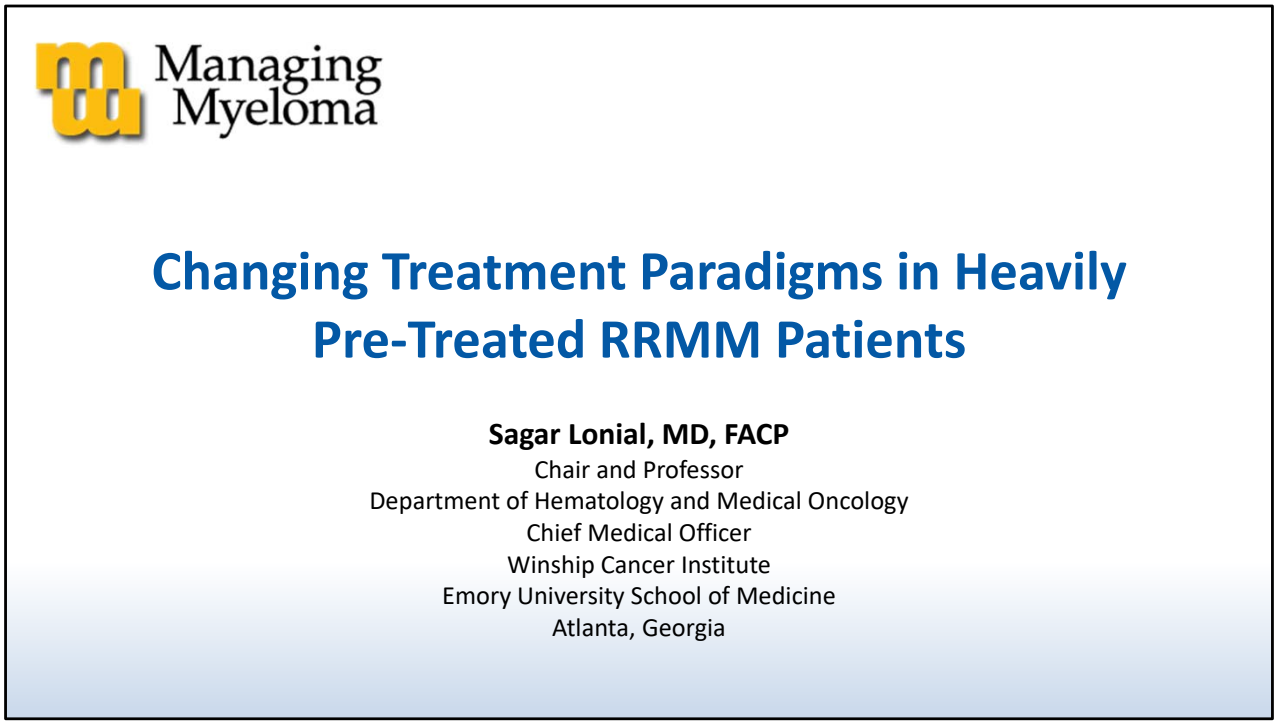
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients



Hello, I am Dr. Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta, Georgia, and I am going to spend the next few moments talking a little about management of relapsed and refractory multiple myeloma, given the new number of agents we have, as well as multiple options and choices at each different stage of care.

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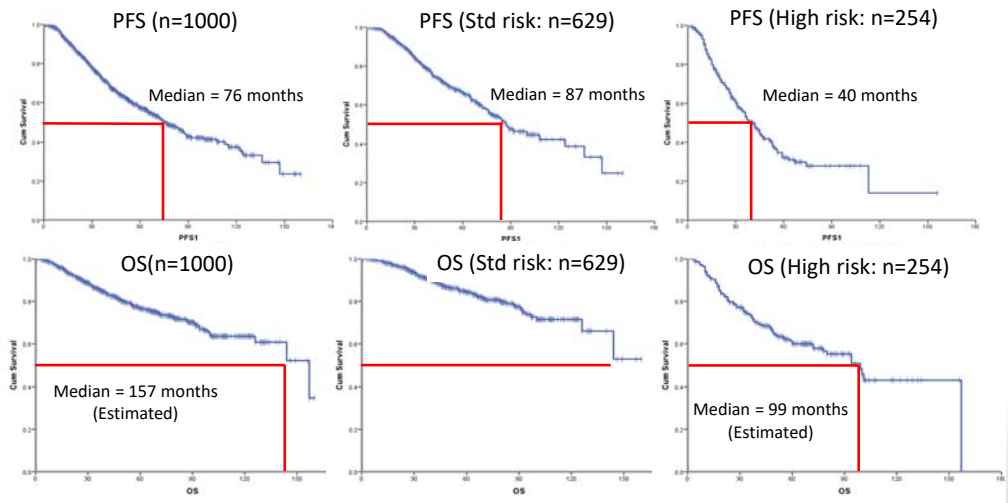
Outcomes for 1000 Uniformly Treated Patients
(Median Follow-up = 72 Months)



Joseph N, et al. ASH 2018.

I think it is important to recognize that, while we talk about great outcomes for patient with multiple myeloma. This is actually some hard data that was actually recently published in JCO by Dr. Joseph from our group, looking at outcome from a thousand newly diagnosed myeloma patients who all received RVD as part of their initial inductions and when I think it is really quite striking is that for both standard-risk and high-risk patients, we are seeing some of the longest progression-free survivals and overall survivals of any group we have ever seen published with newly diagnosed myeloma. Now this approach does in fact include the use of initial therapy with upfront autologous stem cell transplantation, but this is now the largest data set published to date with RVD as the initial induction therapy, autologous stem cell transplantation is consolidation, followed by risk-adapted maintenance. In this paper, is now in press in JCO and I think is a very important resource as it serves as a new benchmark for efficacy of treatments going forward.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Who Are the Players?

- Still have 'older' novel agents
  - Bortezomib, lenalidomide
  - Carfilzomib, dose/schedule
  - Pomalidomide
- 'New' novel agents
  - Ixazomib, panobinostat
  - Elotuzumab, daratumumab

Earlier lines or induction, partner for newer agents

Unfortunately, as good as we think we are with initial therapy for myeloma, we know that there are patients who will relapse, and management of that relapse again has become a little bit more challenging because we have lots of different new agents to talk about. So, we still have the older "novel agents," these include things such as bortezomib, lenalidomide, carfilzomib and pomalidomide, and particularly with carfilzomib, there are lots of different questions about the dose and schedule in a patient who may be resistant to 20/27 or 20/36, given on a once- or twice-a-week schedule may not be resistant to 56 mg/m^2 given on a twice-a-week schedule. So, I think it is important when we think about the dosing schedule of carfilzomib, to think about what a patient has previously seen. There also are newer novel agents such as ixazomib, panobinostat, elotuzumab, and daratumumab; and again we are going to talk about how we incorporate those as well as many of our newer agents into the treatment approach for patients with myeloma

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Factors to Consider for Treatment Selection

Disease-related factors

- Nature of relapse
- Risk stratification
- Disease burden
- R-ISS staging

Treatment-related factors

- Previous therapy
- Regimen-related toxicity
- Depth and duration of previous response, tumor burden at relapse
- Retreatment with previous therapies

Patient-related factors

- Renal insufficiency
- Hepatic impairment comorbidities and frailty
- Patient preferences

Nooka AK, et al. *Blood*. 2015;125:3085-3099.; Palumbo A, et al. *N Engl J Med*. 2011;364:1046-1060.; Palumbo A, et al. *Blood*. 2011;118:4519-4529.; Orlowski RZ, Lonial S. *Clin Cancer Res.* 2016;22:5443.

So, as we begin to think about factors to consider when we talk about treatment selection, there really are three sets of categories that we think through, the first is disease-related factors, then treatment-related factors, and finally patient-related factors, and as you can see from each of the bullets underneath those three columns, each of these things may have a variable impact on what a patient chooses to do in the context of relapsed and refractory myeloma; and particularly understanding that while we may make a decision in first relapse, that decision may be very different in second or third relapse; and while we may err on the side of convenience for earlier relapses, we may not necessarily have that option in later relapses. So putting all of those together really represents the best way to think through how to approach patients and how to sequence drugs in the context of relapsed and refractory myeloma.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Lenalidomide + Dexamethasone vs Triplet Regimens

Relapsed/Refractory Myeloma After 1-3 Prior Regimens

Third Agent	% With Prior Len	% Bortezomib Refractory	% Bortezomib Exposed	% With High-Risk Cytogenetics	Response Rates for Triplet vs Doublet (%)	PFS for Triplet vs Doublet, Months	Interim OS for Triplet vs Doublet, Months
Proteasome inhibitors							
Carfilzomib[1]	19.8	No	66 vs 66	12 vs 13	87 vs 67	**26.3 vs 17.6** (*P* = .0001)	73% vs 65% (24 months)
Ixazomib[2]	12	No	69 vs 69	17 vs 21	78 vs 72	**20.6 vs 14.7** (*P* = .012)	--
Immunotherapy							
Elotuzumab[3]	6	22	68 vs 71	41 vs 42	79 vs 66	**19.4 vs 14.9** (*P* = .014)	43.7 vs 39.6 (*P* = .026)
Daratumumab[4]	18	18	86	15 vs 17	93 vs 76	**NR[a] vs 18.4** (*P* < .0001)	--

[a]NR=not reached

[1]Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152. [2]Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634. [3]Lonial S, et al. N *Engl J Med*. 2015;373(7):621-631. [4]Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.

So let us start off talking about many of the trials that compared with lenalidomide and dexamethasone as the comparator arm,

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Few had received prior lenalidomide

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and what you see are four large randomized Phase III trials here, two of them using proteasome inhibitors, two of them using antibodies as the new drug. And as you can see, each of these was either carfilzomib plus len-dex versus len-dex, ixa-len-dex versus len-dex, elo-len-dex versus len-dex or dara-len-dex versus len-dex. And one of the challenges in this len-dex comparator arms is that very few of the patients in this trial had prior lenalidomide, and this is really important because as we know, most patients that we are taking care of have progressed in the context of lenalidomide maintenance or received lenalidomide as part of their initial therapy. So the treatment approach has changed despite the original design of many of these trials.

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Triplets had higher response rates and superior PFS in all trials

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If you continue to look at this, what I think you will see quite nicely is that the progression free survival clearly is improved for triplets over doublets, that is not a surprise and based on this data we have now accepted and acknowledged that a triplet has become the standard of care for patients with newly diagnosed myeloma where the len-dex control arm has lost in every single randomized trial we have done.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Bortezomib + Dexamethasone vs Triplet Regimens

Relapsed/Refractory Myeloma After 1-3 Prior Regimens

Third Agent	N	% With Prior Len	% Len Refractory	% With High-Risk Cytogenetics (Composite)	Response Rates for New Regimen vs BTZ + Dex, %	PFS for New Regimen vs BTZ + Dex, Months	OS for New Regimen vs BTZ + Dex, Months
CFZ (56 mg/m^2) + dex[1a]	929	38	25	23	77 vs 63	**18.7 vs 9.4**	47.6 vs 40.0
Panobinostat[2]	768	20	--	--	60.7 vs 54.6	**12.0 vs 8.1**	33.64 vs 30.39
Elotuzumab[3]	152	75	33	NA	66 vs 63	**9.7 vs 6.9**	73% vs 66% (2 years)
Daratumumab[4,5]	498	68	33	23%	83 vs 63	**16.7 vs 7.1**	NR vs NR

[a]Doublet vs doublet
[b]Phase 2 study

[1]Dimopoulos MA, et al. *Lancet Oncol*. 2016;17(1):27-38. [2]San Miguel SF, et al. *Lancet Oncol*. 2014;15(11):1195-1206. [3]Jakubowiak A, et al. *Blood*. 2016;127(23):2833-2840. [4]Dimopoulos MA, et al. *Br J Haematol*. 2017;178(6):896-905. [5]Lentzsch S, et al. *J Clin Oncol*. 2017;35(Suppl): Abstract 8036.

There is another set of Phase III trials that use bortezomib-dex as the control arm, and these again are triplets versus doublets except the ENDEAVOR trial

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Significant proportion had received prior lenalidomide

[a]Doublet vs doublet
[b]Phase 2 study

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where again as you will see at the top, carfilzomib uses 56 mg/m² given twice a week. This is a very effective combination probably the highest dose of proteasome inhibition that can be delivered safely, given at that again 56 given twice a week, three weeks in a row with a one-week break. Now there are other combinations where the new drug is either dara-elo-panobinostat, or again compared with carfilzomib, and again what you see is very few patients have had prior len in both of these trials,

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but again what you see is that the triplets or the new drug combination of carfilzomib at 56 clearly is better than the doublets of bortezomib and dexamethasone. So this again sets up the idea that whether you want to partner with an IMiD such as len or with a PI such as bortezomib or carfilzomib, clearly triplets remain better than doublets across the board.

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Questions/Challenges

- How do we make decisions for patients progressing on Len?
- Are the majority of phase 3 trials that use Rd as a control irrelevant for these patients?
- What data do we have on POM-based treatments in early relapse?

But as I suggested before, one of the challenges in the modern environment of myeloma therapy is that len-dex is no longer considered an adequate control arm, because most patients have been exposed to len or are resistant to len when they get to the setting of first relapse. And so the questions become, do we have a significant number of trials looking at either bortezomib or carfilzomib as control arms or looking at pomalidomide as the control arm.?

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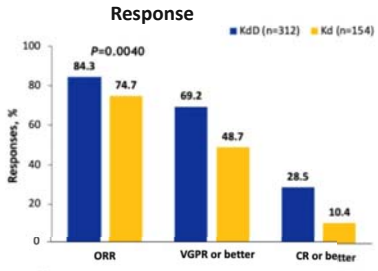
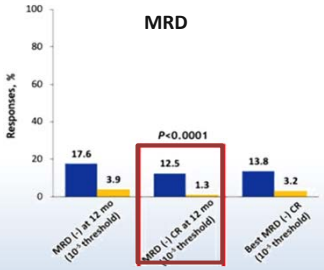
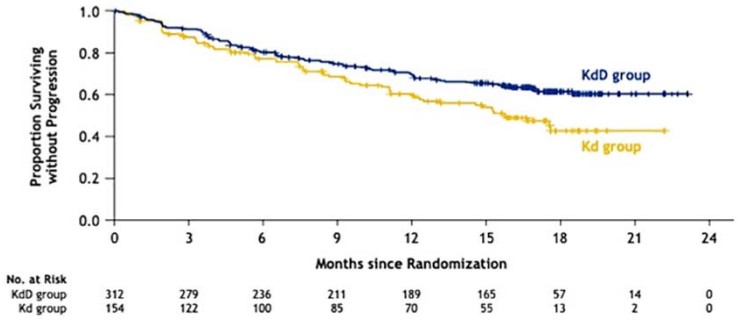
CANDOR: Response and PFS







	KdD (n = 312)	Kd (n = 154)
Median follow-up time, months	16.9	16.3
Progression/death, n (%)	110 (35%)	68 (44%)
Median PFS, months	NE	15.8
HR (KdD/Kd) (95% CI)	0.63 (0.46, 0.85)	
P value (1-sided)	.0014	

Usmani SZ, et al. ASH 2019. Abstract LBA6.

And so let us talk about a couple of these trials as we go forward, so the first is the CANDOR trial, which was presented at ASH this past year that looked at carfilzomib-dex versus dara-carfilzomib-dex, and what I think you clearly see, is a higher overall response rate, higher progression free survival and better outcomes across the board for patients including MRD negativity for patients that received the triplet of car-dara-dex versus carfilzomib and dex, and this again sets up the concept that carfilzomib-dex becomes a good partner for an antibody-based approach going forward.

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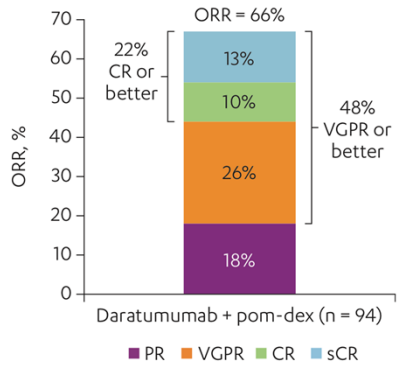
Daratumumab Pomalidomide Dexamethasone: Phase 1b



- DARA (16 mg/kg) + POM-D induced responses, including MRD negativity, in a heavily pretreated patient population
  - Median of 4 prior lines of therapy
  - 71% double refractory to a PI and an IMiD
  - High ORR maintained in double-refractory and high-risk patients
- Median PFS 9.9 months
  - Median DOR 21.5 months
- Median OS 25.1 months
- DARA can be combined with POM-D
  - 77% Grade 3/4 neutropenia in population with 44% baseline neutropenia
  - FN rates consistent with POM-D alone

Chari A, et al. *Blood*. 2017;130(8):974-981.; Facon T, et al. ASH 2017. Poster.

What about looking at pomalidomide as a control arm? Well, this is dara-pom-dex in the initial Phase I study that demonstrated pretty significant activity with dara, given at the typical dose and schedule in combination with pom-dex in a very heavily pre-treated group of patients who had received the median of four prior lines of therapy. And what again you see is median PFS of 9 months, median DOR of 21.5 months and the median overall survival was 2-plus years for a group of patients with refractory myeloma, median of four prior lines of therapy.

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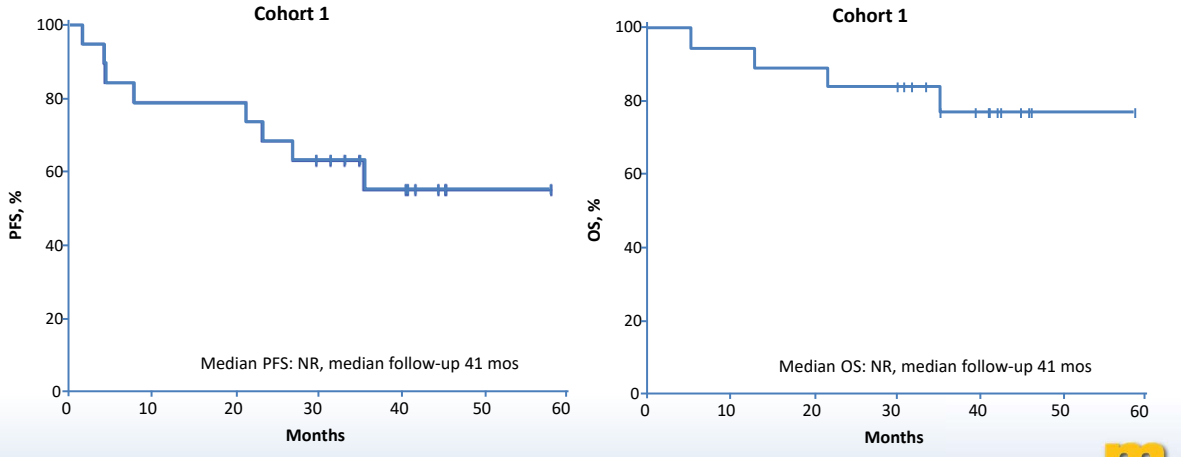
PFS and OS for Daratumumab, Pomalidomide, and Dexamethasone in First Relapse[1]



Cohort 1 consisted of patients who had daratumumab and pomalidomide relapsed/refractory myeloma

[1]Nooka AK, et al. *Cancer.* 2019;125(17):2991-3000.

What I want to show you is a subset analysis from a paper that we published from our group, looking at a small number of patients who received pom-dara-dex in first relapse, and the reason this is important is as you can see, the median progression free survival is over 40 months with a median follow up of 41 months and the median overall survival also not reached with a median follow up of 41 months, suggesting that in the context of first relapse when pomalidomide does become a reasonable treatment option, partnering with daratumumab may be a very effective strategy in managing relapsed and refractory myeloma.

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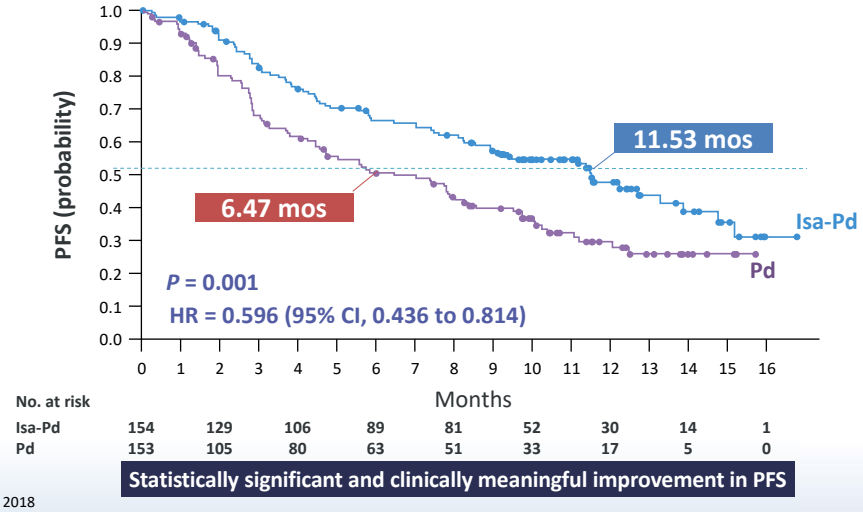
Icaria: PFS Primary Endpoint – IRC Assessment



Statistically significant and clinically meaningful improvement in PFS

Data cut-off 11 Oct, 2018
CI=confidence interval; d=dexamethasone; HR=hazard ratio; IRC=Independent Review Committee; Isa=isatuximab; mos=months; PFS=progression-free survival; P=pomalidomide
Attal M, et al. *Lancet.* 2019;394(10214):2096-2107.

Most recently, we have a large randomize Phase III of isatuximab in combination with pom-dex versus pomalidomide and dexamethasone. And this was a randomized Phase III with a median of 2 prior lines of therapy, and as you can see in the ICARIA trial, the PFS was significantly better, almost double for the group that received isa-pom-dex compared to pomalidomide and dexamethasone. And this again gives us great caution or great comfort in the idea that you can use isa, which is a different CD38 antibody, targets a different epitope than dara, in combination with pom-dex in an earlier relapse setting, this is two prior lines of therapy; and that you can get sustained and durable responses, and that triplet is clearly better than the doublet of pomalidomide and dexamethasone.

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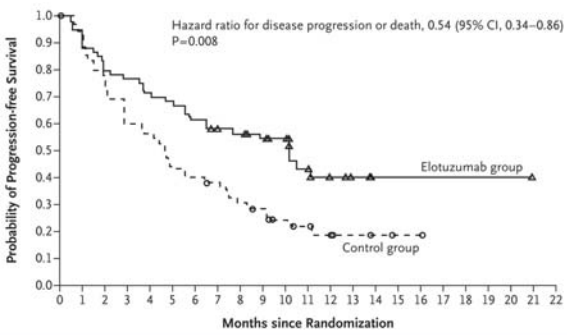
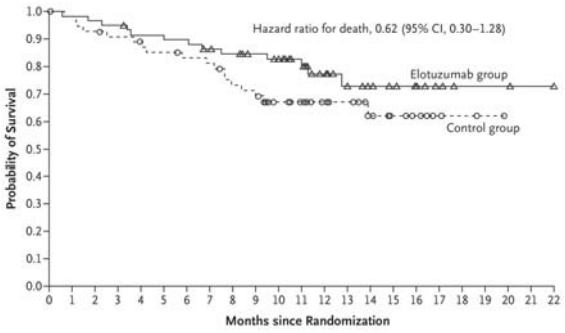
Elotuzumab-Pomalidomide-Dex





Dimopoulos MA, et al. *N Engl J Med.* 2018;379:1811-1822.

What about looking at elotuzumab in combination with pom-dex compared to pom-dex? This is another Phase III trial, a randomized trial and again as you can see the progression-free survival and overall survival favored the use of elo-pom-dex versus pomalidomide and dex, suggesting again that in a pom-sensitive patient population, immunotherapy such as isatuximab or elotuzumab offer significant benefit compared with pomalidomide and dexamethasone alone.

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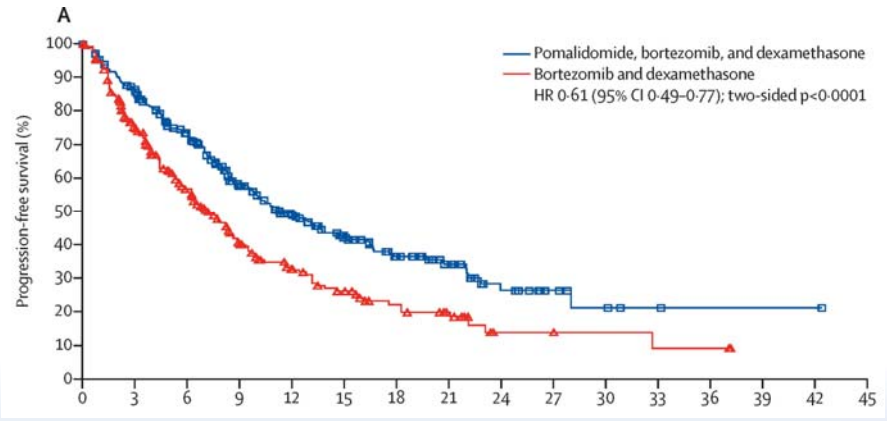
OPTIMISSM: Pomalidomide-Bortezomib-Dex



Richardson PG, et al. *Lancet Oncol*. 2019;20:781-794.

Now this is a different trial, this is the OPTIMISSM trial which used bortezomib-dex as the control arm. And in this randomized Phase III, the idea was to add pomalidomide to bortezomib-dex, so it is PVD versus bortezomib-dex or VD. And again as you can see, the triplet is superior to the doublet across the board with a significant improvement in progression-free survival, overall response rate and complete remission rate for bortezomib with pomalidomide and dex compared to bortezomib-dex alone.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Emory Approach to Early Relapse

Clinical Trial: Check if Patient is t(11;14)

Slow indolent relapse		Aggressive relapse	
+ Len maintenance	- Len maintenance	+ Len maintenance	- Len maintenance
Consider Dara/Pom/Dex	Consider Dara/Len/Dex	Consider Dara/Pom/Dex	Consider Dara/Len/Dex
Consider adding Ixazomib/Dex*	Consider Elo/Len/Dex	Consider Car/Pom/Dex	Consider Dara/Vel/Dex
Consider Adding Elo/Dex*	Consider Car/Len/Dex		Consider Car/Pom/Dex

* Increase Len dose

Car/Pan as second salvage if IMiD used

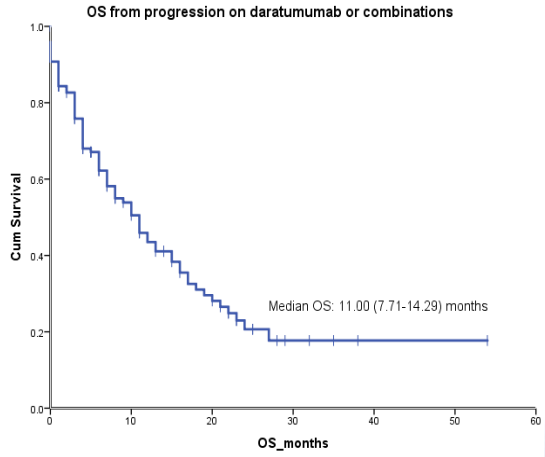
And so, now as you can see, we have a whole series of additional trials that do not use len-dex as a control arm, and offer us new potential opportunities and treatments that are clearly more effective than doublets for patients with relapsed and refractory myeloma.

So, what I am showing you here is our approach, our algorithm at Emory in terms of management of patients with relapsed and refractory myeloma. Again, if a patient is 11;14 positive, we take them down a different path and I am going to show you some of that data as we go forward, but more importantly as you can see, dara has become a standard approach for many of our patients, either in the slow or aggressive relapse category, depending upon whether or not they have received lenalidomide. If they have not, then we can use pom or other potential partners with dara, if they have then len-dara-dex does become a reasonable option. And as you can see, there are other potential options most recently now isatuximab, PVD, elo plus pomalidomide and dexamethasone, each of these are now popping up in the relapse setting. And going back and figuring out, what is the patient sensitive to? What are they resistant to? And how can I best create a triplet that is most likely to induce responses becomes a major goal when we are trying to parse through what the next treatment approach for a patient with relapsed and refractory myeloma may be.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

OS for Refractory Myeloma in the Daratumumab Era

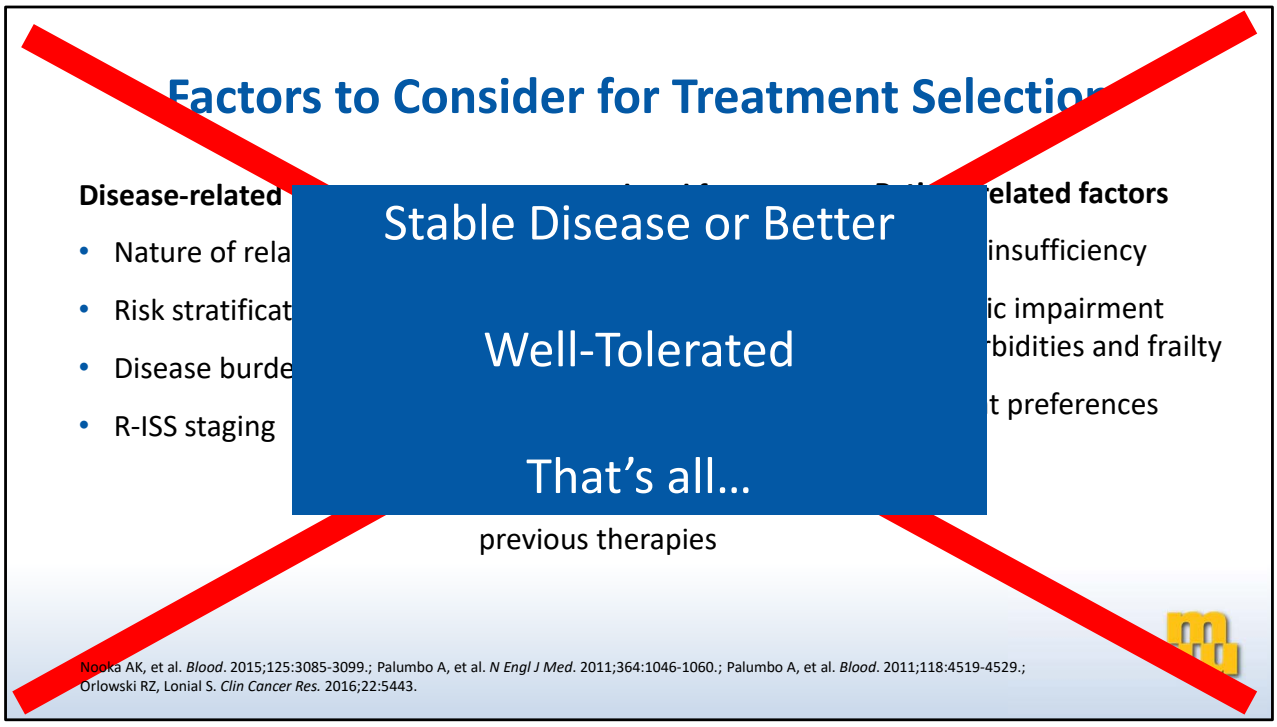
- Median age is 64 years (range 32-82) and 54% were female
- Patients received a median of 6 lines of therapy and the median time to start daratumumab treatment from their diagnosis was 63 months (6-255 months)
- Majority were quad- and penta-refractory (86.9% and 70.8%, respectively)
- 32.3% of patients received daratumumab as a single agent and most patients received a combination of IMiD (DPD: 50.8% and DRD: 6.2%) or a PI (DVD: 6.9%)



Nooka AK, et al. *Blood.* 2016;128(22):492.; Nooka AK, et al. *Cancer.* 2019;125(17):2991-3000.

Again, just as I said early on in the induction therapy setting, as good as we think we are, we unfortunately still have patients who need additional options. And this is data presented by Dr. Nooka from our group, a couple of years ago; looking at the overall survival for patients refractory to daratumumab in the most recent era. And again, this does not mean dara in the early treatment settings; this is typically using dara in the relapsed and refractory setting. And what I think you can see is that for patients that have limited options with quadruplet or penta-refractory myeloma, the median overall survival is likely going to be on the order of less than a year, and in our dataset that was about 11 months. This suggests that we clearly need new treatment options for patients when they run out of available treatment options going forward.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients



And as we go back to that initial slide that I showed you earlier about factors to consider for treatment selection, all of that goes out of the window when you have a patient with refractory myeloma, where they have seen all of the big 5. They have seen bortezomib, carfilzomib, len, pom, dara, elo, and many others that are available as well. This is when the goals of therapy really are to achieve stable disease or better, and that the stable disease is in fact well tolerated. So, again the goals of therapy change a little bit based on the availability of new treatment options as well as the performance status of patients when they get to this status in multiple myeloma.

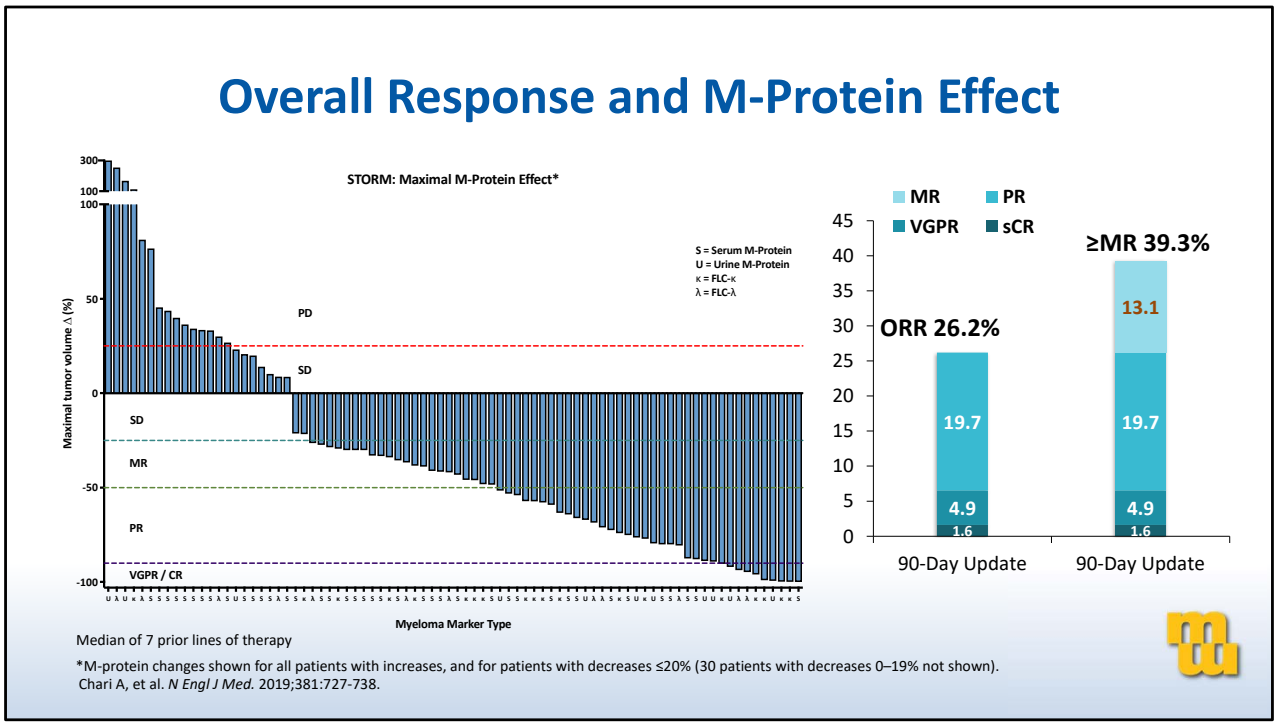
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

New Approaches in Late Relapse

- Most patients have cycled through common agents
- Chemotherapy-based approaches, while short-term response, don't result in long-term control
- Need new MOA or targets
  - XPO1
  - Bcl-2/MCL-1
  - New IMiDs
  - Immune targeted agents

So what are some of the new approaches that we talk about in the context of late relapsed myeloma? Well, again, XPO1 becomes a target, MCL1 or BCL2 becomes a target, new IMiDs become targets, and finally immune-targeted agents as well. These are all potential options in the context of refractory myeloma.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

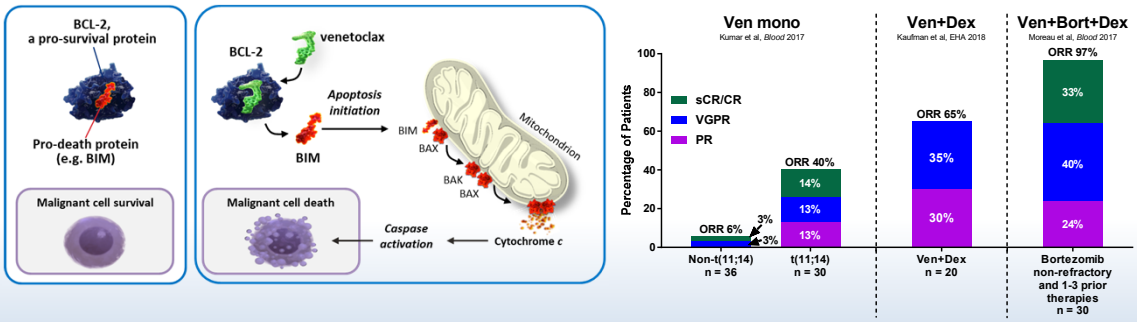


So let us start off talking about XPO1 inhibitors as you know, we are talking about an agent called selinexor and this is data from the STORM trial that demonstrated that while the overall response rate was in the 20s, 26% objectively, you can see that a significant fraction of patients achieved stable disease or better. And that the stable disease could in fact be durable in a subset of patients as well. And so again taking the dictum that I have mentioned earlier, stable disease, well-tolerated, this can offer significant benefit for patients. And this is now being tested in combinations with bortezomib and dexamethasone, carfilzomib and dexamethasone, as well as pomalidomide and dexamethasone. And there are a number of Phase II and Phase III trials exploring selinexor, not just with dex but with other available treatment options in myeloma, and we await many of those trials coming forward.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Venetoclax Targets BCL-2 in Multiple Myeloma

- Pro-survival proteins BCL-2, MCL-1, and BCL-XL promote multiple myeloma (MM) cell survival[1]
- Venetoclax (Ven) is a selective, potent, oral BCL-2 inhibitor[2]
- Ven had encouraging clinical efficacy in t(11;14) MM as monotherapy and in a broader patient population in combination with Bd, with a tolerable safety profile in phase 1 studies



[1]Touzeau C, et al. *Leukemia*. 2018;32(9):1899-1907. [2]Souers AJ, et al. *Nat Med*. 2013;19(2):202-208.

What about venetoclax in the context of multiple myeloma; well, there has been a lot of data looking at venetoclax in myeloma, and most recently many of you may have heard about the BELLINI trial were the trial was halted early by the FDA. And I want to make a couple of important points about that. The first is, that venetoclax alone in 11;14 and in combination with dexamethasone in 11;14 translocated myeloma is clearly a safe and effective treatment. We saw that in Phase I and in Phase II studies; and it was not until the Phase III trial that we began to evaluate venetoclax beyond the 11;14 translocated patients that we began to run into some trouble.

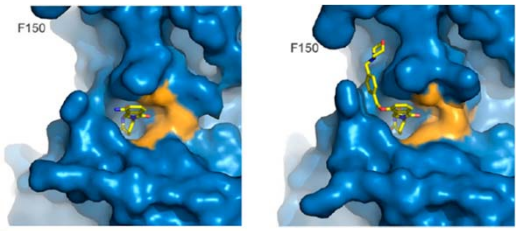
And so I want to talk a little bit about that because I think it is important that we recognize from the BELLINI trial that patients actually who were 11;14 whether they got bortezomib-venetoclax-dex or bortezomib-dex. The use of venetoclax in the 11;14 subset clearly gains significant benefit, and that benefit was not associated with the survival issues we saw in the non-11;14 subset of patients. And so what I want to reassure you about is that, the use of venetoclax-dex in 11;14 patients is in fact safe and can be incredibly effective, clearly increases the fraction of MRD negative patients, increases the overall response rate, increases the progression-free survival, and does not have a negative impact on overall survival as was demonstrated from the BELLINI trial subset analysis. So again think about venetoclax in the 11;14 subset of patients.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

IBERDOMIDE Mechanism of Action

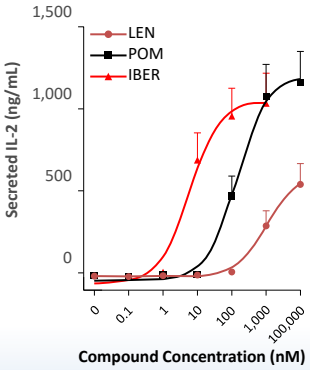
- IBER enhances in vitro immune stimulatory activity versus LEN and POM[1]

LEN[2] **IBER[2]**

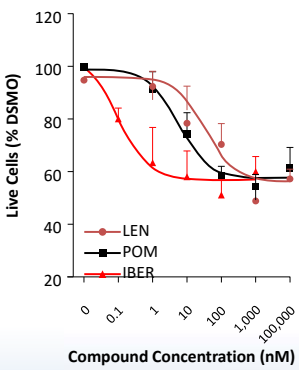


EC_{50}, nM[2]	Ikaros	Aiolos
LEN	67	87
POM	24	22
IBER	1	0.5

IL-2 Secretion by Treated PBMCs[1]



MM Cell Survival in Co-Culture With Treated PBMCs[1]

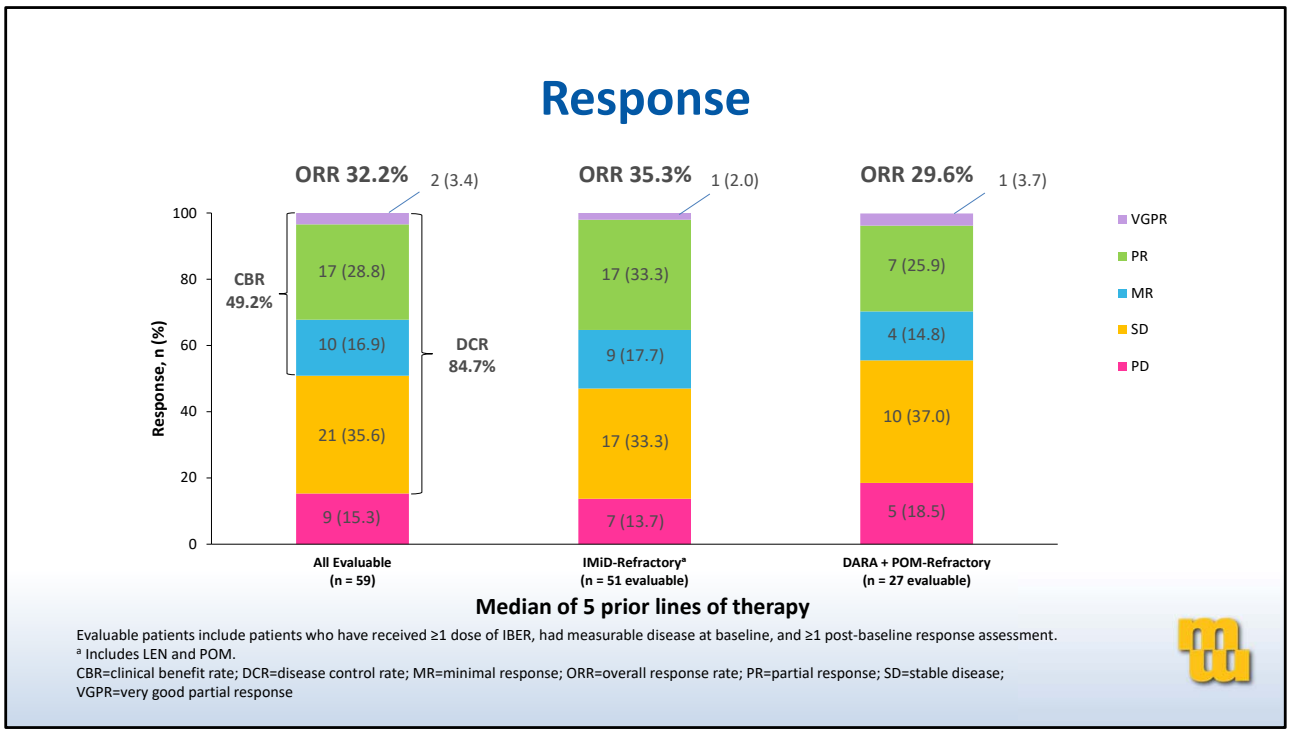


BORT=bortezomib; DARA=daratumumab; DSMO=dimethylsulfoxide; EC_{50}=half maximal effective concentration; IL=interleukin; NK=natural killer; PBMC=peripheral blood mononuclear cell

[1]Bjorklund CC, et al. *Leukemia.* 2020;34(4):1197-1201. [2]Matyskiela ME, et al. *J Med Chem.* 2018;61:535-542.

What about iberdomide? Iberdomide is the newest in the IMiD family of drugs. Iberdomide is more potent than pomalidomide, lenalidomide, or thalidomide; although is a cereblon-binding protein. It is called a CELMoD now; so it is not considered an IMiD because its effects on cellular-emanated immunity are so potent and so strong, far more so than we have seen with either len, thal, or pom.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

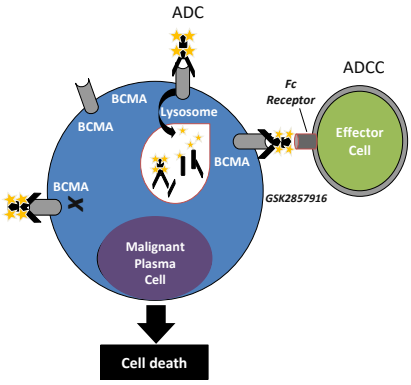


And this is data from a Phase I, Phase II study where we looked at iberdomide and dexamethasone in a median of 4-5 prior lines of therapy with myeloma. And what I think you really nicely see is an overall response rate of about 30% across the board. In fact, if you look at patients who are pom-dara refractory, still 30% response rate for iber plus dex, and this is really impressive again considering the fact that these are patients that have had 4-5 prior lines of therapy, and iber plus dex is oral. It is a very well-tolerated IMiD or CELMoD, and in fact does not appear to have neuropathy, does not appear to have some of confusion that is associated with IMiDs; its main side effect appears to be myelosuppression, and we hopefully will see this drug moving forward in Phase II and Phase III trials in the near future, so that we can have additional treatment options for our patients going forward.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Belantamab Mafodotin: BCMA-Targeted ADC

- Belantamab mafodotin
  - Humanized, afucosylated IgG1 anti-BCMA antibody
  - Conjugated to a microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker
- Preclinical studies demonstrate its selective and potent activity



Fc region of the antibody	• Target specific • Enhanced ADCC
Linker	• Stable in circulation
Drug	• MMAF (non-cell-permeable, highly potent auristatin)

Mechanisms of Action:
1. ADC mechanism
2. ADCC mechanism
3. Immunogenic cell death

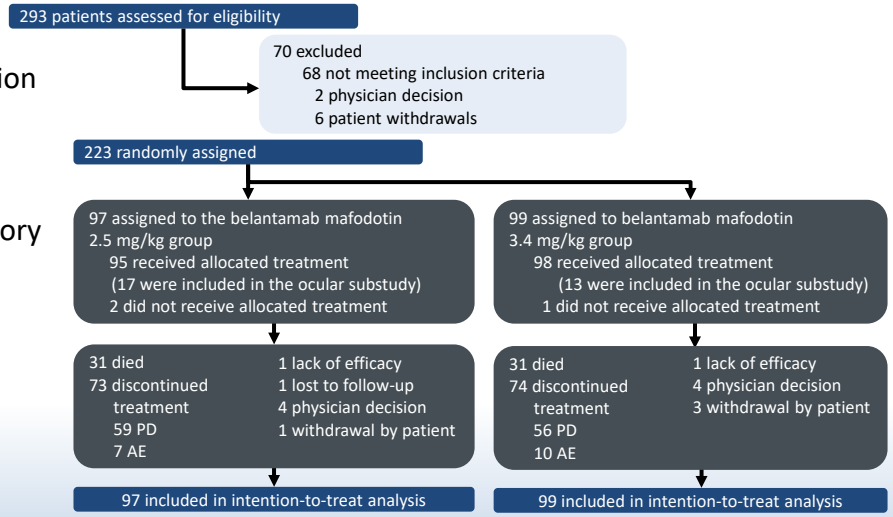
Tai YT, et al. *Blood*. 2014;123: Abstract 3128.

The last area I want to touch on is targeting BCMA, and the reason I want to talk about this is we have a number of different approaches to targeting BCMA that are in clinical trials and probably the furthest along right now is belantamab mafodotin or bela maf, and this is anti-BCMA antibody-drug conjugate, so it is basically an antibody with chemotherapy hooked on to that, much like Mylotarg but with a different chemotherapy moiety, this is MMAF, not calicheamicin or MMAE as you may have seen in other antibody-drug conjugates.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Belantamab Mafodotin: DREAMM-2, Randomized Phase 2 Study

- RRMM with disease progression after ≥3 lines of therapy and refractory to immunomodulatory drugs, PIs, and, anti-CD38 mAb
- ECOG PS 0 to 2



Lonial S, et al. *Lancet Oncol.* 2019;21(2):207-221.

Based on these actually, there was very interesting data in an early Phase I study that suggested very high overall response rates and complete remissions in patients who received belantamab as part of salvage therapy for refractory myeloma. And based on that encouraging data, a Phase II trial was generated, the DREAMM-2 study, that was randomizing between two different doses of bela maf, either 2.5 mg/kg or 3.4 mg/kg. I think it is important to recognize that when we talk about bela maf, the most common side effect we see is myelosuppression, not a surprise we are using a drug that has a chemotherapy moiety on it and is targeted to the bone marrow, but the second adverse event to be aware of is ocular toxicity, and this is pretty much noted as a corneal issue that is reversible with dose holding or dose modification and can allow patients to receive bela maf for a long period of time; though this can be, you do need some experience in managing the corneal toxicity and partnership with your ophthalmologist colleagues as well.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

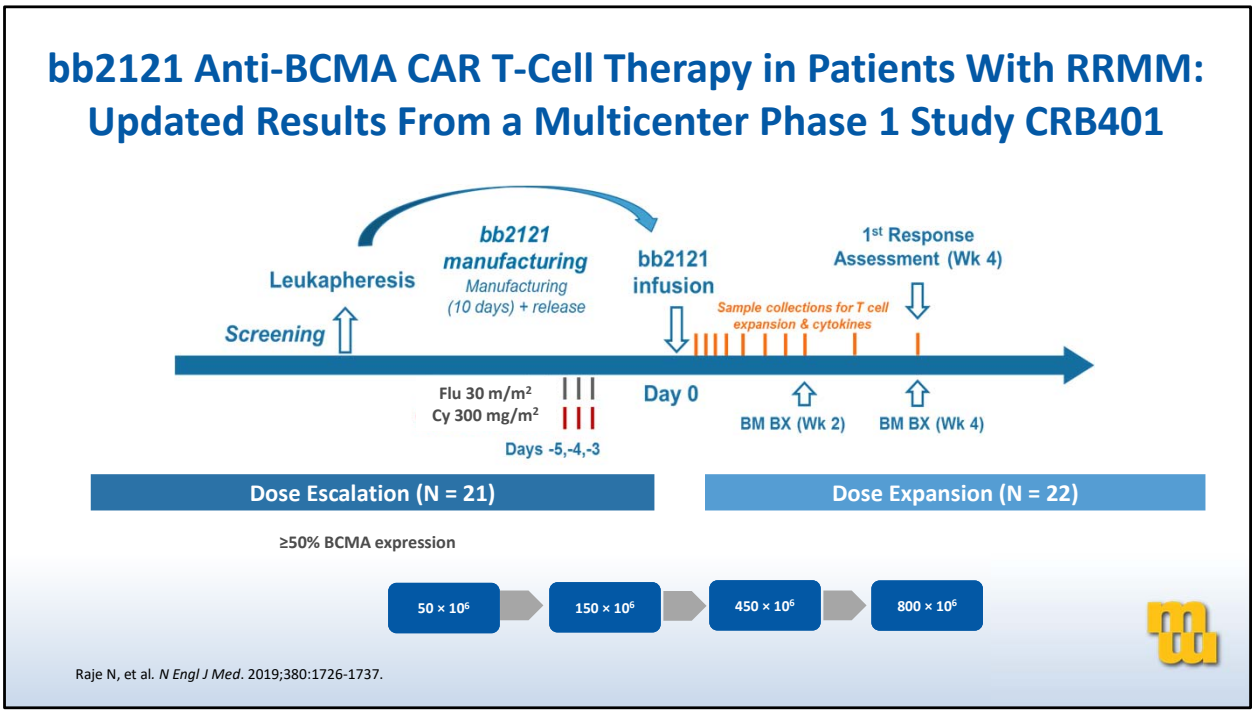
Belantamab Mafodotin: DREAMM-2, Response

- ORR
  - 30/97 patients (31%) in the 2.5 mg/kg cohort
  - 34/99 patients (34%) in the 3.4 mg/kg cohort
  - Adverse events
  - Most common grade 3/4 AE
    - Keratopathy (27% in the 2.5 mg/kg cohort; 21% 3.4 mg/kg cohort)
    - Thrombocytopenia (20% and 33%)
    - Anemia (20% and 25%)
  - Serious AE in 40% in 2.5 mg/kg cohort and 47% in the 3.4 mg/kg cohort
  - Two deaths were potentially treatment related
    - Sepsis in the 2.5 mg/kg cohort and hemophagocytic lymphohistiocytosis in the 3.4 mg/kg cohort

Lonial S, et al. *Lancet Oncol.* 2019;21(2):207-221.

What you see in this Phase II trial is an overall response rate at about 30-34% in both dose cohorts, 2.5 versus 3.4. It did appear that the 2.5 mg/kg dose was a safer dose, and so that is likely the dose that is moving forward in larger randomized Phase III trials, and there were, again, complications that are not unexpected for patients with relapsed and refractory myeloma.

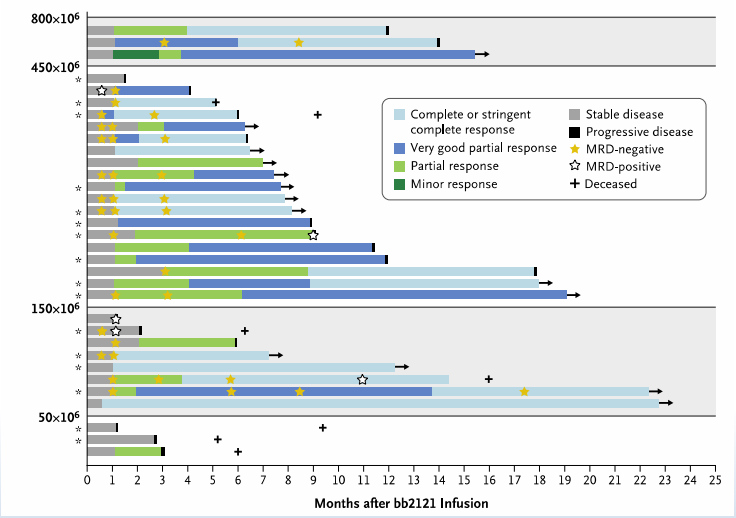
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients



Now other targets that used BCMA as a potential target include bb2121, the anti-BCMA CAR T-cell that was published in a Phase I study by Dr. Raje in the *New England Journal of Medicine*, a little under a year ago now and this is now been experienced in a Phase II trial as well.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Response to bb2121 Infusion



ORR: 85%
CR/sCR: 45%

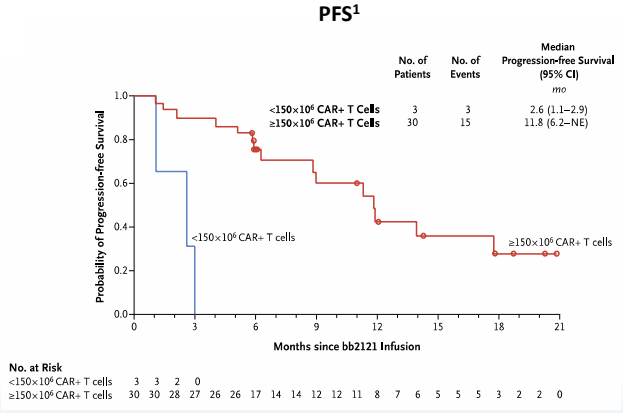
Raje N, et al. *N Engl J Med*. 2019;380:1726-1737.

And what I am going to show you is data from the bb2121 Phase I experience as you can see; the overall response rate for this CAR T-cell was 85% with about half the patients achieving CR or stringent CR. Those responses occurred relatively quickly.

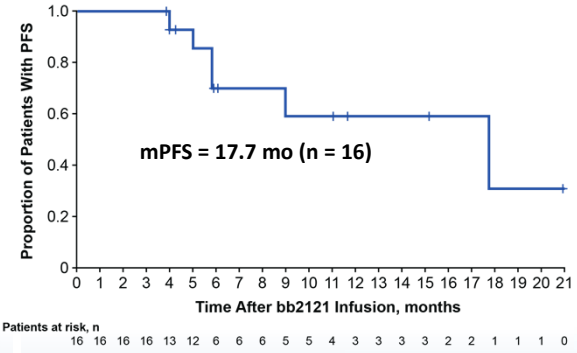
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Progression-Free Survival

PFS[1]



PFS in MRD-Negative Patients[2]



[1]Raje N, et al. *N Engl J Med*. 2019;380:1726-1737. [2]Raje NS, et al. ASCO 2018. Abstract 8007.

In the group of patients that achieved or received the highest dose of the cell, you can see the median progression-free survival is about 11 months, and among patients who achieved MRD negativity, it is 17.7 months. So again, in a median of 6-7 prior lines of therapy, this response rate is clearly quite impressive, quite acceptable, and is among some of the better responses we have seen in a heavily relapsed and refractory myeloma.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

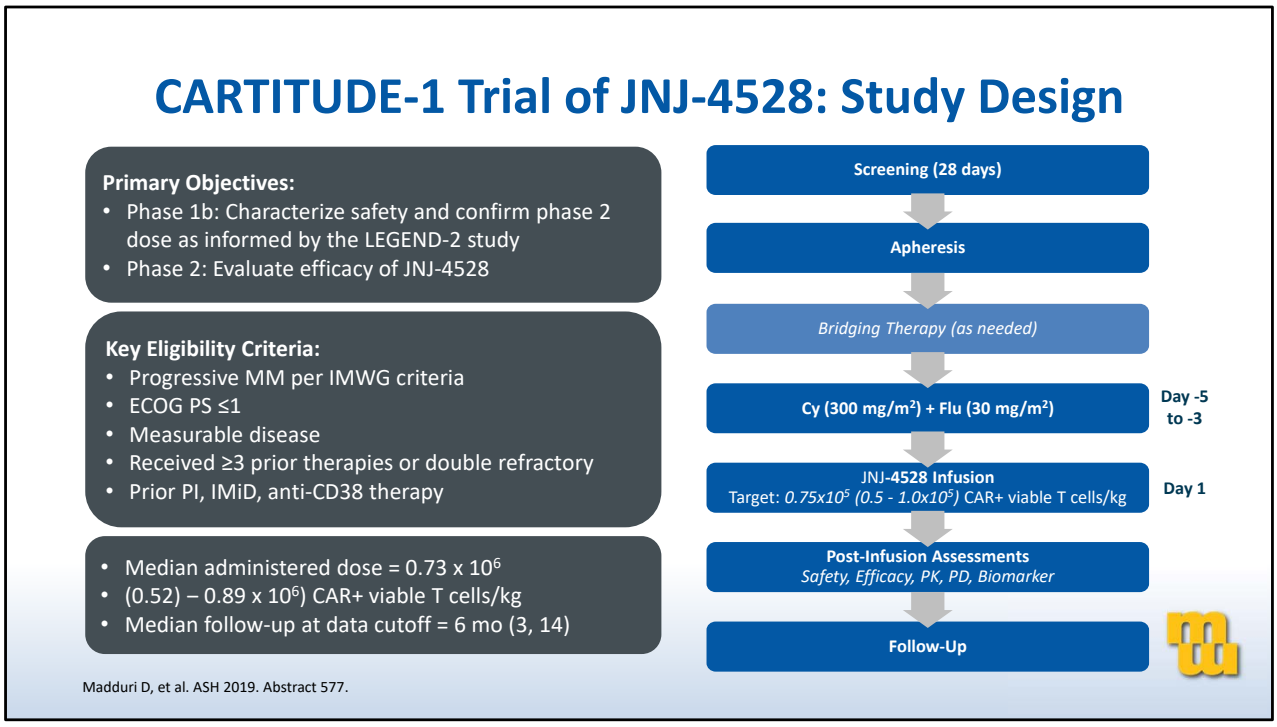
bb2121: Safety

Treatment-Emergent AEs, n (%)	All Patients (N = 33)	
	Any Grade	Grade ≥3
CRS	25 (76)	2 (6)
Neurotoxicity	14 (42)	1 (3)
Neutropenia	28 (85)	28 (85)
Leukopenia	20 (61)	19 (58)
Anemia	19 (58)	15 (45)
Thrombocytopenia	19 (58)	15 (45)
Lymphopenia	6 (18)	6 (18)

Raje N, et al. *N Engl J Med*. 2019;380:1726-1737.

One of the key pieces that differentiates targeting BCMA with a CAR T-cell compared to CD-19 CAR T-cells is the fact that it looks like the safety profile is different for BCMA and myeloma than it is for CD-19 and ALL or large cell lymphoma. What I mean by that is the incidence of Grade 3, Grade 4 CRS and neurotoxicity is significantly lower. And we have seen this across the board, not just with bb2121 but with many other CAR T-cells targeting BCMA and myeloma as well.

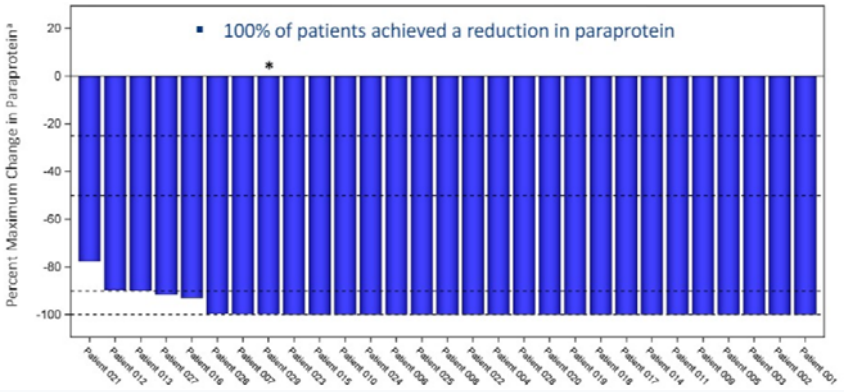
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients



As an example, this is the CARTITUDE-1 study that was presented at ASH this most recent year, this is using a version of LCAR, something that was tested by the Legend Group in China and was presented and appeared to have very impressive initial activity.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

CARTITUDE-1 Trial of JNJ-4528
Reduction in Tumor Burden



- 100% of 17 evaluable patients were MRD-negative at day 28
  - Nine patients MRD-negative at 10^{-6}
  - Five patients MRD-negative at 10^{-5}
  - Three patients MRD-negative at 10^{-4}
- Five patients without identifiable clone at baseline

Madduri D, et al. ASH 2019. Abstract 577.

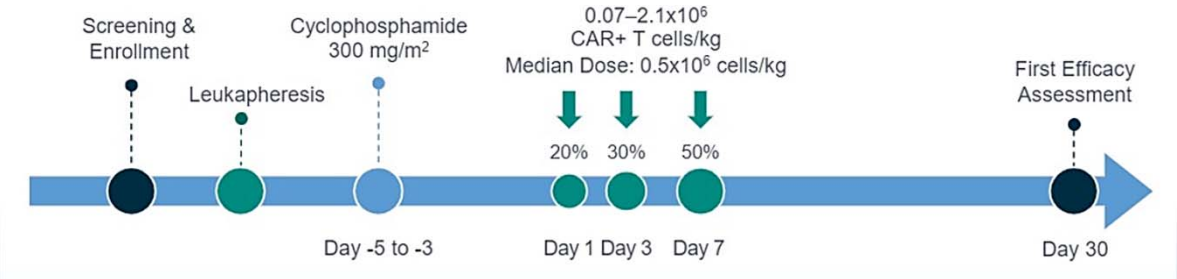
This is the Phase I study using basically the LCAR construct in a US-based trial with an overall response rate of 100% in 17 evaluable patients, and again most of those patients achieved complete remission and a significant fraction achieved MRD negativity.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

LCAR-B38M: LEGEND-2 Study Design

Key Inclusion Criteria:
- Active MM defined by IMWG criteria
- Relapsed on prior regimens

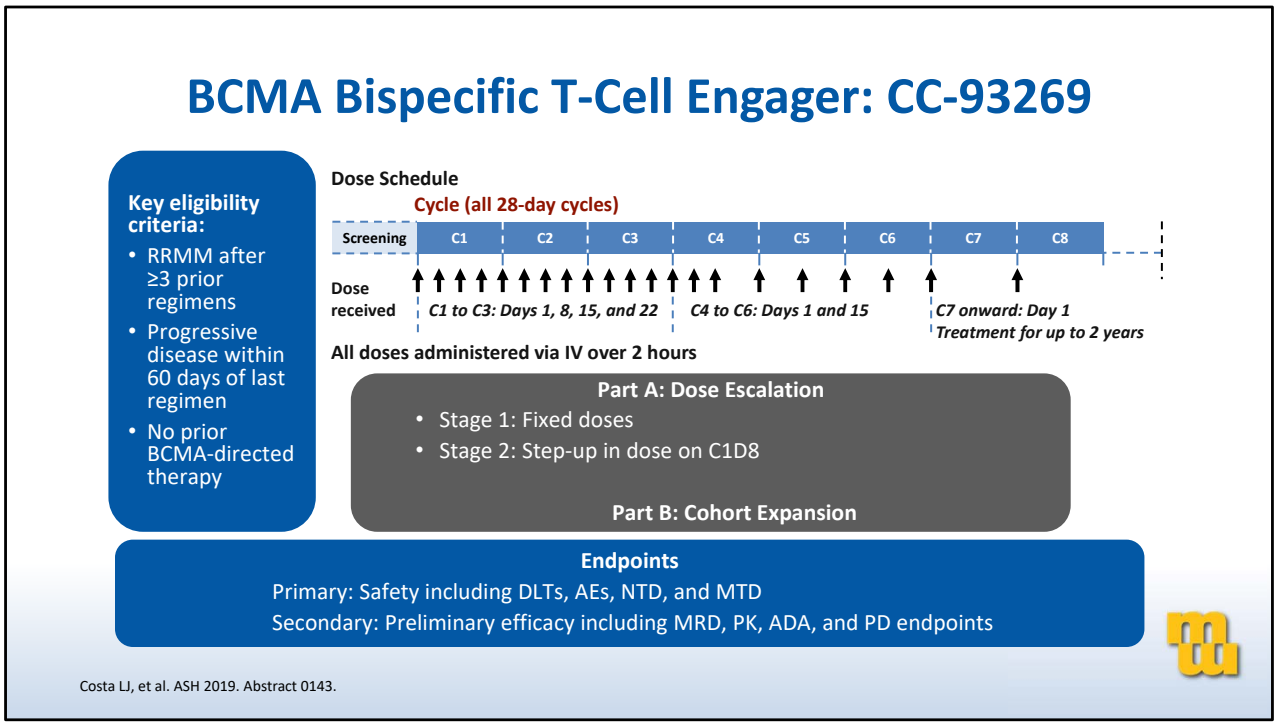
Key Objectives:
- Primary: safety of LCAR-B38M CAR T cells
- Secondary: antimyeloma activity based on IMWG response criteria



Wang BY, et al. ASH 2019. Abstract 579.

This is that same LCAR study that I have mentioned earlier, and what I think you see again is that this was done in China and what we know about this is that with longer follow up, there clearly is a longer duration of remission than we have seen in other trials going forward.

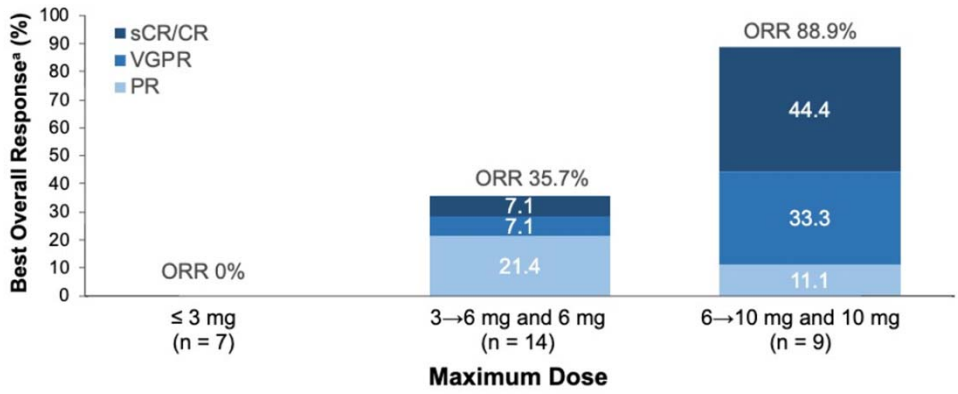
Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients



Now, the last of the BCMA-targeted approaches that I want to mention is CC-93269 or 269 for short, and this is a BCMA bispecific T-cell engager. So this is a variation on the BiTE that we saw from Amgen previously, it is slightly different, it really is named a bispecific not a BiTE because the technology is slightly different.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

BCMA Bispecific T-Cell Engager: CC-93269



- In all patients (N = 30), the ORR was 43.3% with a sCR/CR of 16.7%
- Among patients receiving 10 mg (n = 9), the ORR was 88.9% with a sCR/CR of 44.4%

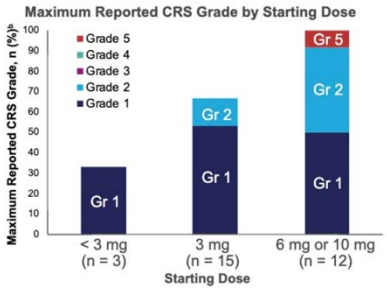
Costa LJ, et al. ASH 2019. Abstract 0143.

And as you can see in the highest dose cohort of refractory myeloma, median of 6 prior lines of therapy and 88.9% overall response rate in a small number only 9 different patients, but that again suggests that this is clearly very active, clearly very effective, and can be tolerated relatively well with only a CRS, anemia, and neutropenia as the main toxicities that we saw.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

BCMA Bispecific T-Cell Engager: CC-93269

Common (≥20% All Grade) TEAEs, n (%)	All Patients (N = 30)	
	All Grade	All Grade ≥3
Patients with ≥1 TEAE	29 (96.7)	22 (73.3)
Hematologic TEAEs		
Neutropenia	14 (46.7)	13 (43.3)
Anemia	13 (43,3)	11 (36.7)
Thrombocytopenia	9 (30.0)	5 (16.7)
Nonhematologic TEAEs		
CRS	23 (76.7)	1 (3.3)
Infections and infestations	17 (56.7)	9 (30.0)
Diarrhea	8 (26.7)	1 (3.3)
Vomiting	8 (26.7)	0
Back pain	7 (23.3)	0
Fatigue	6 (20.0)	0
IRR	6 (20.0)	0
Nausea	6 (20.0)	0



- Deaths (Grade 5 TEAEs) were reported in 4 patients during the treatment period:
  - Suspected to be related to CC-93269: CRS (n = 1)
  - Not suspected to be related to CC-93269: sepsis in the setting of advanced prostate cancer, sudden cardiac death, and general health deterioration due to progressive myeloma (n = 1 each)

Costa LJ, et al. ASH 2019. Abstract 0143.

There were some complications with infections, that is not unknown or unsurprising given how heavily pre-treated these patients are, and I think really speaks to the activity of targeting BCMA, even in a heavily pre-treated relapsed and refractory myeloma.

Changing Treatment Paradigms in Heavily Pre-Treated RRMM Patients

Conclusions

- New targets and agents are important options for refractory MM
- Understanding how to dose and how to schedule new agents is a critical question
- New targets may help to overcome resistance to previous agents
- Short- and long-term outcomes are linked to access

So, I think in summary, we have seen lots of different exciting new approaches, and I think it is important to think through how you are going to manage early relapse, how you are going to manage second and third relapse using the available approved drugs. And then how are you going to get patients to clinical trials, particularly BCMA-targeted approaches, venetoclax targeted approaches or selinexor-based approaches if they develop refractory myeloma. I think having new drugs such as iberdomide and other new targets down the road is certainly very exciting, and I think, at least in our experience, the reason that we think many of our patients do quite well, both in the short term and a long-term, is the availability of clinical trials for those patients.

So I would ask that if you are a physician, partner with your largest and nearest academic center, if you are a patient, make sure you are being seen at a myeloma center in concert with your local physician to make sure you have got access to the best potential treatment options and best potential long-term outcomes as well.
So thank you very much for your attention and I hope you enjoyed this presentation.