pyrexia	3 (3.9)	-
Peripheral sensory neuropathy	-	-
Diarrhoea	1 (1.3)	-
Nausea	1 (1.3)	-
Deep vein thrombosis	-	-
Infections	25 (32.9)	2 (2.6)
Pneumonia <sup>h</sup>	11 (14.5)	-

- Prophylactic G-CSF was not permitted during C1
- Neutropenia was managed with dose interruption/reduction and G-CSF
- Dose reduction of CC-92480 occurred in 17 (22.4%) patients
- No patients discontinued due to treatment-related AEs

CC-92480 is an investigational product, currently not approved by any regulatory agency.  
 \* PR or better; † 1 patient in the 21/28-day 1.0-mg QD cohort had an unconfirmed VGPR at time of data cut-off; ‡ 2 patients in the 21/28-day 0.8-mg QD cohort had an unconfirmed PR at time of data cut-off; § 1 patient in the 21/28-day 0.8-mg QD cohort had an unconfirmed PD at time of data cut-off; ¶ CBR defined as MR; † DCR defined as SD; ‡ 1 patient had a pending response assessment at time of data cut-off; § Includes Medical Dictionary for Regulatory Activities Terminology version 22.0 preferred terms pneumonia, pneumocystis jirovecii pneumonia, respiratory syncytial viral pneumonia, and staphylococcal pneumonia. AE, adverse event; G-CSF, granulocyte colony stimulating factor.  
 Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

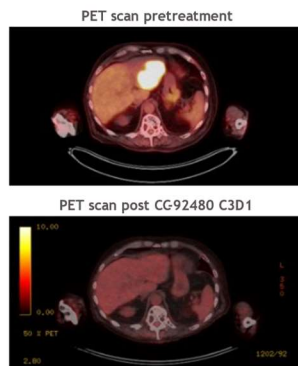
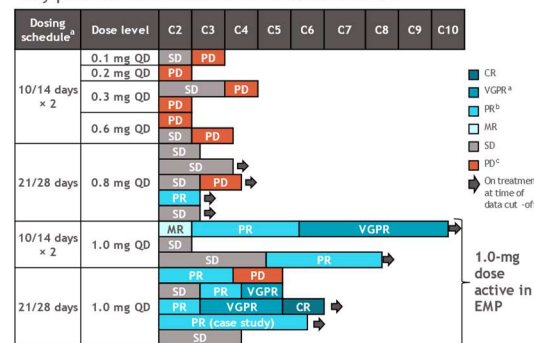
48th EBMT Annual Meeting 2022

38

Now if you look at MEZI in a Phase I trial, you'll see the overall response rate in all patients was about 21%. If you look at the recommended Phase II dose, the response rate was about 54%. And again, what you're seeing, slightly more blood issues, so neutropenia and thrombocytopenia, occurring a little bit more frequently with MEZI than we saw with iberdomide. But again, some of those other IMiD-associated side effects like diarrhea, constipation, fatigue, those seem to be occurring less frequently with the newly minted CELMoD class of drugs, which I think is really exciting.

## CC-92480-MM-001: responses in patients with extramedullary disease

Only patients on continuous schedules are shown



CC-92480 is an investigational product, currently not approved by any regulatory agency.  
 † 1 patient in the 21/28-day 1.0-mg QD cohort had an unconfirmed VGPR at time of data cut-off; ‡ 1 patient in the 21/28-day 0.8-mg QD cohort had an unconfirmed PR at time of data cut-off; § EMP, extramedullary plasmacytoma; PET, positron emission tomography.  
 Richardson PG, et al. Oral presentation at ASCO 2020; abstract 8500.

48th EBMT Annual Meeting 2022

39

And, again, another unique facet: what we know about the CELMoD, the IMiD class in general is that they're not as effective in patients with extramedullary disease (a tumorous area outside of the bones). And what you're seeing here is the slide of a patient with a large plasmacytoma in the liver who got only CC-92480 or MEZI in combination with dexamethasone. And after three cycles of therapy, this patient's liver plasmacytoma had melted away. And we know that patients with extramedullary disease represent a particular and peculiar challenge with modern therapy, and this suggests that MEZI might be a good agent to help manage some of those patients across the board.

### The Future is Very Bright

- New targets and modalities (CART, TCE, ADC) and others in development have the potential to bring together multiple modalities to eliminate the malignant clone
- Trials testing combinations that rely not only on immune but existing targets such as PIs, IMiDs, steroids, and CD38 will be key
- Precision medicine currently a reality and hopefully will be more important as we develop drugs for common mutations

So, to summarize sort of the lecture portion, I guess, if you will, new targets and modalities, including CAR T cells, T-cell engagers, also known as bispecifics, and antibody drug conjugates have really brought together the immune portion of what we do. And in my mind, we have the potential to eliminate the malignant clone across the board.

These trials are testing combinations again that rely not only on immune targets, but also existing targets like PIs (proteasome inhibitors), IMiDs, corticosteroids, and anti-CD38 monoclonal antibodies. And precision medicine currently is a reality, and I would argue it's there in the context of the 11;14 translocated patients. There are other mutations that we're testing in a couple of trials now, particularly BRAF, IDH1, and MEK mutations or RAS mutations. Those are being tested with targeted agents as well, but I think the era of understanding the biology of a specific mutation and using it to target in combination with immune therapies is here today. And I think we have to make sure we pay good attention to those because they can be really important tools to join in our battle against myeloma with drugs like proteasome inhibitors, IMiDs, steroids, anti-CD38s, CAR T cells, T-cell engagers, and antibody drug conjugates ultimately to eliminate the clone and lead to a larger fraction of patients being cured of myeloma.



# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

TRANSCRIPT



**Thanks to:**  
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So, with that, I think I will stop. This is my group, and again we're very appreciative for all the patients, all the sponsors, all the partners in our research, including The Leukemia & Lymphoma Society who support our SCOR (Specialized Center of Research) grant that we work with very closely with the group out in Seattle and are grateful for all of their support and your support as well.



## QUESTION-AND-ANSWER SESSION

**Lizette Figueroa-Rivera, MA**


Well thank you so much, Dr. Lonial, for volunteering your time with us and providing us with so much information regarding therapies and newer therapies for myeloma.

**ASK A QUESTION**  
**UNDERSTANDING MY TREATMENT OPTIONS: MULTIPLE MYELOMA**

**Ask a question byphone:**  
Press star (\*) 1 on your keypad to ask a question  
To remove your question press star (\*) 2 on your keypad

**Ask a question byweb:**  
Type your question in the "Ask a question" box under the speaker video window

Due to time constraints, we can only take one question per person.  
Once you've asked your question, the operator will transfer you back into the audience line.

**42**

It's now time for the Question-and-Answer portion of our program. For everyone's benefit, please keep your questions general in nature without many personal details so Dr. Lonial can provide answers that are general.

Dr. Lonial, the first question today is coming from John. John's asking, "After treatment reaches remission, as determined by blood draw results, is the bone marrow biopsy the best way to determine the best diagnosis of remission?"

**Sagar Lonial, MD, FACP**

So, you know, I think that myeloma is one of the diseases where we have an easily accessible biomarker in the blood that can be used to track whether or not a treatment is effective in most patients with myeloma. And so, oftentimes, we'll do the SPEP, the serum protein electrophoresis. We'll do the free light chain assay to get a better sense for what else is going on. We may often check a urine protein as well to understand whether that protein is present or absent as another indicator of remission. A bone marrow biopsy is a measure that we use; and, in the current approach, we will often do MRD (minimal residual disease) testing on that bone marrow to understand the depth of remission. And finally, we are now doing imaging to also make sure that we don't see other areas of disease outside of the bone marrow that may not be picked up on (routine imaging or) routine bone marrow or bloodwork. And so, a PET (positron emission tomography) scan is another test that we often use if we're trying to understand the extent of a disease control for a given patient. So, there are multiple ways that we assess, and, at least at our center, we do all of them.

***Lizette Figueroa-Rivera, MA***

Thank you so much, and we'll take the next question from our telephone audience, please.

***Operator***

Our question comes from Victor, calling from Oregon. Please go ahead with your question.

***Victor from Oregon***

Is there anything on the horizon for patients with the 17p deletion?

***Sagar Lonial, MD, FACP***

Yeah, so 17p deletion, for the rest of the crowd, is a genetic abnormality where you lose the short arm of chromosome 17, which houses a really important gene called p53. And when you're missing p53, what you're missing basically is the ability to repair DNA damage in the DNA of a myeloma cell. And if you're a cancer cell, that's exactly what you want to do. You want to remove the ability to repair DNA defects so that you can stay alive and do all the things that myeloma cells like to do.

17p deletion, in general, tends to be a high-risk marker and we at our center treat it with aggressive maintenance. I don't think we have specific treatments targeting 17p. What I think we all tend to do is make sure that we offer those patients high-dose therapy because from our European colleagues, there's good randomized data suggesting they do better with high-dose therapy and transplant. We tend to recommend doublet or triplet maintenance after transplant. And then these are patients that we may often refer to bispecific or CAR T-cell therapy a little bit earlier, depending upon their response to salvage therapy to try and get more aggressive treatments in general. But we don't have a way to put that gene back in, at least as of now; and, from a current perspective, we don't have something that can reactivate that gene in patients who have a mutation or, again, are missing a copy of it. So, I think it really is a strategic approach to high-risk myeloma as opposed to something very specific or unique to 17p.

***Lizette Figueroa-Rivera, MA***

Thank you. And you just mentioned doublet or triplet therapy, are we seeing more therapies be triplet therapies, meaning three medications at once?

***Sagar Lonial, MD, FACP***

Yeah, I think triplets certainly in the early relapsed setting have become a standard of care. What I was referring to there is maintenance with more than just lenalidomide. And so, our group has used VRd (bortezomib-lenalidomide-dexamethasone, also known as RVd) maintenance for years for

high-risk patients; that's triplet maintenance. I think we've now more recently using KRd (carfilzomib-lenalidomide-dexamethasone) as maintenance for high-risk patients, again, triplet maintenance.

The FORTE trial from the Italian group used carfilzomib and lenalidomide without the dexamethasone, so that's where the doublet comes in. It's still highly effective therapy in the context of high-risk maintenance therapy, but as you alluded to, most of the time we are using triplets across the board and even in some cases, in newly diagnosed myeloma, we're using four drugs as part of the induction regimen.

***Lizette Figueroa-Rivera, MA***

Thank you. And Ross is also asking, "Will any treatments not require steroids?"

***Sagar Lonial, MD, FACP***

You know, I don't think I've ever been on a patient webinar or a patient meeting where that question didn't come up. And I think it's important to recognize that steroids are highly effectively at killing myeloma. They're also great partners for the IMiD class of drugs, in the sense that if you look at an IMiD alone, the response rate is half what it is when you partner it with steroids.

But the benefit of steroids is likely relatively short-lived, meaning maybe four to six months. And so, I think that what most of us are doing now is beginning to taper those steroids off earlier, like within a few cycles of treatment, particularly if patients have significant side effects. And even feeling more comfortable with discontinuing the steroids before or around the first year of treatment to try and mitigate some of the side effects that I'm sure our question asker is really speaking to. And so, I don't know that we're going to get away completely from steroids, but I think we're reducing the dose and duration of steroids in a large way to try and make it much more patient friendly.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the telephone audience please.

***Operator***

Thank you. Our next question comes from Mary calling from North Carolina. Please state your question. Your line is now live.

***Mary Richardson from North Carolina***

Yes, my name is Mary Richardson, and I have had all of what you have talked about; and once my myeloma started going up, they changed me over to another drug, which is pomalidomide, and start with a D. That I started taking those. And I've been on those now for six weeks, and hopefully they will



get my myeloma back down like it was before when I was on Revlimid and the other one. I can't remember it right now. So, I've been on it now for six weeks and hoping that things would get better for me. And I also take dexamethasone once a week. But the pomalidomide I take every day for 21 days and then I'm off, and they I go back again. What else can the doctor do in order to get my myeloma to come down?

#### ***Sagar Lonial, MD, FACP***

Yeah, that's a tough question to answer without having a lot of records and things in front of me. Again, would need to sort of see the treatment history and what drugs have not worked to treat your myeloma and where we are in terms of the armamentarium that we just described. But certainly, I think the good news is that either on clinical trials or with recent approvals, there are a number of agents that hopefully will be of benefit to you if the current treatment, which sounds like pom-dara-dex (pomalidomide-daratumumab-dexamethasone), is not helping you. Just I would ask them to look at again new approvals and work with a myeloma specialist that's near you to help come up with the next best treatment plan in that context.

#### ***Lizette Figueroa-Rivera, MA***

Yes, and I think this program is really proving that there are still many new treatment options that are available to patients right now, so it is a very exciting time for myeloma treatment.

Doctor, James is asking, "What is the prospect of using these new CAR T and other novel treatments earlier in the treatment process, perhaps as first-line therapies? Do you anticipate that non-heavily pretreated, newly diagnosed myeloma patients would have better and longer-lasting response rates?"

#### ***Sagar Lonial, MD, FACP***

Yes, that's a really great question; and you're not the only one asking that question. There have been several randomized, phase III trials launched looking at CAR T cell as an alternative to transplant in first remission, looking at CAR T cells as an alternative to salvage therapy in the context of first-relapsed myeloma. We're likely, hopefully, going to see some of this data presented in the next six to 12 months from many of these trials looking at the two FDA-approved CAR T cells, both cilta-cel (Carvykti™) and ide-cel (Abecma®).

So, I think there's theoretical reasons to believe that the T-cell health may be better earlier in the disease and that with better T-cell health, you'll get a better product and then it might ultimately result in better outcomes for patients than we see in the relapsed and refractory setting. Those are, I think, really important hypotheses to test; and the only way we're going to get those answers is from randomized trials, and those trials are currently ongoing.

#### ***Lizette Figueroa-Rivera, MA***

Thank you, and I know that you just mentioned transplant. George is asking, "What's the difference between autologous and allogeneic transplants? Is it true that an allogeneic transplant will be done after failing more than one autologous transplant?"

#### ***Sagar Lonial, MD, FACP***

Yeah, autologous transplant means you use your own cells. So, in that example I showed earlier about the CAR T cell, you take your own T cells out, they get manufactured, and then they're given back to you. That's sort of a similar principle except there's no manufacturing with an autologous transplant, which by far represents the majority of transplants that are done for patients with multiple myeloma.

An allotransplant for myeloma means that you take a donor, a healthy donor, that is matched to a certain degree with your blood types and with your HLA (human leukocyte antigen) types and use that donor to try and bring in a fresh immune system to try and kill out the myeloma. That is a very high-risk procedure in the context of multiple myeloma. The mortality of an auto is less than 1%. The mortality of an allo is significantly higher because of a number of factors, including age, graft-versus-host disease, and ultimately still-relapsed myeloma.

And so, allos are very rarely performed (for myeloma) in 2022 in the U.S. anymore because of all the new drugs and treatments that we have that are so effective and don't potentially expose a patient to the risk of death and side effects like graft-versus-host disease that an allotransplant does expose patients to, and it's just not done very frequently anymore at this time.

#### ***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the telephone audience, please.

#### ***Operator***

Our next call is from Ralph from California. Ralph, please state your question. Your line is now live.

#### ***Ralph from California***

Hi, I've got a technology question; and it's about the robustness of the FISH (fluorescence in situ hybridization) testing. The gentleman that had the 17p deletion, I have a 14q deletion, but there was some research decades ago in France at the Pasteur Institute. A fellow said that there are many substances that during the DNA transcription leave it unwound, and I wonder if that's actually true, can the FISH test, are they actually spotting unwound DNA instead of that it's deleted because they're not seeing the coiled?

### ***Sagar Lonial, MD, FACP***

Yeah, I mean I think, the beauty of FISH testing, unlike routine cytogenetics, is that it doesn't require a rapidly dividing cell in order to see it. And so, the probes are engineered to look for common binding areas in those genes that don't necessarily have to be wound or unwound in order for it to be seen. There may be rare instances where that technically can happen.

What is more likely the case where a FISH test may be a false-negative is that the lab doesn't do plasma cell enrichment, meaning that you don't just look at myeloma cells. You look at whatever is in the bone marrow. And if you see a negative result there and the marrow is diluted out without as many myeloma cells in there, then you may get a false-negative in that context, as well.

You know, 17p, we also often look for p53, not just looking for that whole arm of the chromosome but certain probes on that arm as well. And so, I think the modern way of testing FISH is a little bit more effective at getting around that complication that you described.

### ***Lizette Figueroa-Rivera, MA***

And thank you for that question. The next question comes from Paul, and he's asking, "Do some myeloma patients have minimal side effects that might not be noticed?"

### ***Sagar Lonial, MD, FACP***

Well, there's always a spectrum of adverse events and tolerance of adverse events. There's some patients who seem to experience a lot more; there are others who seem to experience a lot less. It doesn't mean that you're having a better or a worse response to the drug. It doesn't mean that the drug is not working, if you don't have side effects. So, that was a question that I often get from people who are tolerating their treatment relatively well.

I think everybody's a little bit different; and it's hard to predict where patients are going to be. But I think if you are experiencing side effects that make it difficult for you to have good quality of life, it's important to explain those and relate those to the team. At least in my team, that's something that our nurses and nurse practitioners really focus on a fair amount and try and make sure that it's not just a matter of you'll stay on, and we're going to do whatever we have to do. We do want to make sure we appreciate and understand the impacts that the treatment is having on your quality of life and your activities of daily living. And if those are significant, we need to make adjustments to make that drug and that treatment more tolerable to allow you to enjoy both the benefit of therapy as well as the benefit of potentially being in remission. So, I think there are a number of factors that play into that.

### ***Lizette Figueroa-Rivera, MA***

Thank you, and we do have a few questions about side effects. Elizabeth is asking, "What's the difference between bone pain and muscle pain?"





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***Sagar Lonial, MD, FACP***

Yeah, that's, you sort of have to have it to know it. Muscle pain is just more achy, whereas bone pain you can actually feel it in the bones. You know, muscle pain tends to, like when you ran a marathon or you're not a frequent exerciser and you get up and do more than you can normally do, that experience is more typically muscle pain. Whereas bone pain tends to be a little bit more central, is a little bit more difficult to manage, and is more of a dull pain that's sort of, it just qualitatively is a little bit different.

***Lizette Figueroa-Rivera, MA***

Thank you, and Robert is asking, "Do the medications used to treat myeloma have any effect on legs, like peripheral neuropathy, feet being numb, legs being weak, or lower back pain when standing for too long of a time?"

***Sagar Lonial, MD, FACP***

Yeah, so probably the biggest offender in this area is bortezomib, also known as Velcade. Velcade does cause peripheral neuropathy and both numbness and sometimes tingling or, in extreme cases, electric shock-like feeling in the feet or in the hands.

I think the goal of being an active patient in the management of your disease is that, if you're beginning to develop those side effects, make sure you let the infusion nurse know or you let the doctor or nurse practitioner know as well. Because those are signs that we need to potentially hold the drug or reduce the dose of the drug or change the schedule of the drug. And, in the case of a drug like bortezomib or Velcade, we may go from twice-a-week to once-a-week dosing. If you're already at once a week, we may reduce the dose; and that is a significant issue.

It can be seen in other drugs like lenalidomide less commonly but can be seen. Pomalidomide, it can also be seen, again, less commonly, but it can be seen. And even carfilzomib, in rare situations, we may see peripheral neuropathy. It's, again, much, much less common though than we see it with bortezomib. And it can impact your ability to stand for a long time. The low back-pain that's being described sounds more like spinal stenosis than it does like peripheral neuropathy; but certainly peripheral neuropathy can limit the ability of a patient to stand for long periods of time because of pain or discomfort in the soles of their feet.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the telephone audience.

### ***Operator***

Our next question is from Cheryl from Michigan. Cheryl, please state your question. Your line is now live.

### ***Cheryl from Michigan***

Thank you very much. Hi, everybody. I would like to know, I'm on Ninlaro® (ixazomib). I was on Revlimid and Velcade and was having a lot of the neuropathy and some bad side effects. And now on Ninlaro, once you take the medication, should you see your kappa chains and light chains decreasing, or do they just stay the same? And I actually had the transplant, the autologous I know I'm not pronouncing it right, the one that they use your own body to do the transplant. And is there a way that we can get information like with all the different meds you listed, like a transcript of today's meeting as well?

### ***Sagar Lonial, MD, FACP***

Well certainly, the first question as related to should you see the light chains continue to drop, it depends on where they are. It sounds like the treatment was switched from Velcade to ixazomib because of neuropathy. Hopefully, that will make the neuropathy better. Ixazomib is an oral version of Velcade. It does have slightly less peripheral neuropathy than Velcade, and it's oral; so, it's a little bit easier to take. But there can be patients who develop neuropathy with ixazomib as well, so I think it's worth being very cautious about your symptoms as you continue on the treatment.

There are some patients where they do reach a plateau and stay stable with low-level disease without necessarily going down to a normal range. That's okay as long as everything else is okay and you're tolerating the treatment pretty well and, again, most of the myeloma has gone away. Those are sort of judgment calls that your doctor, probably worth asking them a little bit more in specific.

In terms of access to the things we're talking about here, I'm going to defer that to our host here.

### ***Lizette Figueroa-Rivera, MA***

Yes, we will have a transcript on our website as well as this video recording will be on our website. You can go to [www.LLS.org/Programs](http://www.LLS.org/Programs), and we will have that for you. So, all of the medications, all the treatments, the slides are actually already up on the program page, but everything will be spelled out for you.

Doctor, Irwin is asking, "For smoldering myeloma treatment for two to three risk factors, what are the treatment options?"

#### ***Sagar Lonial, MD, FACP***

Yes, so for patients that fit into what we now call the high-risk smoldering category based on the 20/2/20 criteria (International Myeloma Working Group risk stratification system), I think that there are now two randomized trials demonstrating delays in developing myeloma, either with lenalidomide alone or lenalidomide and dexamethasone together, based on the Spanish and the U.S. trial. Now this is a very controversial area within our field; and actually, based on that, I think what I would say is it really is worth a significant discussion between you and your doctor as well as, perhaps, a myeloma specialist to determine whether early intervention is a good idea for you. I think it is an important discussion to have.

But certainly, I would suggest, rather than doing this off of a clinical trial, to try and enroll on a clinical trial. And, in fact, there is a national trial that almost every center should have access to that is randomizing patients to either Revlimid and dex versus Revlimid, dex and daratumumab, really trying to understand whether myeloma-like therapy is more effective than prevention-like therapy, which is what we've tested in the past. And that trial is available across the country, and I think is really important for us to help answer that question about whether patients benefit from early intervention.

#### ***Lizette Figueroa-Rivera, MA***

Thank you. And Stewart is asking, "Any progression-free survival or overall survival data for patients that have myeloma with AL amyloidosis?"

#### ***Sagar Lonial, MD, FACP***

Yeah, I think the amyloid adds in another wrinkle from the perspective of adverse event tolerance, but what we know is that if patients can achieve both a hematologic remission as well as an organ remission, that they can do quite well. And I think the Mayo Clinic has data on this; the group in Boston at BU (Boston University) has pretty significant data on amyloidosis and outcomes.

I think what we found is if patients can tolerate the treatment and get into a remission, they can do quite well. I have many patients that are eight, nine, ten years out from their autotransplant back to normal doing very well with both myeloma and amyloidosis. So, I think for certain patients without significant organ damage, patients can do quite well.

#### ***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the telephone audience please.

#### ***Operator***

Our next question comes from Kenneth from Virginia. Kenneth, please state your question. Your line is now live.

***Kenneth from Virginia***

Okay, hello. My question: is myeloma curable?

***Lizette Figueroa-Rivera, MA***

Is myeloma curable?

***Sagar Lonial, MD, FACP***

Yeah, that's a controversial question. I would argue that there's probably about 10% to 15% of patients who have what we call functional cure, meaning that the myeloma never really comes back and perhaps they end up having another cause of death from cardiovascular or other means or ends. But I think for a majority of patients, the myeloma does come back at some point; and the question at that point is not can we cure it or not, it's can we put it back into remission? And that really remains a major goal no matter when we see a patient.

***Lizette Figueroa-Rivera, MA***

Thank you for the question. In our next question, Taylor's asking, "Do you find that the timeline for CAR T manufacturing is accurate? I'm hearing that the length of manufacturing is the biggest barrier to accessing this treatment. Are there long wait times?"

***Sagar Lonial, MD, FACP***

Yeah, yeah. There are probably two barriers. The first is the time for manufacturing, which is probably practically within three and five weeks is the average turnaround that we're getting roughly. The second is the number of slots for manufacturing that we have. So, I know many large centers have waiting lists of over 50 to 60 patients, and that is not because the manufacturing time is so long. That's because we only get a very limited number of slots per month to be able to put patients through the process. And so, I think it's a combination of both limited manufacturing slots and time for manufacturing that really is the big limitation in access for patients.

***Lizette Figueroa-Rivera, MA***

Thank you. And Sandra is asking also about CAR T-cell therapy. She's asking, "Does disease burden impact the CRS or cytokine release syndrome and neurotoxicity during the treatment?"

***Sagar Lonial, MD, FACP***

Yeah, there is certainly good data suggesting that the risk of severe CRS and neurologic toxicity is lower with lower disease burden; and so, I think sometimes you don't have a choice. You go whenever you can go, whenever you get the slot, whenever you get what you get.

But I think if you have a choice, going in a situation where the disease is lower or perhaps even a little bit better controlled is one way to reduce the adverse events associated with the acute infusion of a CAR T cell.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from the telephone audience please.

***Operator***

Our next question is from Marla from New York. Marla, please state your question. Your line is now live.

***Marla from New York***

Facing a possible CAR T clinical trial, but I want to know what happens to the other 40% or so that the CAR T may not work. Can you do a second CAR T or what are the options after CAR T?

***Sagar Lonial, MD, FACP***

Yeah, I mean I think the response rate is higher than 60%, certainly, so it's probably a much smaller number, depending upon the product that you get. You know, I think that if you're going to retreat with a CAR T cell, that typically means using a different product. Probably the same product is not necessarily going to give you the same mileage or opportunity for a benefit.

I think that there are patients who have not responded or lost their response to a CAR and then responded to a T-cell engager or an antibody drug conjugate. There are also other targets beyond BCMA like, as I mentioned, GPRC5D or FcRH5. All of those potentially remain options in the context of clinical trials as well. So there certainly are other options in that setting.

***Lizette Figueroa-Rivera, MA***

Thank you. And we have Pearly asking, "If you would try these new treatments, so CAR T, bispecifics on a 76-year-old?"





#### ***Sagar Lonial, MD, FACP***

Yes, absolutely. Age to me is not a reason to say yes or no to any given treatment. I think that if the 76-year-old is functional, then I would definitely do it. I've given a CAR T cell to a patient over the age of 80 without any hesitation or reservation. This was a very fit 80ish year old. And so, for both of these options, it's really more about comorbidities and function than it is age.

#### ***Lizette Figueroa-Rivera, MA***

Thank you. That's really good to know. We do get questions a lot in regards to a person's age and the type of therapies that they would be able to have, so thank you so much.

The next question is from Dennis. Dennis is asking, "If extramedullary plasmacytoma extramedullary plasmacytoma (tumorous area outside of the bones) and nonsecretory myeloma (the absences of detectable protein in the serum or urine), are the treatments the same as for general myeloma?"

#### ***Sagar Lonial, MD, FACP***

Yes, certainly the extramedullary, particularly at the time of presentation, is functional high risk; and so, you would treat that like you would treat a high-risk myeloma patient. In terms of nonsecretory or oligosecretory (low levels of protein in the serum and urine), the treatments are quite similar to what we would do for myeloma. We just observe them differently in that we need more imaging, and we probably need more bone marrow biopsies to understand exactly how much disease we're dealing with because the SPEP (Serum Protein Electrophoresis) and the light chain assays don't help us very much in that context.

It is important certainly for nonsecretory patients who present that way at the time of diagnosis. They can do remarkably well for very long durations of time. I have several patients that are ten plus years out from an autotransplant with nonsecretory myeloma doing well. So, it doesn't necessarily mean that the myeloma is harder to treat. That's different from extramedullary which is probably a little bit more challenging to treat overall.

#### ***Lizette Figueroa-Rivera, MA***

Thank you. And we'll go to the phone for our next question please.

#### ***Operator***

Thank you, our next question is from John from Florida. John, please state your question. Your line is now live.

### ***John from Florida***

Yes, good afternoon. In the context of a bad lambda light chain, there's reduction of over 95% within four months on the mg/dL range where the quote "normal" range is 2.6 or below. Do you follow me, doctor, in that context?

### ***Sagar Lonial, MD, FACP***

Yes.

### ***John from Florida***

So, within four months, there was a reduction of over 95% from a bad 480 to a quote "pretty good" range of five to seven, never reaching the magic 2.6. Basically, the consensus is on a cost-benefit scale that's good enough for now. It's not technically remission, but you're in the five to eight range. You're not 2.6. We've been doing this for months. You've been stuck in that range for six months. You're not getting any lower, and this was on a combo of dara-Velcade and dex basically.

### ***Sagar Lonial, MD, FACP***

Yes. So, I think that there are patients who don't necessarily get to the complete remission benchmark; and if their symptoms are well-controlled, they're tolerating the treatment well, and it's a prolonged low-level disease burden, that's okay. One of my longest patients that I call, he's not in complete remission, but he's in a remission, never achieved a complete remission. But this is like 14 or 15 years now. And so, as long as you can stay that way and you've reversed organ damage, that's okay. I don't know all the specifics of your case, but I think there are certainly a lot of situations where I, too, would be happy with where that is.

### ***Lizette Figueroa-Rivera, MA***

Great, thank you. And I know that you just spoke about complete remission, can you talk a little bit about MRD, minimal residual disease, for myeloma patients?

### ***Sagar Lonial, MD, FACP***

Yeah, so MRD is really just another level. So, 25 years ago a complete remission by the old SWOG (Southwest Oncology Group) response criteria was a 75% reduction in the protein in the blood. The most recent complete remission definition means absence of the protein in the blood. Now we've got MRD, which is looking at 1 in 10,000 cells, 1 in 100,000 cells, or one in a million. So, if your MRD is negative at  $10^{-6}$ , that means there are fewer than one in a million myeloma cells in that sample. If you're one times  $10^{-5}$ , that means fewer than 1 in 100,000 cells.

And so, each of these are just a deeper way to measure how low the tumor burden is, but it doesn't necessarily mean that you're cured of myeloma because we know that patients, who achieve MRD negativity, relapse or can relapse.

And so, I think that they are important prognostic tools. They're important to tell patients that, yes, you've achieved this depth of response. But right now, we don't have the data that says that if you don't achieve a remission at  $10^{-6}$  by MRD that you should change treatment. And that's what many people want to do, but it may be a biologic signal saying that this myeloma's harder to get rid of or you're not going to get rid of it, but it's going to stay where it is. And just cycling through drugs and not seeing them respond may be giving you misinformation.

And so, what I would tell patients is it's okay to do MRD testing. I'm just not sure I would act on MRD testing right now to make major treatment discontinuation or treatment changes at this timepoint. I don't think we have the data for that.

***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from our telephone audience please.

***Operator***

Our next question comes from Victor from Oregon. Victor, please state your question. Your line is now live.

***Victor from Oregon***

Thank you. Yes, I was curious if stem cells that have been collected and frozen have any other potential usage. For example, can they be used as T cells or for any other treatment other than a transplant?

***Sagar Lonial, MD, FACP***

That's a good question. There are more modern ways right now to take a frozen product and select out the T cells so that you could, in theory, do that. I don't think that that's covered under the FDA approvals of either of the CAR T products currently, but certainly that is one potential way you could do it.

The concern would be that the growth factors that you use to mobilize that stem cell product for transplant can have an impact on T-cell function. And there is at least a theoretical concern that you may be making them sleeper T cells, if you will, just to be simple, than if you just collect them without any growth factors at all, which is typically what we use now to collect those cells as well.

So, I think you can use them for that purpose. We certainly use T cells, those frozen stem cell products many years down the road, if a patient has low blood counts because of chronic treatment and we need to re-boost their immune system, or even in the context of patients who develop low blood counts after a CAR T-cell infusion. If they're three and six months out and their blood counts have not recovered and their bone marrow looks pretty empty, we've used that frozen stem cell product in that context as well. So, I think there are indications beyond a classic transplant in which those cells can be used.

#### ***Lizette Figueroa-Rivera, MA***

Thank you. And the next question is from Gail. Gail's asking, "How does having chronic kidney disease caused by the myeloma affect eligibility for the CAR T cell and other new treatments?"

#### ***Sagar Lonial, MD, FACP***

Yes, so, what we know about renal dysfunction or kidney dysfunction really is that the most important thing you need to do is dose-adjust the drugs where that's important. And so, for instance, in drugs like lenalidomide, making sure you have dose adjustments. For drugs like bortezomib and carfilzomib, we don't have to make dose adjustments. For the antibodies, typically we don't have to make adjustments. And in the context of transplant, you just need to use a lower dose of melphalan (Alkeran®), potentially, but it should not preclude referral to a transplant center. Even a patient that's on dialysis can be transplanted. And, in fact, we've gotten patients off dialysis by taking them to transplant and really reducing their amount of light chain burden in the blood to allow that to happen. So, I don't think it's that you can or can't get certain therapies. It's really a matter of how to adjust the doses of the medication to make sure that they're being adjusted for some level of kidney dysfunction.

#### ***Lizette Figueroa-Rivera, MA***

Thank you. And we'll take the next question from the telephone audience, please.

#### ***Operator***

Our next question comes from Gloria from New York. Gloria, please state your question. Your line is now live.

#### ***Gloria from New York***

Hi, my husband wants to know how long does this disease last; and does he have to be under treatment for the rest of his life?

***Sagar Lonial, MD, FACP***

I think that from the perspective of treatment, the current treatment paradigm for most patients is continuous therapy, meaning continuous maintenance therapy or continuous therapy even in the salvage setting until the drugs no longer work.

Now the caveat to that is tolerance and side effects. If patients have significant side effects, then sometimes treatment can be held or discontinued because of those side effects. We know, for instance, that after CAR T cell, the current FDA label, you give no therapy afterwards; and so that's another way where perhaps people can discontinue treatment. We know that with some of the T-cell engagers, for instance, there are patients that have had significant infectious issues early, discontinued, and are now a year or two out, not on the drug, but remain in remission. So, I think understanding these newer immune therapies and how long we have to give them, balancing that with the risk of infections is really important, and that is something that many centers are beginning to look at more carefully.

***Lizette Figueroa-Rivera, MA***

Thank you. And our next question is from Lulis. Lulis asks, "If someone goes into remission, how long will they have to continue on Revlimid?"

***Sagar Lonial, MD, FACP***

So, in the maintenance setting, what the DETERMINATION study proved was that longer Revlimid maintenance is better than shorter, which is what the French version did. The U.S. gave it continuously. The French only gave it for a year. The remission duration was much longer in the group that got continuous versus shorter duration.

At our center, we've demonstrated as well in the RVd 1000 Series that the longer patients can stay on the better. So, I keep patients on for as long as they can tolerate it and as long as their blood counts are okay. We don't discontinue in that context.

***Lizette Figueroa-Rivera, MA***

Great, and now Lawrence is asking, "Is there an alternative to Revlimid for maintenance therapy?"

***Sagar Lonial, MD, FACP***

Well, there is randomized data using ixazomib (Ninlaro®), the oral form of Velcade, in maintenance therapy. The remission doesn't seem to be quite as long as what we saw with Revlimid. There are studies now looking at daratumumab, with or without Revlimid as a maintenance strategy as well. But I think the most data by far is with Revlimid. In the high-risk setting, there's pretty good data for



Revlimid with either Velcade or carfilzomib; and I think there is some data with the oral form of Velcade, but again, the remission duration might not be quite as long.

***Lizette Figueroa-Rivera, MA***

Thank you, and we'll take the next question from our telephone audience.

***Operator***

Thank you. Our next question comes from James from Texas. James' line is live. Please state your question.

***James from Texas***

Thank you. Good afternoon. My question is if you're at one-year post-transplant, and I'm still experiencing GI issues, nausea and vomiting, do you have any recommendations on ways to manage that?

***Sagar Lonial, MD, FACP***

Yeah, GI issues a year out don't necessarily fit with the typical toxicity of a transplant. That typically is gone within the first 30 or 60 days. So, I think it would warrant more aggressive investigation with perhaps an endoscopy and perhaps even a biopsy as there can be viruses that can sometimes cause nausea and vomiting, like CMV (cytomegalovirus), that are pretty uncommon in the post-transplant setting, but we certainly have seen it and can cause nausea and GI issues. So, I think a more extensive GI workup to better understand that would be my next step because it's unusual for this to be lingering that long purely from the melphalan.

***Lizette Figueroa-Rivera, MA***

Thank you so much for that question.

Our last question today is from Lisa. Lisa's asking, "Is it okay for myeloma patients to take the new bivalent COVID (coronavirus disease 2019) vaccine?"

***Sagar Lonial, MD, FACP***

Yes, absolutely. I think we would encourage patients to take the new vaccine as a booster. It's important for patients who are getting daratumumab-based therapies or BCMA-directed therapies to also get some form of antibody protection as we know that their responses to any of the COVID vaccines is less robust. Our group published that data a little over a year ago now and showed that



patients with dara- or BCMA-directed therapies were less likely to mount a significant immune reaction to the vaccines. And so, in that context, we have recommended the use of Evusheld™ (tixagevimab co-packaged with cilgavimab) for now. I'm not sure how helpful Evusheld will be with the next wave, but certainly with the last wave of COVID, Evusheld did provide some protection in that context.

## CLOSING REMARKS

**Lizette Figueroa-Rivera, MA**

Well, thank you, Lisa, for that question which is our last question for today. And thank you so much, Dr. Lonial, for your continued dedication to patients and for being able to present this program for us today. We are very happy that you were able to be with us and provide us with this information.



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43

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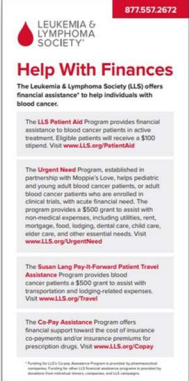
**The Bloodline with LLS** is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit [www.TheBloodline.org](http://www.TheBloodline.org)

44

# Understanding My Treatment Options: Multiple Myeloma

Patient Education Telephone/Web Program

And we do offer a variety of education and support resources, including online chats which are free live forums that are moderated by oncology social workers; and we also offer free education videos and podcasts.




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To order free materials: [www.LLS.org/Booklets](http://www.LLS.org/Booklets)



We also offer programs to help individuals with blood cancer. So for more information, please contact us at [LLS.org/Finances](http://LLS.org/Finances) for information about financial assistance as well as order our free materials at [LLS.org/Booklets](http://LLS.org/Booklets).

Please note that continuing education credit is not being offered for this program.



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Again, we'd like to acknowledge and thank Bristol Myers Squibb, Genentech & Biogen, GSK, Janssen Oncology & Legend Biotech, and Karyopharm Therapeutics for their additional support of this program.



And thank you, Dr. Lonial, for sharing your knowledge with us today. To all of the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.