TRANSCRIPT

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. Ajai Chari for sharing his time and expertise with us today. We have over 1,200 people participating in today's program from across the United States and Canada.

Now, before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer, who will share a few words.

Louis J. DeGennaro, PhD

I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day.

Today, you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time, and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers.

Thank you for joining us.

Lizette Figueroa-Rivera, MA

And this program is provided by LLS, and we'd like to acknowledge and thank Celgene and Takeda Oncology for their partial support of today's program.

Following the presentation, we will take questions from the audience.

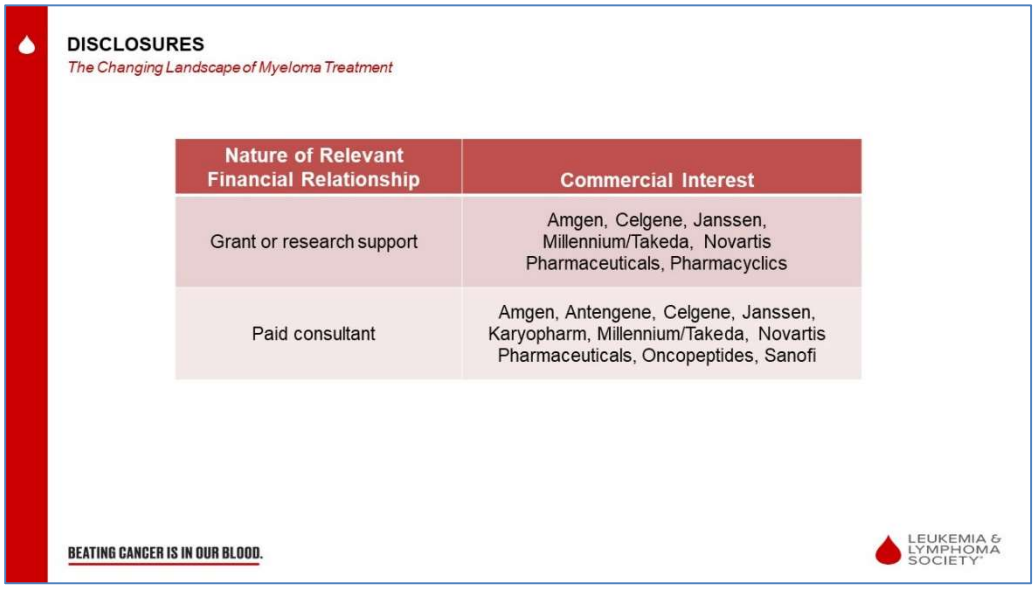
PRESENTATION

Lizette Figueroa-Rivera, MA

I'm now pleased to introduce Dr. Ajai Chari, Associate Professor of Medicine and Director of Clinical Research, Multiple Myeloma Program at Icahn School of Medicine at Mount Sinai in New York, New York. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time, Dr. Chari. And I'm now privileged to turn the program over to you.

Ajai Chari, MD

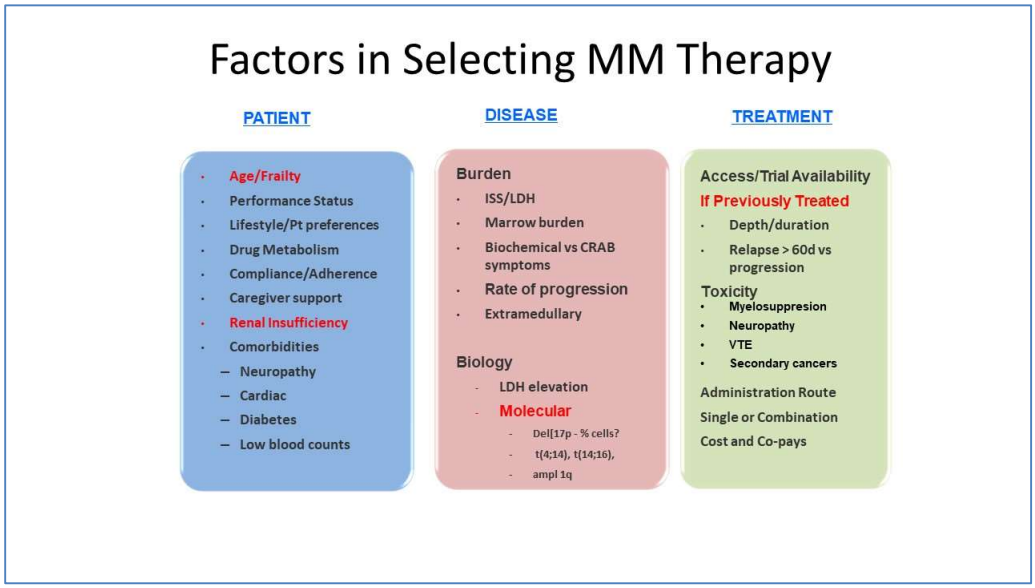
Thank you, Lizette. First, it's a privilege to be here, and I thank LLS for all of your efforts to advocate for patients. And I think, fortunately, we've had a lot of progress in myeloma, but with that comes a lot of information. [It's] hard to keep up for community doctors, let alone also for patients and caregivers. But I hope this program helps, and we'll get started.



These are my disclosures, both grant and research support, as well as consultancies.

So, there's a lot to cover, and I'll be speaking about 50 minutes. But, importantly, I wanted to make sure that people know these slides can be downloaded and also it will be available on the LLS website. So I'm not going to necessarily go through all the content on each slide, but I think, from past experience, I think we have very seasoned individuals on the call, as well as some folks that might be newer, so I'll try to present at a level that everybody can participate but then some of the details, for those who are interested, will be on the slides.

So, the first part of the talk will be about newly diagnosed myeloma, some general considerations for initial therapy, how we approach the so-called transplant-eligible population and the ineligible population.



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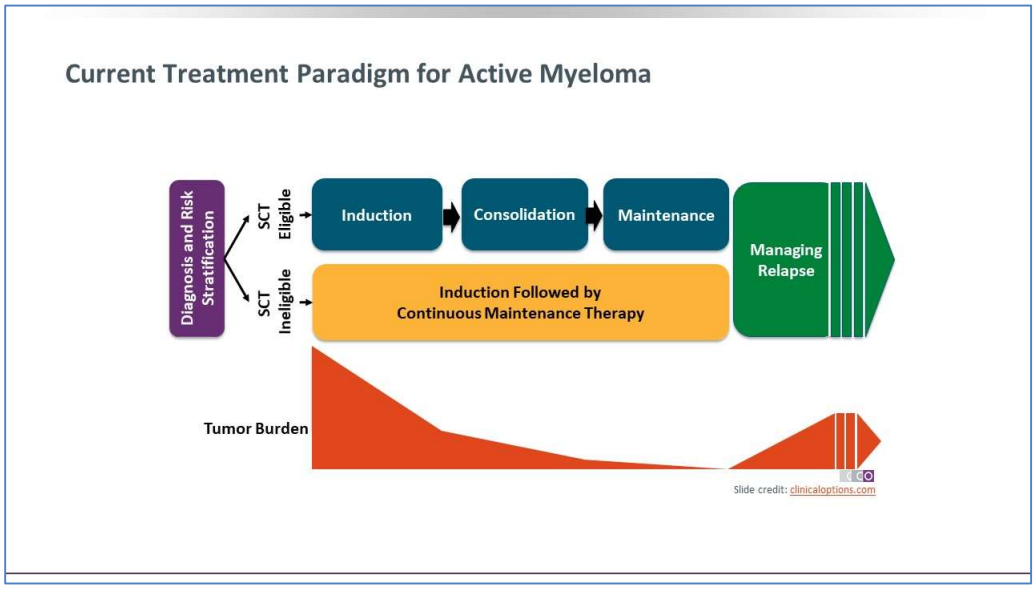
So, what are the factors in picking a myeloma treatment? I think we can broadly divide them into patient factors, disease factors, and treatment factors. More specifically, in patient factors, we have to consider age and frailty. We know that most patients with myeloma have an age in the 65 to 70 range, but my youngest patient is 18 and my oldest is over 100, and we can't treat people the same way. And so that's a really important issue in picking drugs and doses. We also want to think about kidney function, where a lot of the drugs that we use are cleared by the kidney. And, we need to make sure we're picking appropriate drugs in somebody who has kidney problems. And we also know that the myeloma patients have a lot of comorbidities, meaning other conditions like neuropathy, heart, diabetes, [and] blood cancer.

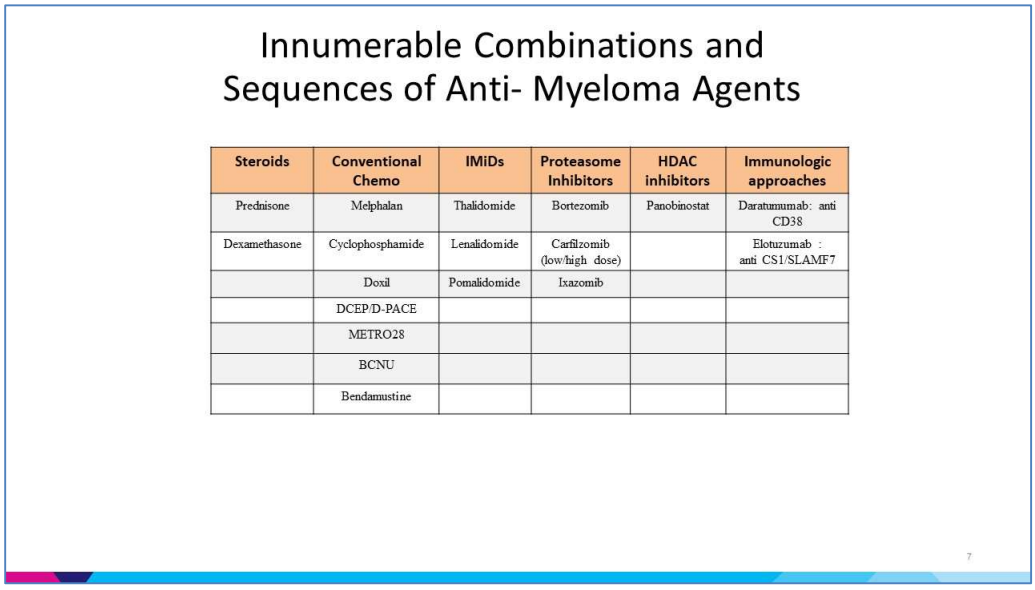
Next, we have disease-related factors, which includes the stage, how many symptoms patients have, the CRAB symptoms; for those who don't know [these symptoms] are hypercalcemia, renal failure, anemia, and bone disease. Those are the symptoms that determine the need for treatment of myeloma. Sometimes we see myeloma outside of the bones called extramedullary disease, and then biology, what kind of risk. So, we know that not all myeloma is treated equal. The genetic changes in each patient's plasma cells can be very important in determining their prognosis, and in particular, deletion 17p, translocation 4;14, 14:16, extra copies of chromosome 1. Those are considered to be high risk. Deletion 17p, it does matter how many cells are deleted.

And the last part is treatment. And clinical trials are how we've made all of these advances, and those are super important. If patients have had previous therapy, obviously, we need to know what drugs they've had and whether they worked, and how well they were tolerated. And, fortunately, we're able to now also pick, do we want to do oral or intravenous, how many drugs, and, of course, costs and copays where, again, LLS has done a great job making treatments become available to patients with these assistance programs.



So, going to the kind of overview of how we approach myeloma, once we determine that somebody needs treatment, we determine, again, about eligible and ineligible. We'll talk about how that's done,

but for the transplant-eligible patients at the top, they get initial or induction therapy, followed by transplant consolidation, which consolidation means we want to keep the disease down and then keep it away with maintenance therapy. And then for transplant-ineligible, we don't have the transplant part, but they also get initial therapy and, ideally, are then treated on a lower dose or maintenance treatment to keep the myeloma in remission. And then, unfortunately, when relapse occurs, we do have to treat that again, but, fortunately, there's a lot of new options for that as well.



So, this is our current arsenal. And, actually, there's a column missing from this. But there's really now seven different classes of drugs. We have steroids, sometimes patients' least favorite I think, and those include prednisone and dex (dexamethasone); conventional chemos (chemotherapies), which includes melphalan, cyclophosphamide; IMiDs (immunomodulatory drugs), which include thalidomide, lenalidomide or Revlimid® and pomalidomide, also known as Pomalyst. We have three proteasome inhibitors: bortezomib known as Velcade®, carfilzomib or Kyprolis™ and ixazomib also known as Ninlaro®. We have the HDAC (histone deacetylase) inhibitor panobinostat or Farydak® and then immunologic approaches, including the antibodies to CD38, which is known as dara (daratumumab) or Darzalex™, and elotuzumab (Empliciti®), which is an anti-CS1. And then the latest column that was just added in 2019 is the XPO1 inhibitor selinexor.

So, I should mention that when we have so many drugs, we have seven different drug classes available for myeloma now, with multiple drugs in each class, clearly the number of combinations are really endless. And also, the other important question that we all struggle with is the sequence, which is, if you start with combination A, then what should follow with B and then C and so on and so forth. Is there an optimal sequence? And, fortunately, we're able to tailor this for each individual patient.

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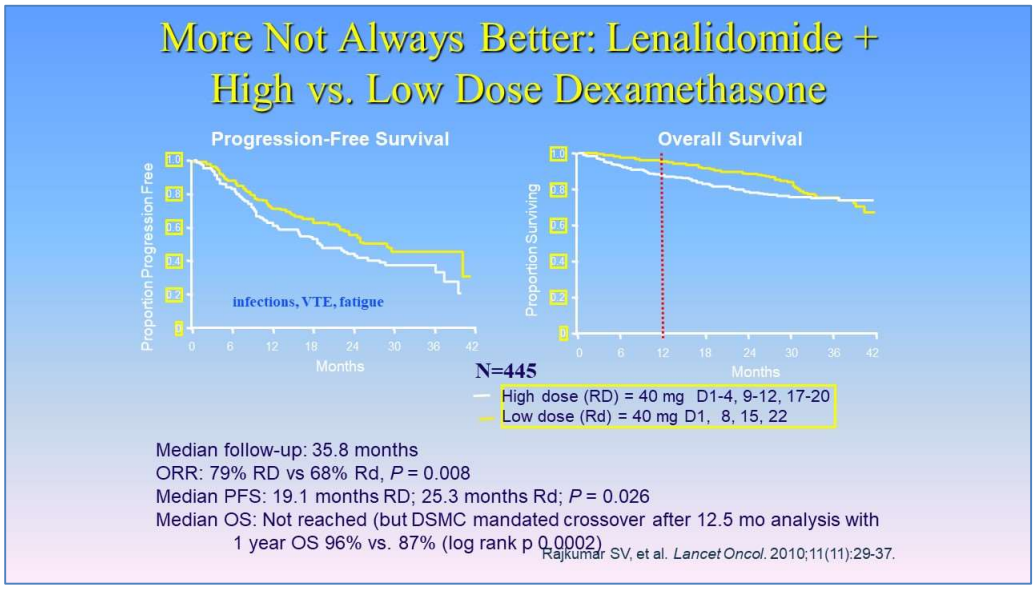
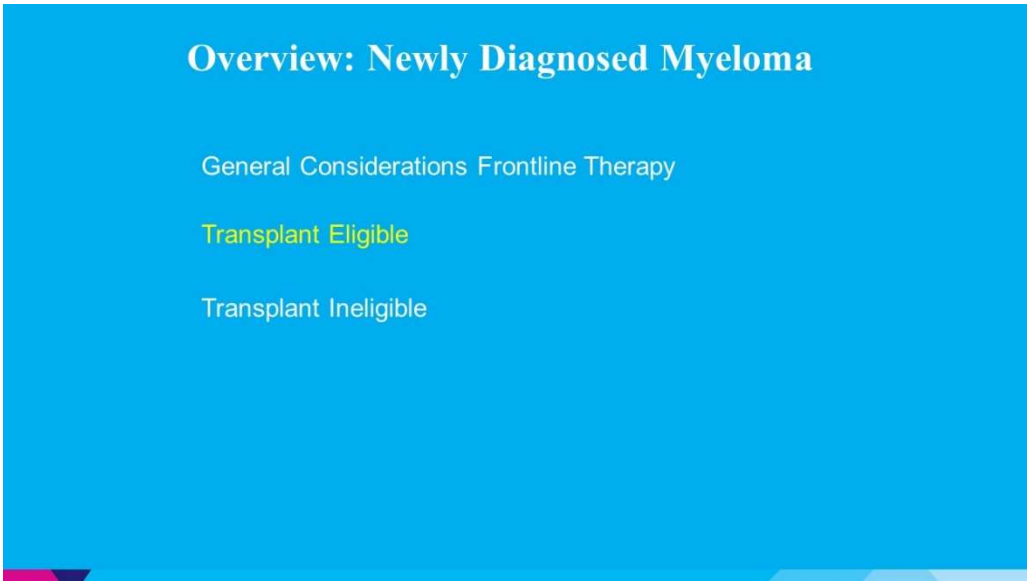


This next slide is important because there's this tendency that, okay, if we have two drugs, that three is better and if four, four is better than three. But it's not always more is better. And I think this study is an important study that looks at lenalidomide or Revlimid with high-dose versus low-dose dex. The origin of this study itself is quite interesting, and it basically was initiated by one of our patients at Mount Sinai who said, "You know, we have all of these drugs approved, why do we keep still taking these high doses of dexamethasone?" And so, dexamethasone can be typically given in oral form at 4 milligrams (mg) each. And if it's a younger patient below age 70, we often give 40 mg, which is 10 pills. But before we had all of these new drugs, we used to give not only 10 pills once a week, but four days in a row, four days on and four days off. And that is a lot.

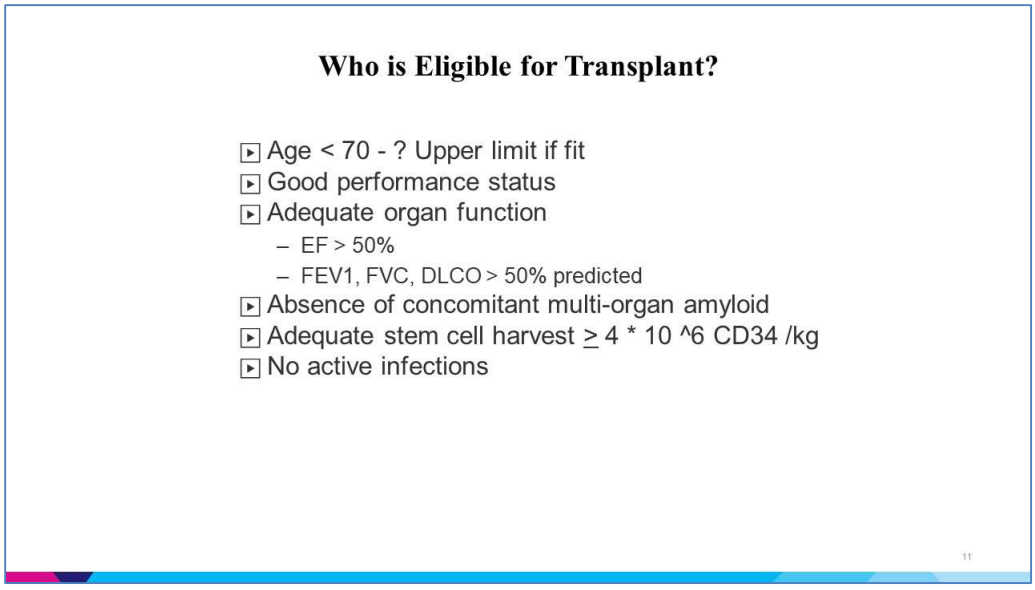
So, to convert this to prednisone, 40 mg of dex is almost 200 mg of prednisone, which very few other patients in any other medical condition receive, let alone for four days in a row. And as I always ask in my clinic, "How are you tolerating?" The patients often say, "Fine." And it's the family member who shakes their head left and right, no, because steroids cause irritability, insomnia, agitation. And so, this patient lobbied for this question of, "Why do we need to do this?" And, guess what, this study showed that while the high-dose dex of four days on and off versus the low dose, the high dose did have a better response rate, but the duration of remission in the yellow line was actually better with the low dose. And on the right side, how long people lived was actually better with the low-dose dex. And the reason for that is when you give the high doses of dex, patients have infections, blood clots, fatigue, and so this is a great example of patient advocacy that led to a clinical trial. and this clinical trial answered an important question. So right now, there's really no need for this kind of high-dose dexamethasone with the probable only exception of things like spinal cord compression or renal failure. But it's a good example of why we need clinical trials as well.

So, what are the goals of initial therapy? Well, I think at the end of the day, we want to optimize risk and benefit. Benefit specifically, first and foremost, we want our patients to live longer, have longer remission, reverse those symptoms. We'll see some very interesting impact of what the CRAB symptoms do to patients and the quality of life, and how we can improve that. For transplant-eligible patients, we need to collect cells. Ideally, we want to overcome high-risk disease and get to that, what we call MRD or minimum residual disease negativity, if possible, to try to eradicate the disease.

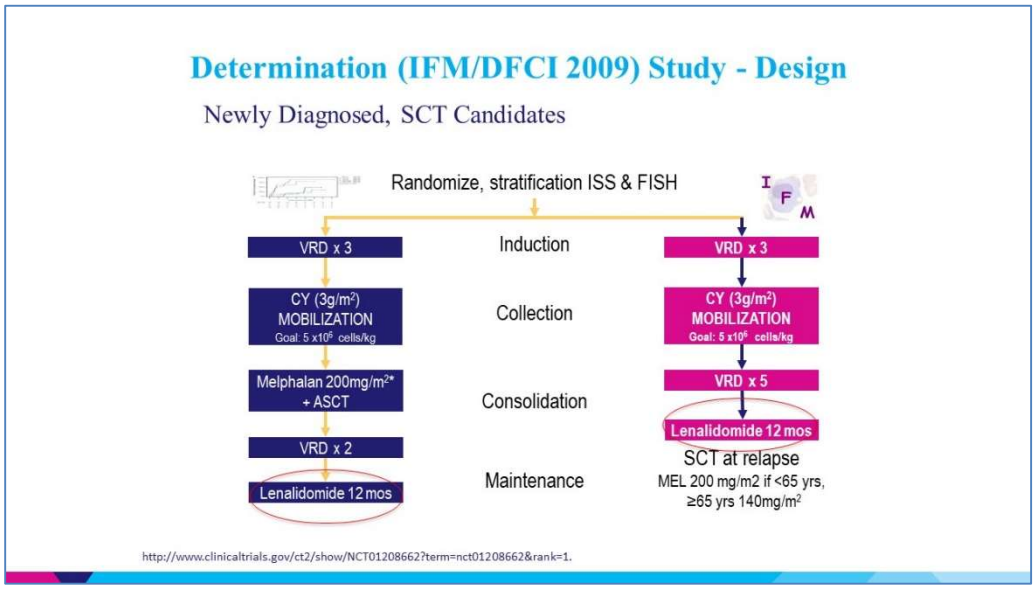
On the other side, we also want to do these but minimizing risk, including death, side effects like blood clots, cancers, shingles, low blood counts, heart failure. We also want to make sure that nothing we're doing will cause a detriment in the next treatment. Are we going to somehow get resistance with—There's always a concern with that with antibiotics and, fortunately, we'll see that that's not been borne out in myeloma; and then, of course, we have to also think about costs both for the patient as well as the system, and that's going to be an increasingly important thing in the future.



So now let's take a deeper dive into the transplant-eligible population.



The first question that often comes up is, who is eligible for transplant? Typically, anybody below the age of 70, but Medicare can pay up to the age of 80 so, really, there is no upper age limit. And I think we're moving in oncology away from numbers to more of a fitness. So, it's not just if you're 72, but are you a fit 72 or, conversely, are you a very weak and fragile 52? And that really depends on how well people function. So that's called performance status: Are people pretty independent and ambulatory? Is the heart function good, which is what we look at 50% of how much of the blood gets pumped out? And then the lung function test should be also 50% of predicted. Not having a lot of multiorgan amyloid, having good stem cell collection and no active infection.



So, let's say we have a patient that meets those criteria; this is an important study that was recently done by the French group, and there's an American version of the study. And the question being asked here is we have pretty good regimens, like VRd, which is Velcade-Revlimid-dex[amethasone] or some people call it RVd (Revlimid-Velcade-dexamethasone). And so, the question is, if the treatments are so effective, why do we need to do the transplant?

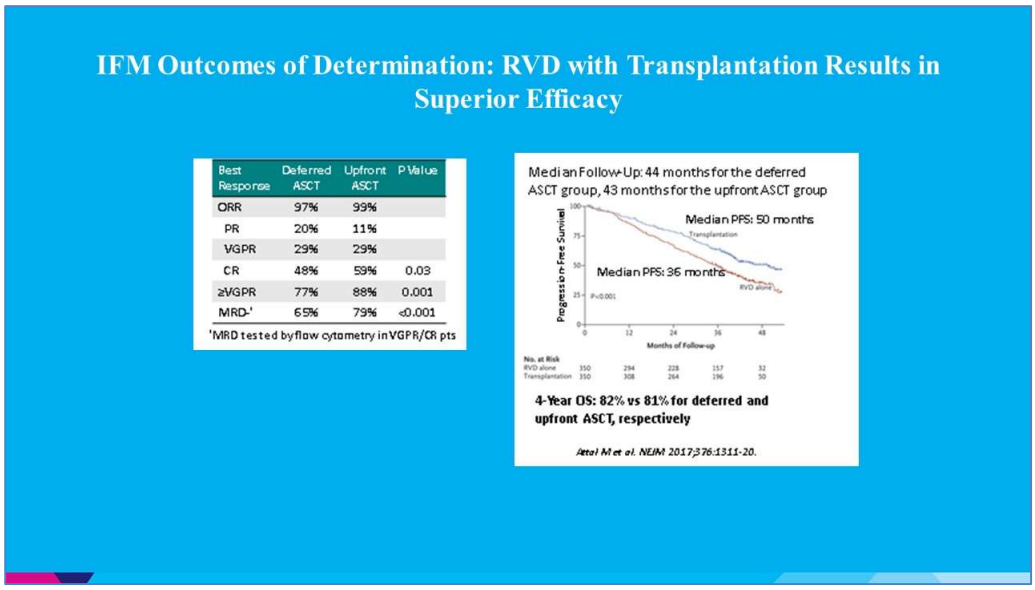
And so, this was one effort to answer that question. And you can see at the very top, everybody got three cycles of chemo. And this is done in France, so everybody gets cyclophosphamide to collect their stem cells, which is a chemotherapy that not only kills the myeloma but allowed for good collection. On the left, people were assigned to go to transplant and then they got two cycles of chemo followed by the Revlimid maintenance for one year. On the right side, no transplant. They had their cells collected, but they went on to chemo and got Revlimid for a year. So, the question is, which group did better?

And you can see from a response point of view, the patients who had the upfront transplant had a 99% response rate versus deferred 97%, so that looks pretty comparable. And you really don't see much differences until you get to the deeper responses. So complete response, which is CR, which means we don't detect any disease, that was 59% in the early, versus 48%. And that was significantly different, which is indicated by that *p* value. Anything less than 0.05 is considered significant. And also, MRD negativity was 79% in the early transplant versus 65%. And so that was also significant. So, we're able to attain deeper responses with early transplant.

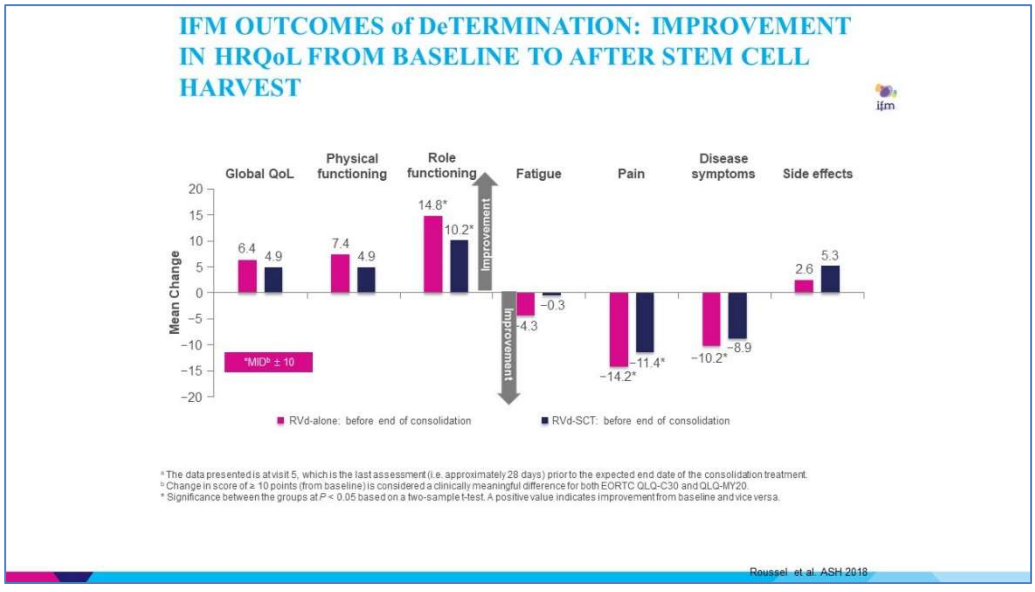
Then the question is, well, does that translate into better remission duration? And you can see on the right side, the graph, the people who went to early transplant, as shown in the blue curve, had a duration of remission of 50 months versus the nontransplant 36 months. And right now, at four years, there's no difference in how many patients were alive. So, this suggests that in 2019, it's not necessarily a bad thing to do transplant, but there's a couple of caveats. One is, if you look on the previous study, the design of the study was that in both groups after transplant or after the chemo on

the right side, patients only got Revlimid for one year. And that's important because many feel that the group on the right in a way had their odds stacked against them because this would be like having blood pressure or diabetes and stopping your medications. We know that if you stop the Revlimid, the myeloma numbers would come back.

So, the American version of the same study is, in both arms the Revlimid is taken until it stops working. So Revlimid till progression.

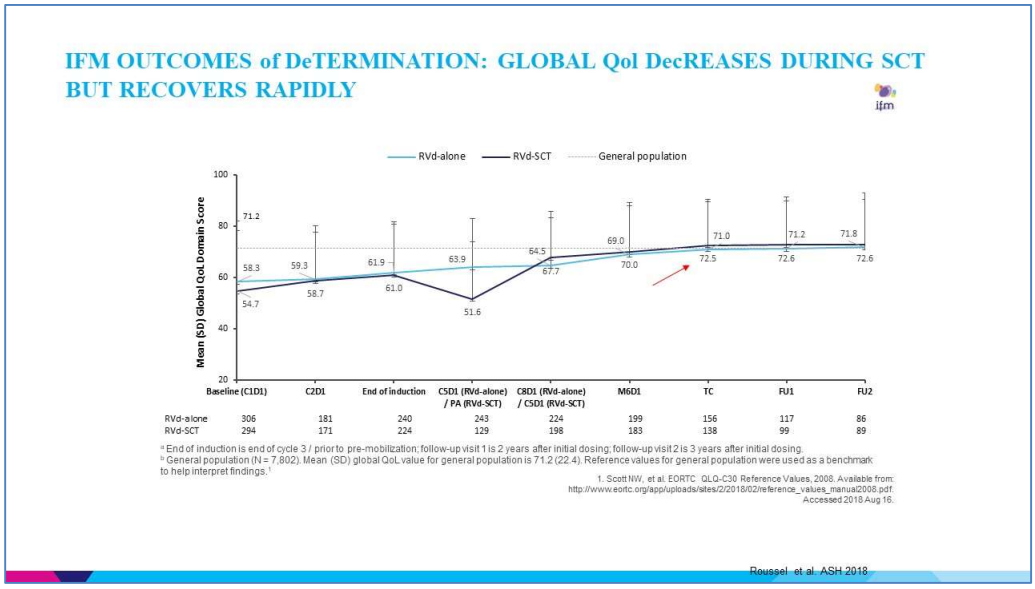


So that data we need to answer this question because the US study will answer the question of if the control arm who did not get a transplant had continued the Revlimid, might this difference of 50 months versus 36 months have been narrower? So, stay tuned for that.



And then the other question, of course, is what is the patient experience? Because when you have regimens that are both active and efficacious, we also need to think about not only the risk and benefit, but the cost and the patient experience.

So, here's some very interesting data from the same study that was presented at our national meeting last year, and it looks at the quality of life. So, on the left is before transplant. You can see that in both groups, whether you got a transplant or not—the pink is the nontransplant group, and the blue is the transplant group—the quality of life was improved in both groups after initial chemo, physical functioning is improved in both groups, and role functioning. So basically, what this means is that myeloma when newly diagnosed, the CRAB symptoms are causing problems to patients. And when we treat the disease, people feel better. On the right side are the side effects, and you can see that there are some side effects from the chemo, but the pain was markedly improved, disease symptoms improved and, overall, people feel better.



Now when we look at the two different groups in terms of quality of life, I think this next slide is very interesting because the transplant group basically, the quality of life is identical, except you see in the dark blue curve the transplant group has a dip after the transplant until about three months recovery. And it's this transient period where people do feel tired, and I think this is an important thing to acknowledge. You know, sometimes I think transplant gets a little blown out of proportion into the impact it has, but then sometimes it's also minimized. And I think we have to walk that line between not overstating the risks, but not underappreciating the risks either. And what this tells us is that, yes, patients do feel more fatigued and have a decrease in quality of life, but after those three months, they're essentially identical. And so then now we have to think about that extra remission duration that we saw in this study.

So, again, in 2019 the risk benefit, there is definitely a benefit for early transplant of approximately 14 months, perhaps shorter if the Revlimid was continued.

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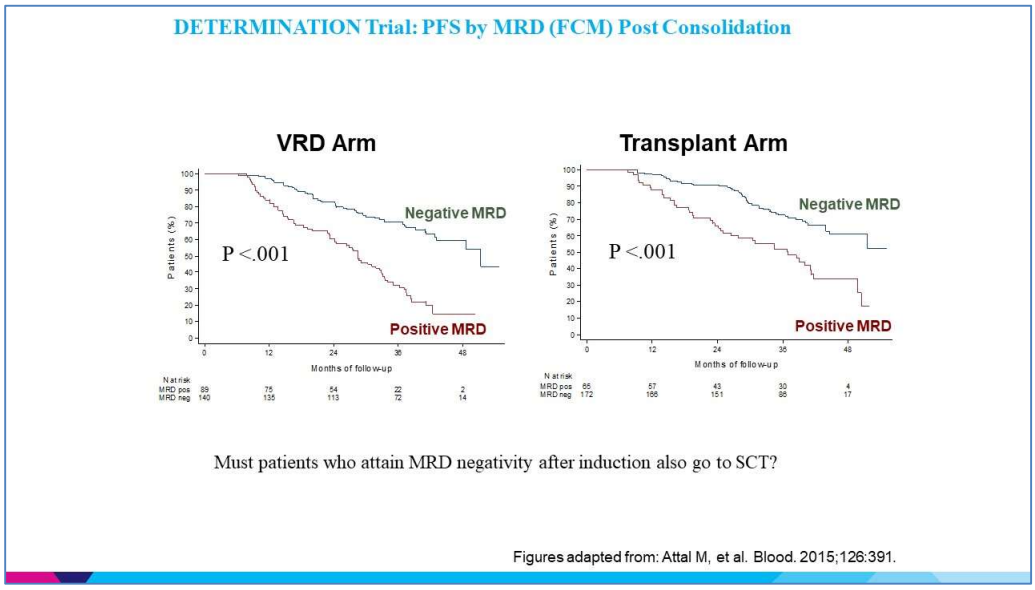

But then there's another important question that's being asked, which is, does everybody still need transplant? Is there any way to be more elegant about it? And it's also worth mentioning for those who have not had a transplant, I neglected to define what transplant is. In some ways it's a misnomer because, really, transplant is high-dose melphalan chemo—it was one of the drugs in the table—with stem cell rescue. The stem cells that we collect from patients don't do anything to the myeloma. It's really the chemo that destroys the myeloma, but also the normal bone marrow, and the stem cells are used to rescue the bone marrow. So, it's really high-dose chemo with stem cell rescue.

And in this slide, we see another way of potentially trying to figure out who may or may not need transplant, particularly going forward. And what this uses is this technique called MRD, minimal residual disease. And we can detect disease at increasing sensitivity. Back in the day, we would use immunoglobulins. Then we got to M (monoclonal) spike then we got to immunofixation and light chain. So, as we get each new test approved, we're able to detect smaller and smaller amounts of disease. And in this study, minimal residual disease you can see on the left arm, the VRd. This is the nontransplant arm. If people did not get a transplant but they achieved negative MRD, meaning we couldn't detect myeloma in their body, they had a very good outcome compared to those who had residual disease.

What's striking is in the transplant arm that you see the same thing, patients who achieved negative MRD did better than those who had positive. Now some of the differences in the two sides is, now it's more likely to get to an MRD negative with the transplant. You can see, for example, the blue curve at the bottom numbers, there's a lot more in that blue line, 172 at transplant versus 140, and more patients stay MRD negative. However, this is an important slide because it says that even patients who did not get a transplant on the left side of the graph, if they obtain MRD negativity, they seem to be doing just as well as transplant. So, it raises the question of, perhaps in the future if we use very effective drugs for newly diagnosed patients, can we pull out some patients who may not benefit from transplant?

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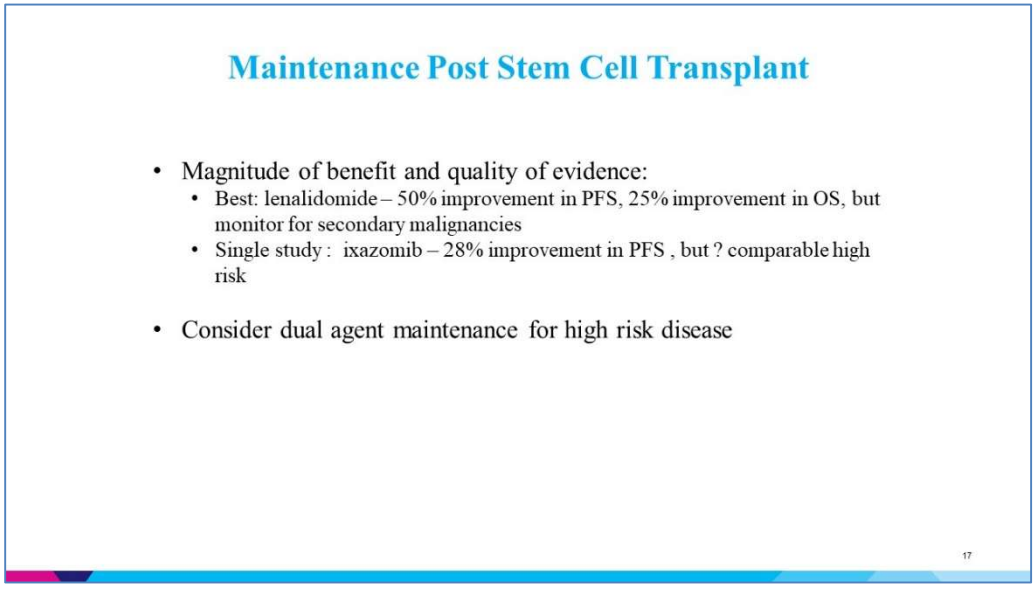
The only caveat I would mention though, ~~is that, going back to the previous slide for a second,~~ we've made a lot of progress in myeloma. And I think the majority of that progress has been in standard-risk patients. So, we have now that, based on this latest ISS staging system (International Staging System) if somebody has standard risk myeloma, we don't even know how long these people live because with long follow-up, we don't even have a median. And so, most of that benefit is coming from chemo and transplant, and maintenance therapy. And so, I think it's important not to throw the baby out with the bathwater. However, for high-risk patients, we may need to do better than a transplant, and we'll talk about some novel therapeutic approaches. But I think we may be able to be a little bit more elegant. And perhaps at least if somebody who has initial therapy and is still positive after treatment for MRD, at least those patients should be encouraged to go to transplant.

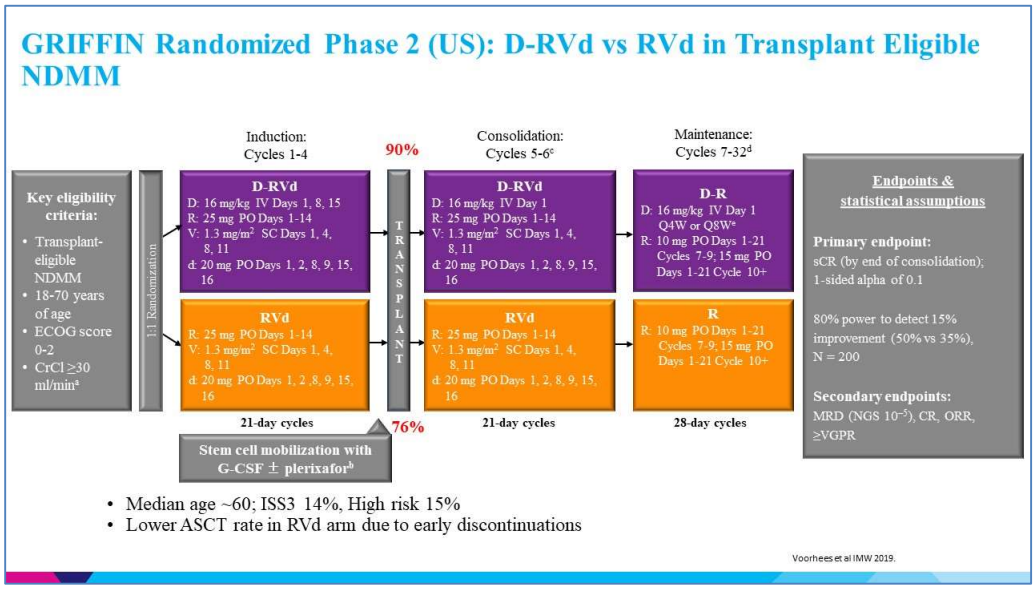


Moving to posttransplant, I'm not going to spend a lot of time on this because, again, the definition of this talk was really changing landscape. Not that much changed, but what do we know about maintenance therapy? Revlimid or lenalidomide, when given after transplant, results in a 50% improvement in the duration of remission. What does that mean? It means if somebody gets typical initial therapy and transplant, their remission typically lasts about two years. With Revlimid maintenance, it goes to about four years. And you saw that in the French study, it went to about 50 months. So that's the reason we give the lenalidomide maintenance for the doubling and the remission duration. More recent data has shown that not only is there doubling, but people also live 25% longer with the Revlimid maintenance. There is a small risk with this associated, which is increased risk of secondary cancer. So, anybody getting transplant and Revlimid maintenance should be monitored closely for secondary cancers. The rate is in the control arm and the non-Revlimid maintenance was about 3 to 4%. And with Revlimid maintenance, it can go to 6 to 8%. And it can be any kind of cancer, so we recommend just doing skin exams, mammograms for women, colonoscopies when due, and just paying attention to one's health.

The one more recent study that was presented was the Ninlaro or ixazomib study. And I think one of the disappointing things is there was only about a 28% improvement in the remission duration and

maybe some benefit and high-risk data. We don't see any secondary malignancies, but this is not yet approved for maintenance. And the benefit in the remission duration was a little bit less than what we saw with the Revlimid. So, stay tuned. But for somebody who did not tolerate Revlimid maintenance for whatever reason, this may be an option.

And then the last point in maintenance is, this is one area where treatment diverges. We think for high-risk patients, one drug may not be enough. It may be important to do two drugs. And, again, one could consider, for example, Revlimid with the Ninlaro because this is a double oral regimen, but, again, that not on-label. It's not official, but it's one option.

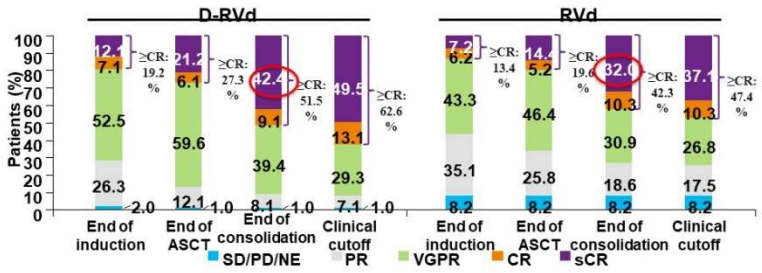


And then what's the latest in newly diagnosed patients? So, we talked about RVd, and then the role of transplant. And one of the questions is, what's the role of daratumumab? Dara is an important drug that was approved in 2015. This is that anti-CD30 and monoclonal antibody or also known as Darzalex®, the brand name. Because of its efficacy and safety, and also combinability, it's very quickly moved from heavily treated patients in 2015 to even newly diagnosed patients.

This is a study that basically asked the question of, we know that RVd is a pretty good regimen. It results in very good responses and that's used in the US extensively. And the question is, if you add dara to this, how will it change the outcomes? And so, in this study, which is known as the GRIFFIN [study], half the patients got RVd at the bottom and the other half got the addition of dara. They all got transplanted. Now one of the differences is that in the control arm not everybody went to transplant. 76% did versus 90%. Then they got two cycles of what we call consolidation to kind of mop up what little disease might be there, followed by maintenance where the control arm just got Revlimid and then the dara got both dara and Revlimid.

And what we were looking to see—this is because we don't have a lot of long-term follow-up—is what the depth of remission was after that initial therapy followed by transplant, followed by consolidation. So, it's right before maintenance the question is, how do these differ? And we have some data there.

GRIFFIN : D-RVd vs RVd Efficacy



Post consolidation DRVd vs RVd:

- sCR: 42.4 vs 32% (OR 1.57 95% CI, 0.87-2.82; 1-sided $P = 0.068$ ie primary endpoint met @pre-set 1-sided α 0.1
- ORR: 99% vs 91.8%, 2-sided P = 0.0160
- MRD neg (10^{-5} by NGS): 44.2% vs 14.6%

Response rates and depths were greater for D-RVd at all time points

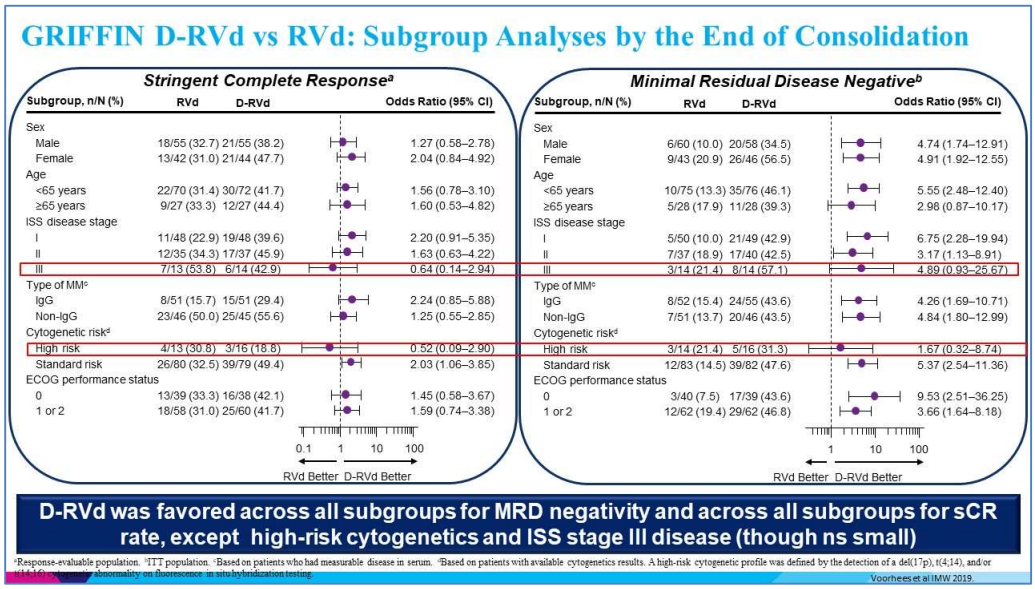
SD, stable disease; PD, progressive disease; NE, not evaluable

Voorhees et al IMW 2019.

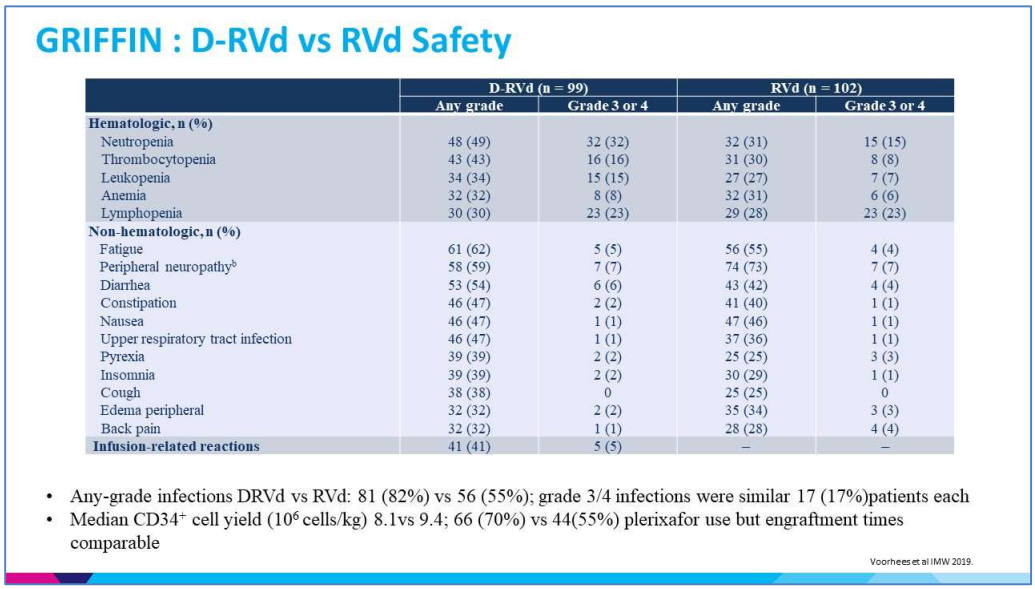
On the next slide, the depth of response, stringent CR rates, and maybe it's easier to look at the text at the bottom; the stringent CR rates are 42% in the dara-containing arm versus 32%. That was statistically significant. Overall response rate was also better, and MRD negativity was better. So, we saw that MRD negativity was 44% with the dara versus 14.6%. So, in all of these different timepoints the addition of dara seemed to help.

And the other important study, this study is not yet mature, but in the French version of the study, instead of using Revlimid, they used thalidomide, which is an older drug. [It] has more toxicity issues. But in their study, not only did they find the same thing, that the addition of dara led to deeper responses, but also, already by 18 months after transplant, remission durations were longer. So, I think this suggests that the addition of dara may be beneficial.

TRANSCRIPT



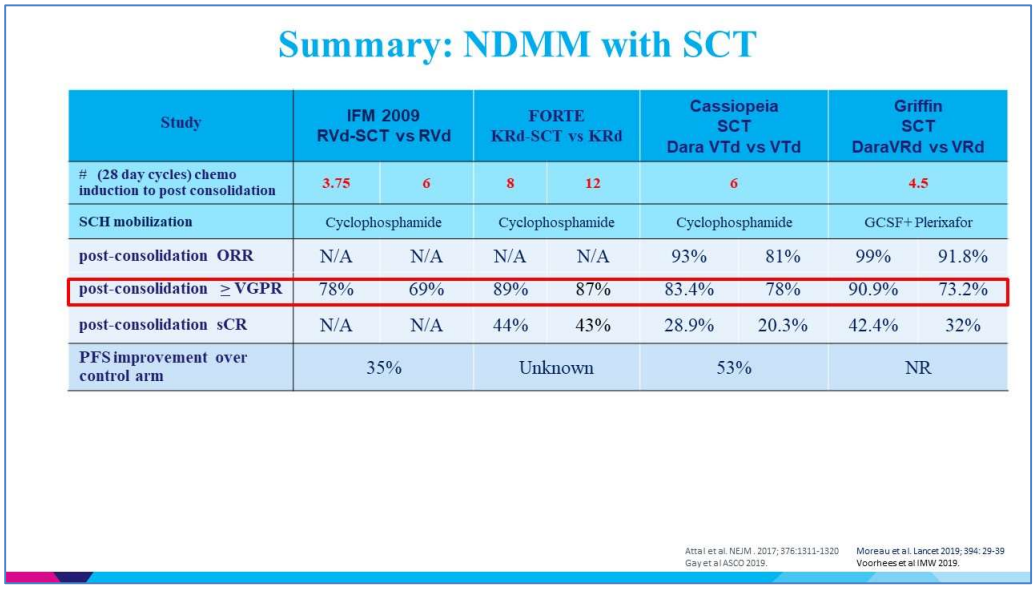
This is a very busy slide and if you care to go through it, again, you can download it. But the point of this is that, are there particular groups of patients that benefit more or less? And the various groups are outlined on the two sides. The left side is the stringent complete response and the right side is MRD negativity. And we can look at the MRD negativity for the sake of time and look at basically anything, that dotted line, anything purple dots to the right of the dotted line means that the dara was better. And you can see pretty much regardless of gender, age, ISS stage, performance status, everything favored. The one thing that doesn't completely favor, although it's in the right direction, is high-risk patients. And I think we'll see this is an ongoing issue that we've made a lot of progress particularly for standard and intermediate risk, but we need to do more for high-risk patients because we're not fully overcoming that.



TRANSCRIPT

The side effect profile of the dara is shown here. And the main take-home points are, there is a higher rate of neutropenia, which is the white cell called neutrophil. That helps prevent infections and so you can see that when you look at all rates of neutropenia, it was 49% with the dara, 31% without the dara. And when you look at severe neutropenia, which is how we define as grade 3 and 4, it was 32% with the dara versus 15%. And with that, there is also a slight increased risk of infection. And you can see at the bottom I've indicated that 82% in infections versus 55%.

Part of the infection story is that myeloma patients, plasma cells are part of our immune system, and if you don't have a good immune system and good antibody production, that itself can lead to infections. But here, we did see a slight increase in infections, but severe infections were comparable. And stem cells were able to be collected.



Study	IFM 2009 RVd-SCT vs RVd		FORTE KRd-SCT vs KRd		Cassiopeia SCT Dara VTd vs VTd		Griffin SCT DaraVRd vs VRd	
# (28 day cycles) chemo induction to post consolidation	3.75	6	8	12	6		4.5	
SCH mobilization	Cyclophosphamide		Cyclophosphamide		Cyclophosphamide		GCSF+ Plerixafor	
post-consolidation ORR	N/A	N/A	N/A	N/A	93%	81%	99%	91.8%
post-consolidation ≥ VGPR	78%	69%	89%	87%	83.4%	78%	90.9%	73.2%
post-consolidation sCR	N/A	N/A	44%	43%	28.9%	20.3%	42.4%	32%
PFS improvement over control arm	35%		Unknown		53%		NR	

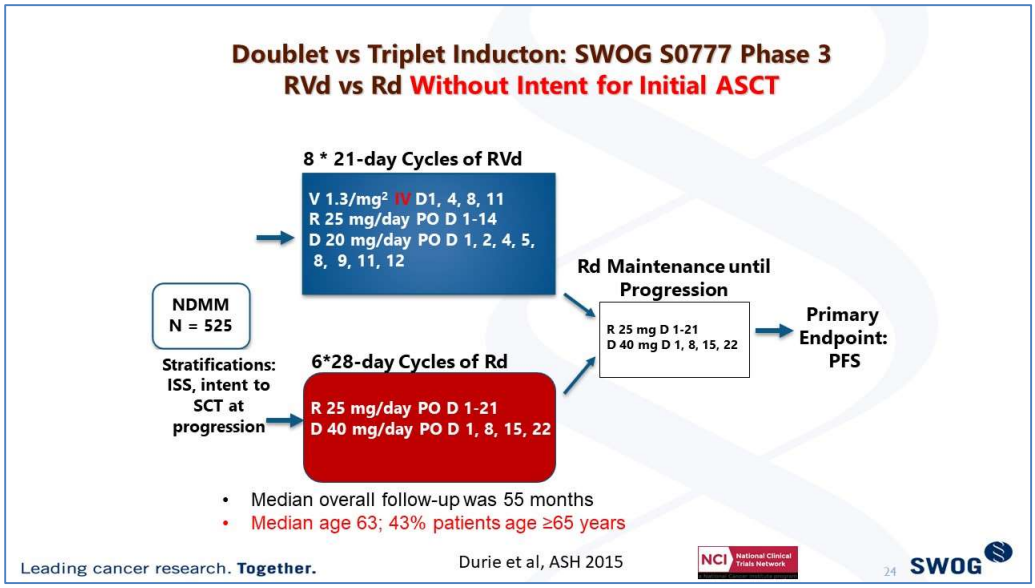
And so, what does that mean for a newly diagnosed patient? This is my take-home slide, if you will, for newly diagnosed patients who are eligible for transplant. The IFM study, which we saw was about early versus late transplant, 78% versus 69% so favoring the transplant group. The FORTE study comparable. This is with carfilzomib, Revlimid, and dex. The GRIFFIN study, which we just covered last which is dara with Velcade, 90% versus 73%. So, we're doing really well in terms of the depth of response and the dara definitely seems to be giving us the highest that we've seen in recent years.

One of the big differences though, and from a patient perspective, is the first two rows. So, the first row tells us how much chemo do you need to get that response? And you can see that it can be as short at 3.7 cycles for RVd, to as long as 12 cycles for the FORTE study where carfilzomib, Revlimid and dex was given without a transplant. And so that's an important question. If you're not going to do transplant, how much chemo is really needed?

And then the next row, which is called stem cell harvest, or mobilization in the European studies, the first three columns, they all require Cytoxan (cyclophosphamide). And this is important because sometimes this drug can cause hair loss. And so particularly somebody who's getting initial therapy,

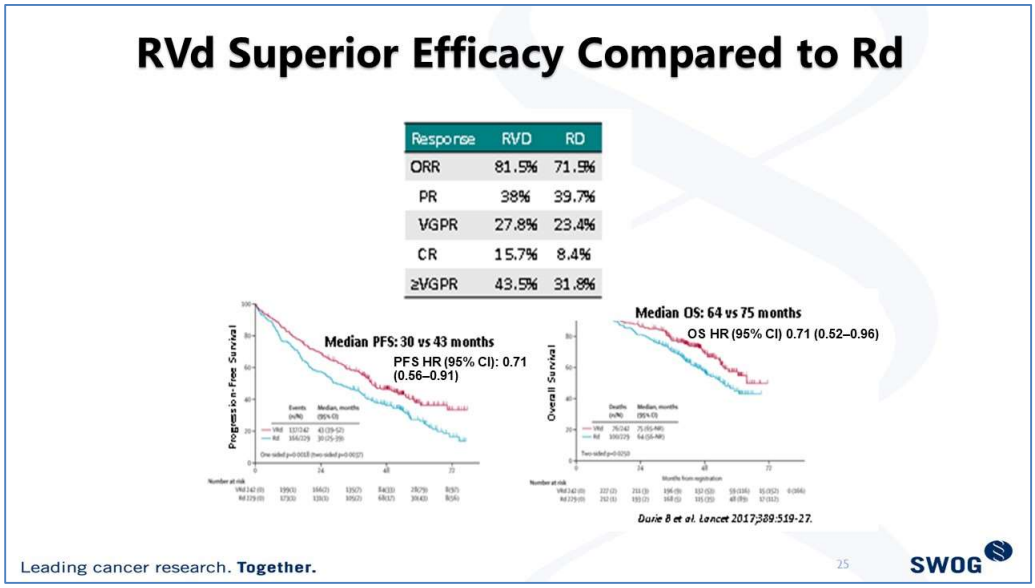
but they don't want to go to transplant and they just want to collect their cells, it may be a bit to go through. But the American version of this study, which is the last column, we don't typically do that. So, I think the take-home message is, in 2019 for transplant-eligible, definitely RVd is a good option and maybe the addition of dara once the insurers approve that but stay tuned.

Moving to the transplant-ineligible population.

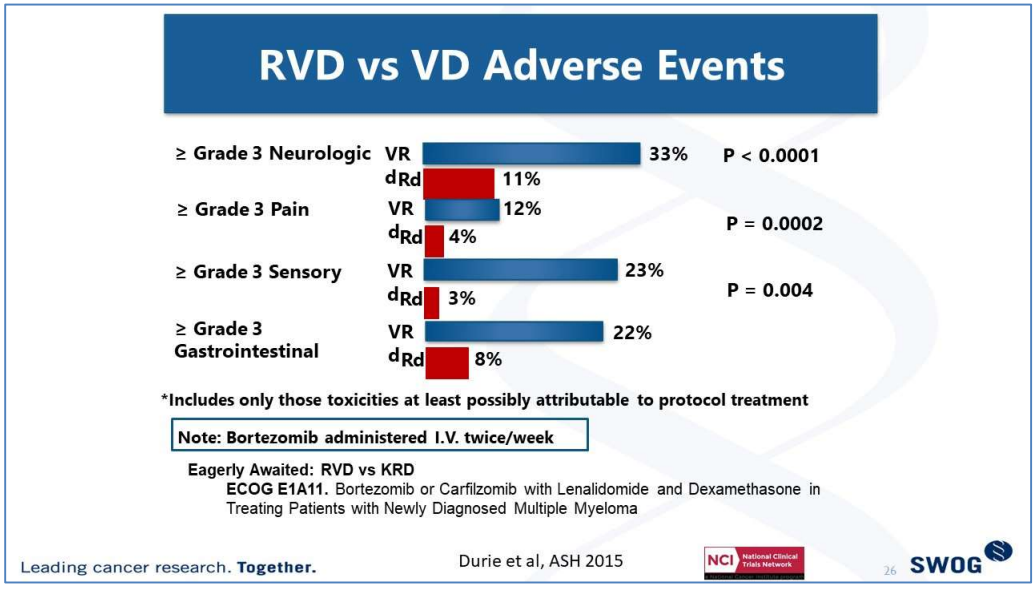


This was an important study that was done where we compared Revlimid and dex with the addition of Velcade. And so, this was for 21-day cycles in the top and 28 days. And then after the initial treatment, people were maintained on Revlimid and dex. Important consideration here is that although this is [for] patients who are quote "transplant ineligible," really the definition of this study

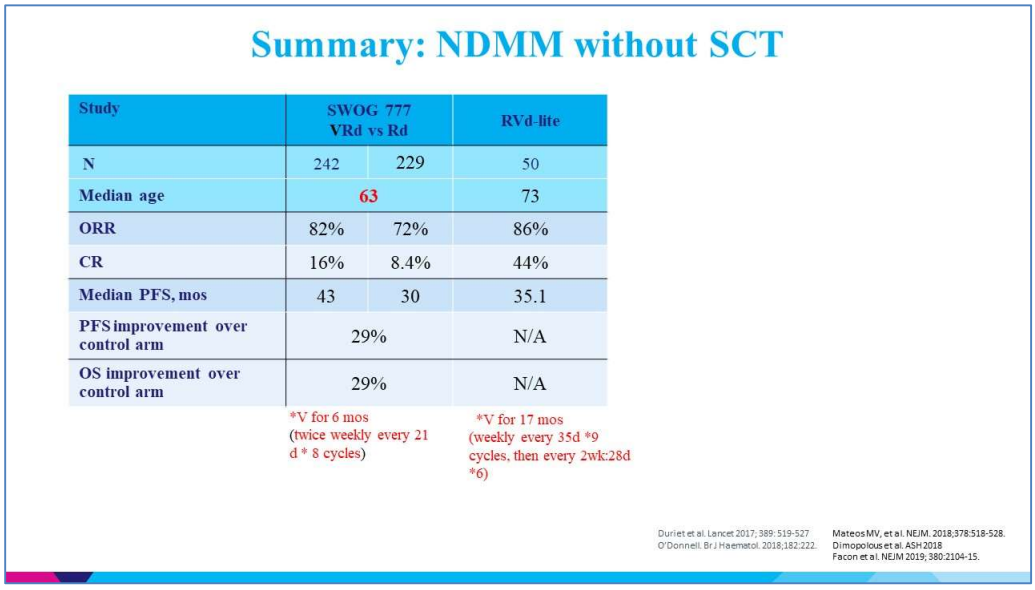
was without the intent of transplant. Why am I bringing that up? It's because the median age in this study was only 63, which is, we think, quite young. Many of these patients would be eligible for transplant. Only less than half the patients were over 65.



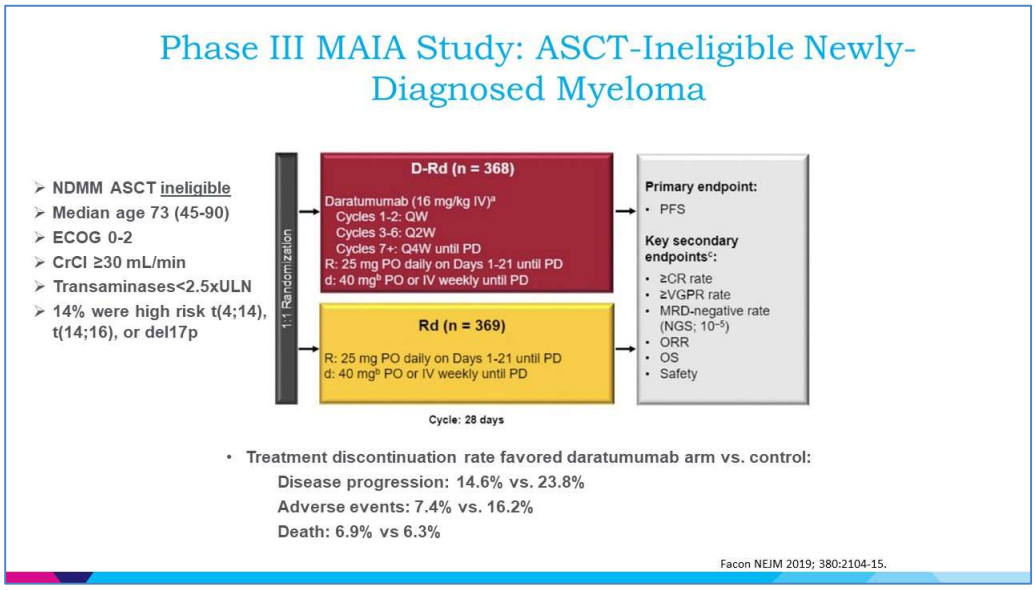
So, at many centers in the US, this is not a transplant-ineligible population. But we can see that the addition of the Velcade in the top led to a deepening of responses, 81.5 versus 71.5%. The remission duration was longer with the Velcade, 43 months versus 30 months in the lower left graph. And, finally, people lived longer, 75 versus 64. So, it looks like we should be adding Velcade to Revlimid, because depth of response, remission duration and, importantly, people lived longer.



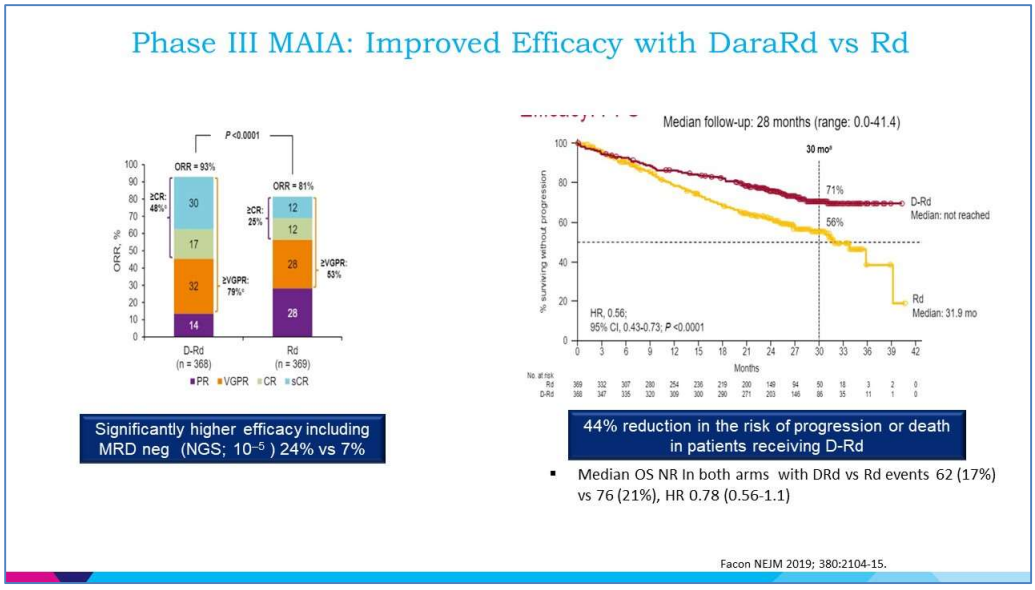
So that seems like a straightforward study, but we have to always remember the side effects. And the main side effects shown here are the neuropathy, which even caused pain with the addition of Velcade, and then some GI (gastrointestinal) symptoms. But this is back when we were giving Velcade intravenously, and we don't do that anymore. We do it in the skin and it's because when you give the drug in the skin, it absorbs slower and you don't get a high level of the drug in the body, in the blood particularly. Whereas when you squirt it into the vein rapidly, you get a high level. And it seems like the side effects are more related to how quickly you give it, rather than how much you give. And so skin administration is better, so a lot of these side effects will be less prominent when you give it in the skin. But to summarize, the study was the median age of 63, had a good response rate, and did better than the Revlimid.



Now, another version of this study, particularly for transplant-ineligible, and this came from the Boston group, this was what we call RVD-Lite. And at the bottom you can see that the Velcade in the study that we just covered, was given twice weekly for six months. And the problem is, older patients who are transplant ineligible typically will have more side effects, as we saw, those neuropathy and GI symptoms. So, what's often done for older patients is to give the Velcade only once a week, use a lower dose of Revlimid. And this is called RVD-Lite. And you can see that the responses were as good, 86%. Complete responses were actually even better, 44%. Duration remission was good, 35 months. And so, this was a small study, but many of us, when we treat older patients, we're not giving that big gun, twice-weekly chemo that can be quite toxic.

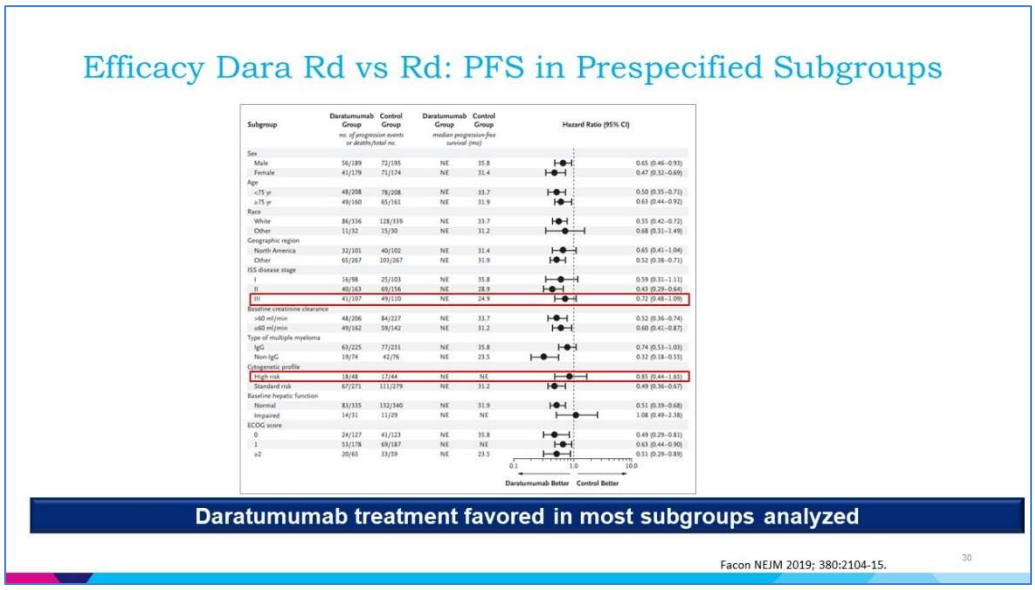


But what's new in this population? We had an important study that is now FDA-approved, which is the so-called MAIA study, where everybody got Revlimid and dex in the yellow, and then the experimental arm got the addition of dara. So, these are in an older population. And this is truly not like the SWOG (Southwest Oncology Group). The median age here was 73. So, appropriate to consider for nontransplant although as I stated at the very beginning, it really depends on not just the age, but how fit these people were.

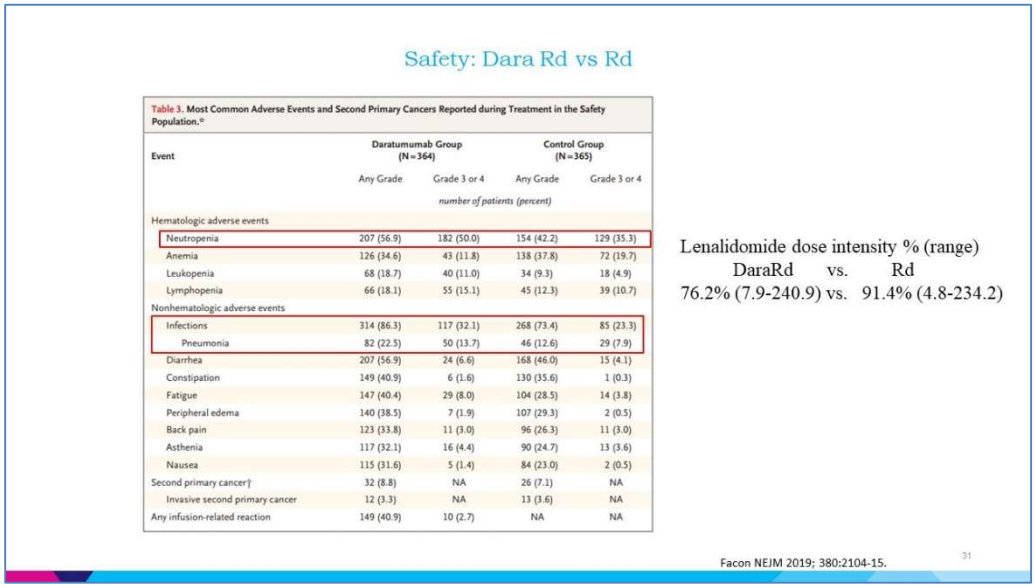


And so, what you can see is that, in this next slide, response rate was 93% with the dara-RD versus 81%. So better responses, deeper responses, on the left and also on the right, the remission duration was longer. You can see that DRd (DaraRd), the patients are doing so well, that red bar is still pretty flat, which means that not everybody has even relapsed. So, people are remaining well controlled,

whereas the Revlimid 50% had come off and that's typically at 32 months. So, this means that there's a 44% reduction in the risk of progression with the addition of dara.

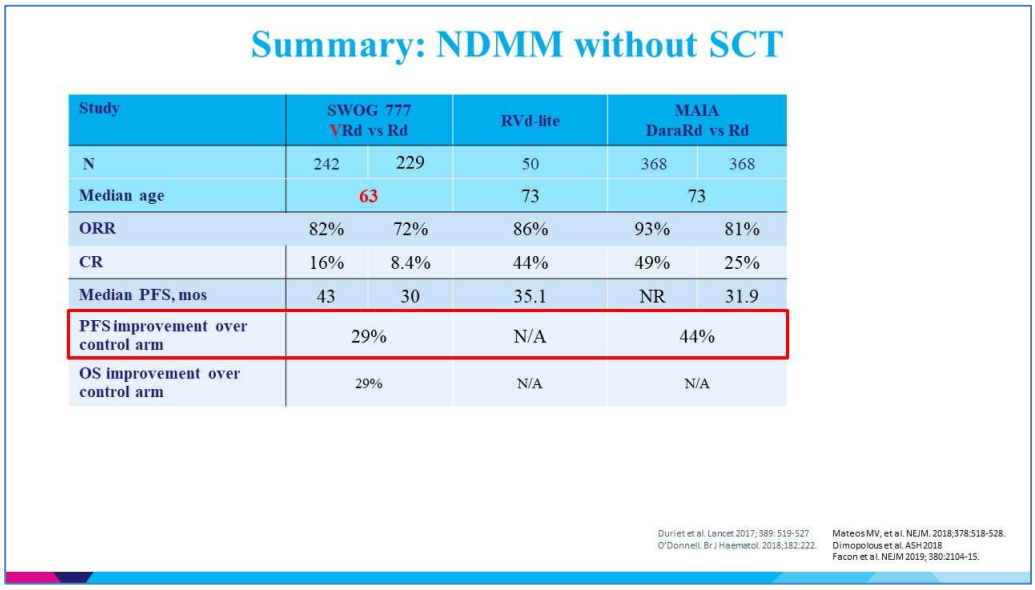


And similar to that other slide, pretty much on this slide everybody, if the dots are to the left, everybody was benefiting from the dara regardless of… even people over the age of 75. That's shown there in the age category, and across all the numbers. The only thing, again, is high-risk patients that that bar crosses one. Which doesn't mean that the dara hurts these patients, it's just that we haven't fully overcome high risk. So, a good option for these patients.

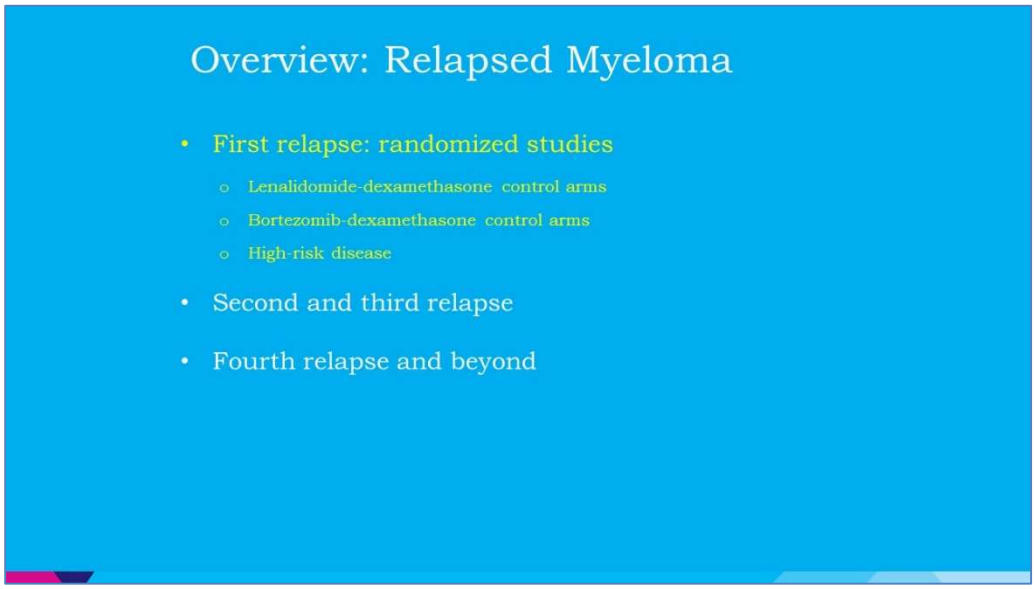


Safety, kind of similar to what we saw earlier. We do see more neutropenia, that lowering of white count. We do see more infection. So, I do always ask all my patients, even if they have a local doctor

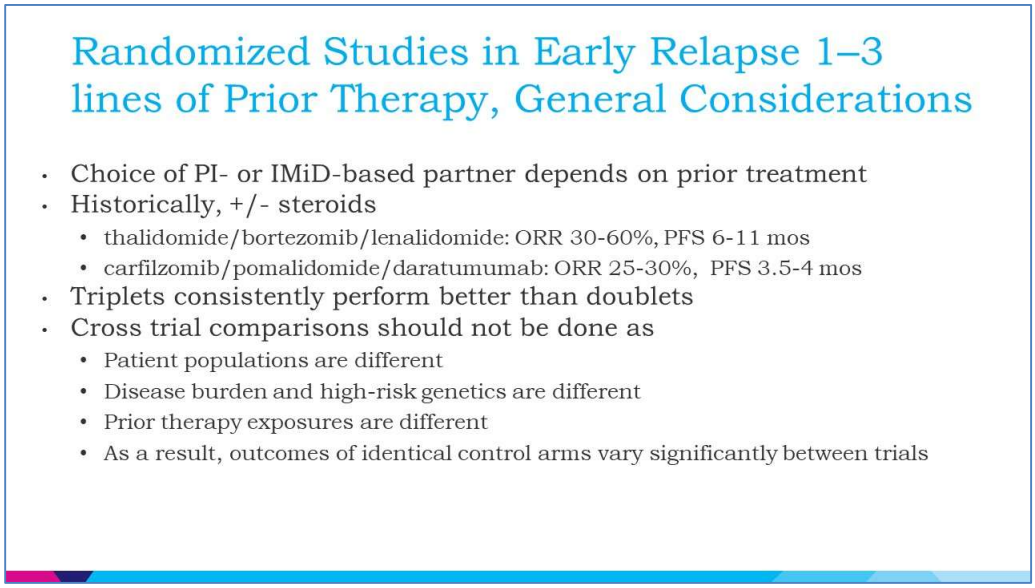
or primary doctor, to really keep us posted about any symptoms of infections like fevers, cough, sweats, burning with urination, because we want to make sure that we're following the frequency of infections. And we think that part of the reason why people may be getting infections is, obviously, myeloma but also, we're seeing that some of these patients who are getting dara, their good antibody levels, known as the IgGs (immunoglobulin G), get so low that they may need to be boosted with intravenous immunoglobulin treatment. So, do keep us posted. The indications for IVIG (intravenous immunoglobulin) are typically myeloma patients who've had more than three to four bacterial infections in a year, or fewer than that but very severe ones, and have low IgG levels. There is a shortage of IVIG too, nationally, but I think this is an important intervention that can help our patients.



So to lose the newly diagnosed chapter for this older, nontransplant-eligible population, we can see that the three studies head to head, the SWOG, the addition of Velcade to Revlimid in the red box, 29% improvement, whereas the addition of dara to Revlimid, 44% improvement. So I think, when you see that it's a more potent combination and, at the very top, this is in an older population, 73 versus 63, this tells us that the addition of dara to Revlimid and dex can really help with disease control. And I think it's a great option for patients that you can actually give. And to remind folks, dara is given weekly for eight weeks, every other week for four months and then, eventually, it's once a month. So, when people are in long-term disease control, they're coming in once a month for the dara, and then taking the Revlimid at home.

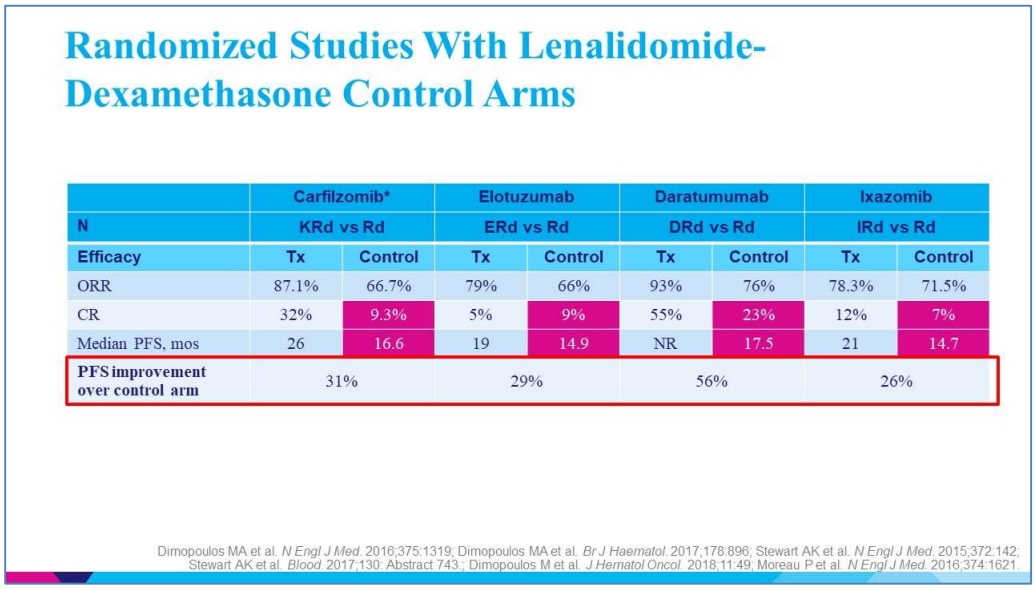


Moving to relapsed disease, while we've made a lot of progress, and, as you can see, some of those dara-Revlimid-dex [patients], not everybody had even relapsed. So, if patients haven't relapsed, great. We want to continue that initial control. But if relapse and the myeloma comes back, what are our options? And, fortunately, we have a lot. And it's hard to go through all the different combinations, but what I'm just going to give you is an overview of the Revlimid-based backbones, Velcade-based backbones, a few words about high-risk disease, and then we'll talk later about how to treat later relapses.



So, some important considerations are that, whether you pick a Revlimid- or Velcade-based backbone depends on what people have had before. An important consideration, which we're going to come back to, is that we saw that Revlimid maintenance is used extensively. So, somebody gets

initial therapy, whether it's with or without a transplant, often people are ending up being maintained on Revlimid. So then, if somebody's progressing on that Revlimid, you may have to change the treatment. Typically, three drugs do better. And we want to try to always compare across the studies, but every study has slightly different patient populations.

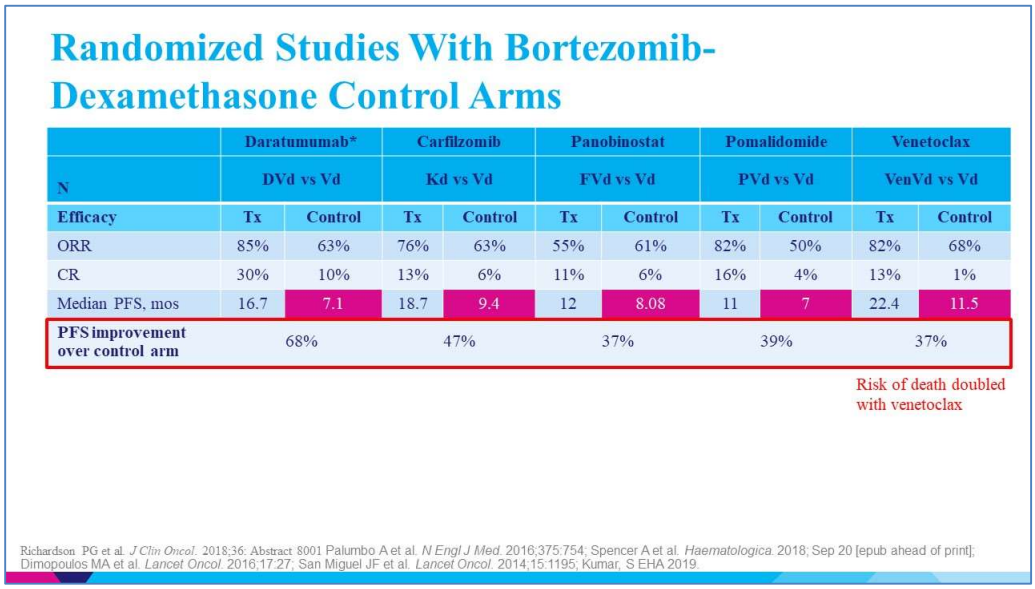


	Carfilzomib*		Elotuzumab		Daratumumab		Ixazomib	
N	KRd vs Rd		ERd vs Rd		DRd vs Rd		IRd vs Rd	
Efficacy	Tx	Control	Tx	Control	Tx	Control	Tx	Control
ORR	87.1%	66.7%	79%	66%	93%	76%	78.3%	71.5%
CR	32%	9.3%	5%	9%	55%	23%	12%	7%
Median PFS, mos	26	16.6	19	14.9	NR	17.5	21	14.7
PFS improvement over control arm	31%		29%		56%		26%	

And you can see here, for example, there's four important studies that were done, and all of these are approved with Revlimid as a backbone. And you can do Kyprolis or carfilzomib, elotuzumab, dara, or ixazomib or Ninlaro. And you can see that in the purple is the outcomes of the control arm, meaning all of these groups in all patients, they got Revlimid and dex as a default, which is the standard of care.

And then the experimental question, or the question being asked is, will adding a third drug help? And you can see that the control arm had a CR rate, or complete remission, of anywhere from 9% to 23%, and the duration of remission was anywhere from 15 to 17.5 months. Now when we added the third drug, at the very bottom you could see how much improvement there was over that backbone. And that was 31% with the carfilzomib, 29% for elo (elotuzumab), 56% for dara, and ixazomib 26%.

So, what does this mean? If somebody has relapsed disease and they've, for some reason, not been on Rev (Revlimid) and you want to do a Revlimid-based backbone, you could pick any of these regimens, and each of them have pros and cons. For example, carfilzomib is given intravenously either weekly or twice weekly. Might be good for somebody with aggressive disease without any cardiac issues. Elotuzumab very well tolerated, a gentle drug, intravenous. Great for elderly patients who may not have a lot of symptoms. Dara, clearly a very powerful drug, has the highest reduction, 56% improvement in the control of the disease, compared to without the dara. And, finally, ixazomib for somebody who wants a completely oral regimen, this is a three-drug regimen with only pills. So, it's great to have all of these options for patients, and there's never going to be one right answer.

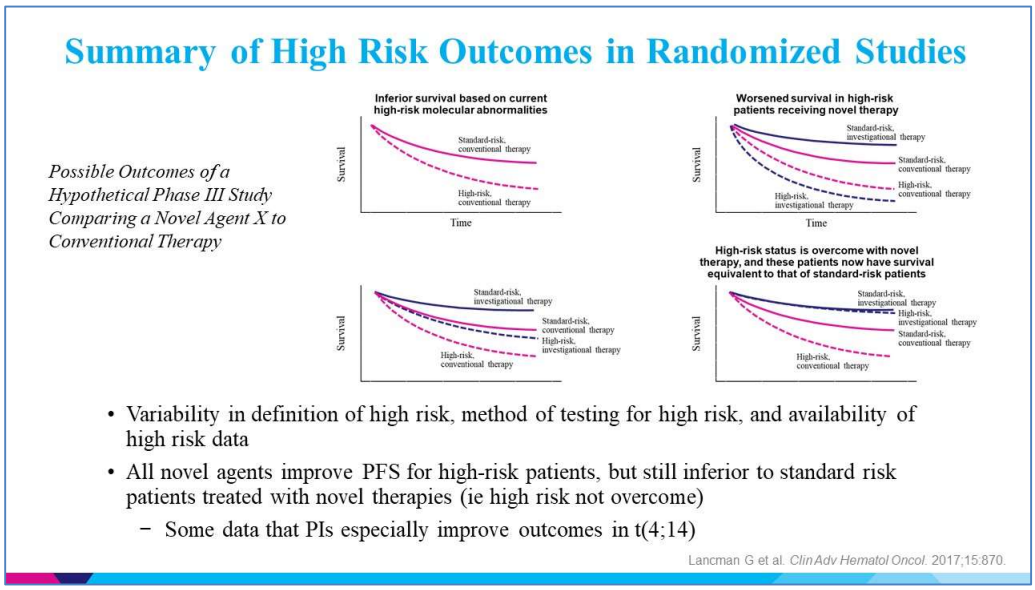


	Daratumumab*		Carfilzomib		Panobinostat		Pomalidomide		Venetoclax	
N	DVd vs Vd		Kd vs Vd		FVd vs Vd		PVd vs Vd		VenVd vs Vd	
Efficacy	Tx	Control	Tx	Control	Tx	Control	Tx	Control	Tx	Control
ORR	85%	63%	76%	63%	55%	61%	82%	50%	82%	68%
CR	30%	10%	13%	6%	11%	6%	16%	4%	13%	1%
Median PFS, mos	16.7	7.1	18.7	9.4	12	8.08	11	7	22.4	11.5
PFS improvement over control arm	68%		47%		37%		39%		37%	

Similarly, with the Velcade, you can take Velcade-dex as a comparator group and add to that dara. You could compare to the high-dose carfilzomib, panobinostat. There's a recent study known as OPTIMISMM where you combine it with pomalidomide or Pomalyst, and then venetoclax. So, a lot of options. And I'm not going to go through all the numbers in detail, but let's just go to the bottom line at the very last row. The addition of dara led to 68% improvement in the remission duration, carfilzomib 47%, pomalidomide 39%, and venetoclax 37%. So, again, a lot of different options. Again, dara being kind of a standout of 68%, but there may be rationales to use the other drugs depending on patient circumstances.

And one other kind of interesting thing that we learned about the last study in the graph venetoclax, so as with all of these studies you can see that the response rate was 82% compared to 68%, which favored the venetoclax, 13% CR versus 1% and PFS (progression-free survival) was 22.4 months versus 11.5 months. So, the drug, adding venetoclax, helped in the overall population. People had deeper responses, longer duration. And this drug, of note, is already FDA-approved for other blood cancers like CLL (chronic lymphocytic leukemia) and it's an oral medication.

What was surprising with this study for the first time is, even though the responses were better, more people died with the addition of venetoclax. And we think, with further analysis, it's basically the high-risk patients that seem to be benefitting less and they had less expression of a protein called BCL-2, which is the target of venetoclax. And I think this is giving us one of our first insights into myeloma personalization because, you know, our colleagues in lymphoma, they don't treat all lymphoma the same. Depending on what subtype you have, you get different medications. And I think this is a great example, that perhaps patients who have translocation 11;14 or high BCL-2 expression, which is a particular subgroup of myeloma, they did tremendously well with venetoclax. But those who didn't were actually hurt. And I think going forward, you'll see more of this in the future, that we're not going to treat all myeloma the same. 11;14 myeloma will be pulled out and probably be treated specifically with a drug like venetoclax. And so, I think that'll be great because to improve the advancements that we've already had in myeloma, we really need to personalize treatments.

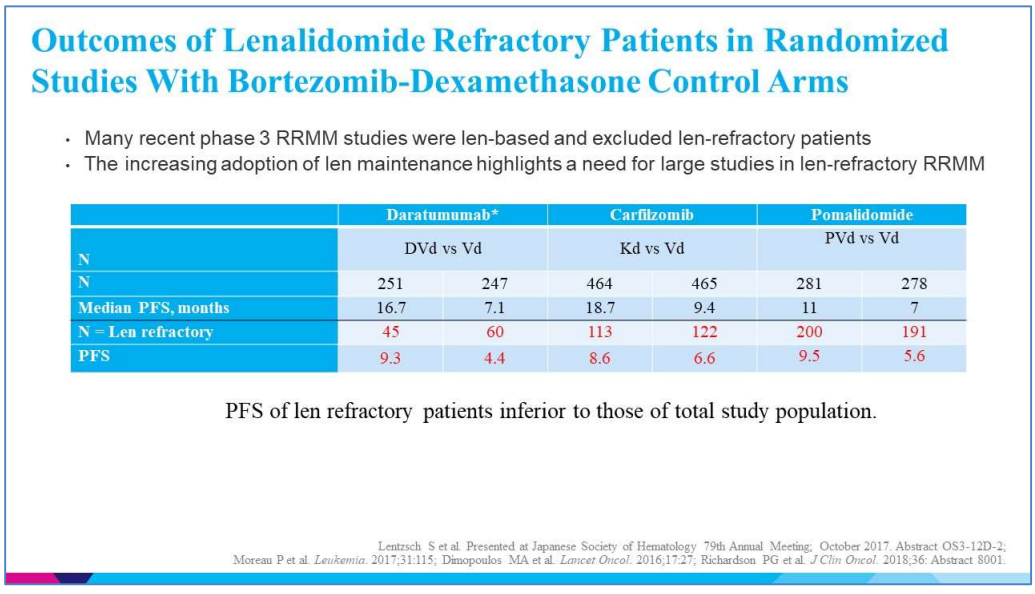


Just a brief word about high-risk, because I think there's a lot of discussion and patients are often told they're high risk and they're asking, "What does that mean and how do I treat this?" And rather than going through all the studies, I'm just showing you kind of a schematic of what we think of when we think of high-risk disease. Now the first thing is, high-risk patients respond as well as standard-risk, so we can't just look at the response rate. So high-risk patients may have a 95% response to the initial therapy, as do standard-risk. The question is not, "do they respond"" The question is, "how long do the remissions last?" And you can see in the upper left graph, these are what we call Kaplan-Meier curves which tell us how long people are in remission. And you can see that the standard risk, in the solid pink line, is consistently better than the high-risk, who relapse earlier.

Now, the other three panels show what could happen with a new drug to try to overcome or improve the high risk. And you can see in the upper right panel, the dotted blue line for high-risk patients actually is worse than the dotted pink line high-risk patients, meaning when you give a novel therapy, which is the blue line, and they're high-risk patients, you could actually worsen their outcome. An example of this is venetoclax. As we just heard, those patients did not benefit, even though you can see in the top blue line the standard patients actually did better.

When we go to the lower left, this is the typical pattern we see, which is that when patients get drugs like dara, for example, we saw that the high-risk patients, which is in the dotted blue, do better than the dotted pink line, but they're still not as good as standard-risk. But our goal and the need for new treatments is the bottom right panel, where high-risk patients do just as well as standard-risk. And I think this is where a lot of research needs to be done, and this is the area where some of the exciting new treatments that we're going to talk about at the end will, hopefully, be moved up earlier so that we keep these high-risk patients in remission. And the closest we've probably gotten to overcoming high risk so far is the last statement in this slide, which is the translocation 4;14. That's a specific translocation that seems like proteasome inhibitors like Velcade, carfilzomib, ixazomib, may seem to do better than other drugs. But stay tuned.

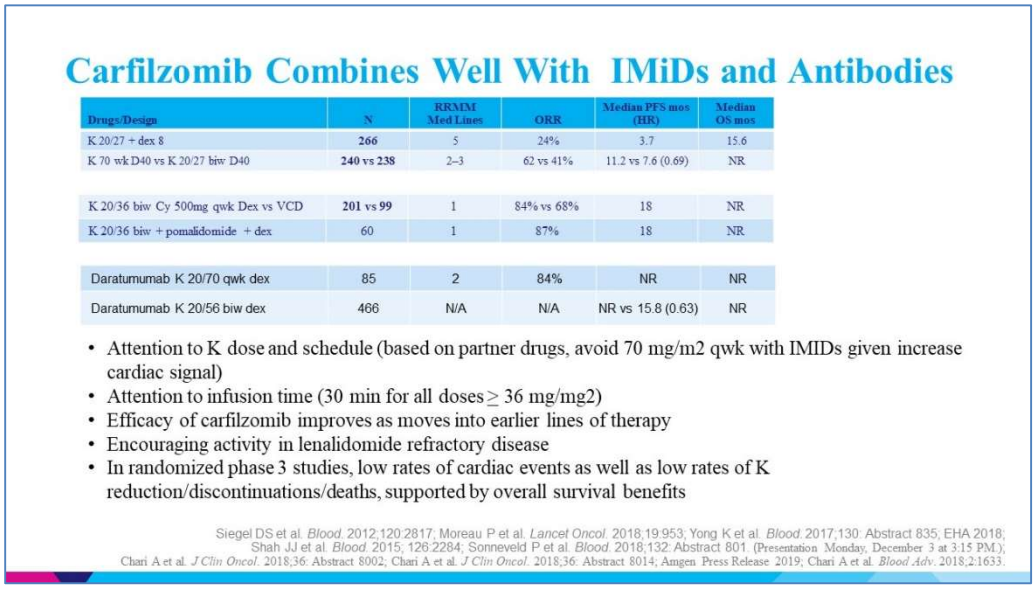
What if now there's a second relapse? So, somebody had their initial therapy, whether it contained a transplant or not. They relapse and they got their first control, and now they're in their second relapse, what do we do? And we can think about, I think, three concepts: lenalidomide refractory, carfilzomib-based backbones, and pomalidomide-based backbones.



	Daratumumab*		Carfilzomib		Pomalidomide	
N	DVd vs Vd		Kd vs Vd		PVd vs Vd	
N	251	247	464	465	281	278
Median PFS, months	16.7	7.1	18.7	9.4	11	7
N = Len refractory	45	60	113	122	200	191
PFS	9.3	4.4	8.6	6.6	9.5	5.6

So, we kind of alluded to this before. If most patients are getting Revlimid in their initial therapy, even prior to the second relapse, they may become refractory to Revlimid. So, if you had initial therapy, transplant and Revlimid maintenance, and Revlimid is no longer working, we now know that that could have an impact. So, for example, in the studies that we saw, where you look at dara-carfilzomib or pom (pomalidomide), at the top in the black are the numbers and outcomes of patients who [are] in

the overall study, so, for example, dara-Velcade-dex the median duration of PFS or remission was 16.7 months. Now, when you go to the bottom of this slide with the len (lenalidomide) refractory, meaning Revlimid is no longer working, that 16.7 drops to 9.3. That's also true of the Velcade arm. 7.1 drops to 4.4. And we see the same thing across the board. And so, what we're learning is, that when patients become refractory to Revlimid, it does have an impact and we need to be mindful of that and pick really active drugs.



Fortunately, we have options, and on this next slide we see that carfilzomib is a good option. And you can give carfilzomib by itself with dexamethasone. And that initial approval worked in 24% of patients for 3.7 months. Now, that may not seem like that long or that good, but that was with people who had already failed five lines of therapy, and that's shown in the second column. More recent data where patients with less heavily treated myeloma, only two to three lines, you can see that the response rate was 62% and 41% and the remissions were longer, 11.2 versus 7.6.

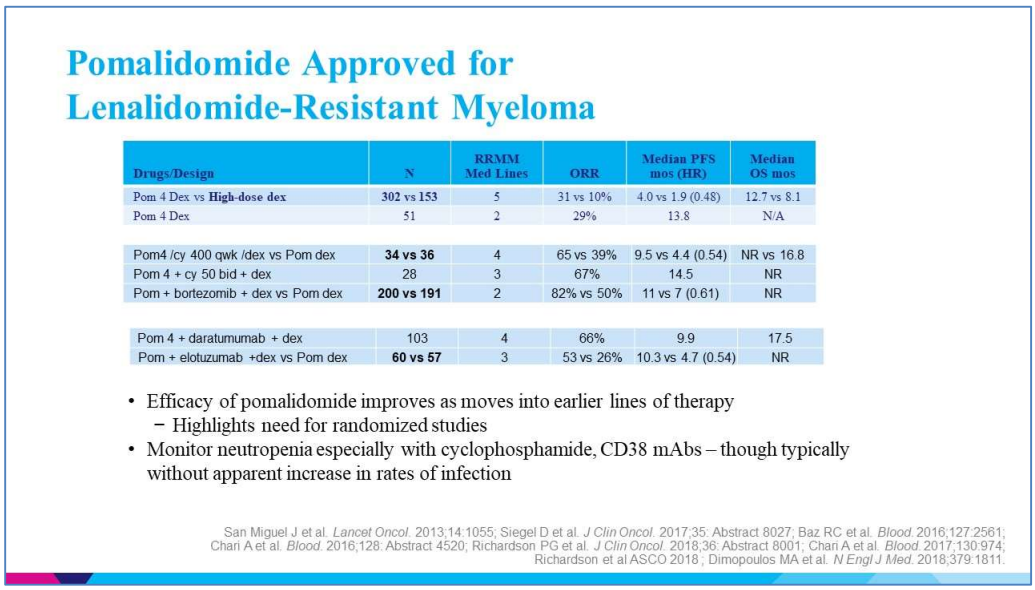
The other interesting thing about this particular study, which is known as the ARROW study, I think the main goal of the study was to look at carfilzomib, which is given at 70 milligrams per meter squared, which is the higher dose, once a week, and that's in the first column, versus the standard carfilzomib 20/27 twice a week. And so, what was initially a study that was done to look at patient convenience: Can we give this drug once a week at a higher dose instead of having patients come in twice a week? And it was mainly a convenience. A lot of us thought that, well, what this is going to show is that it's perhaps not going to matter. Well, not only did it not matter, but it actually helped to go to the weekly dose at a slightly higher dose. So, 62% versus 41 was the response rate, and the 11.2 versus 7.6. So, I think in 2019, if somebody is only going to be getting carfilzomib, 70 once a week is probably the way to go.

In the next two rows, you can see [it] can be combined with cyclophosphamide and pomalidomide. And most recently we found that you can also combine it with dara. And we actually published this recently. You can give dara once a week with the carfilzomib and get an 84% response rate and the

remissions are very long lasting; so long that we don't even know how long they last. This is already now FDA-approved, and there was another study that was done.

Some important things for patients to know about, and physicians also, the first one is more for the physicians, but just we have to make sure we're picking the right dosage schedule of carfilzomib. For example, you may have heard that carfilzomib has some cardiac issues. Generally, in all of the studies with carfilzomib, when carfilzomib is given, the better myeloma control is leading to living longer. However, there are some patients who have cardiac issues to begin with. Maybe they've had coronary artery disease or other problems. They are the ones who potentially can have more side effects. And for those patients we do want to be thoughtful about the use of carfilzomib.

But we like to give it over 30 minutes to avoid getting the rapid high doses. And I think what we've seen is, as I alluded to earlier, that this is a very active drug and overall, the cardiac issues are low. But perhaps in people over the age of 70, we need to be a little bit more mindful because we know that those are the patients where there can be more heart issues probably because those patients also have more heart issues to begin with, compared to the younger patients. But important in patients getting Kyprolis or carfilzomib to check your blood pressure, weigh yourself if you think you're gaining fluid or retaining fluid, and report any symptoms of breathing issues so that we can promptly evaluate.

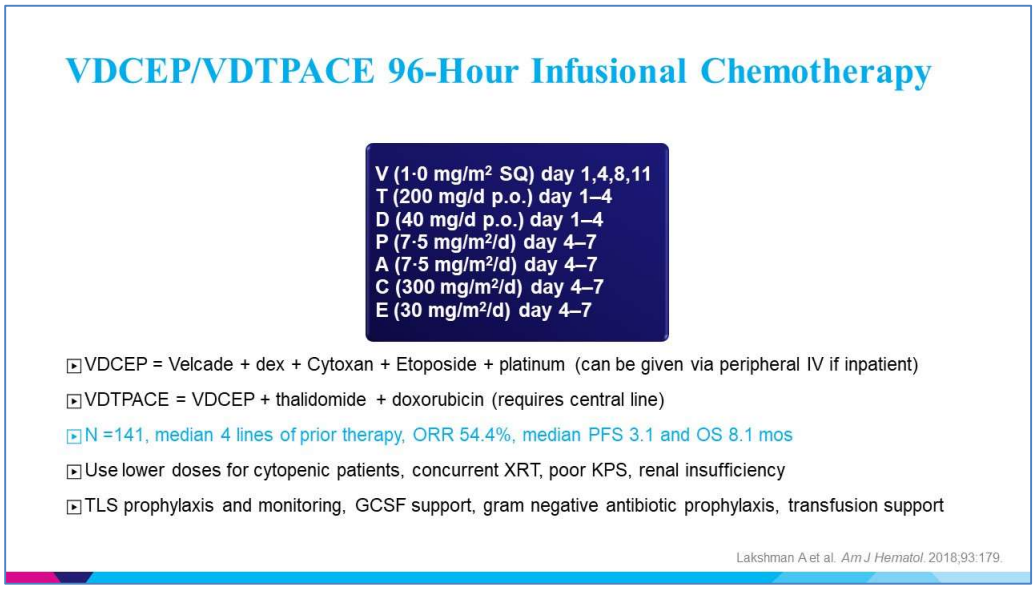


Moving to pomalidomide, which is the next generation compound so pomalidomide comes after Revlimid. And so, in the first two rows you can see that the initial drug approval pom with dex was given in five lines of prior therapy. It worked in 31%, and the remission duration was only four months. Again, it doesn't seem like a lot, but when you move it to the next row to patients who have only had two treatments, the remission duration goes up to 13.8 months. So that's good. And you can combine it with cyclophosphamide, again, an oral medication. You can combine it with Velcade. Or, at the bottom two rows in this table, you can combine it with antibodies. And these are both exciting. Daratumumab with pomalidomide response rate was 66%. Remission duration was 9.9 months. So,

this is approved now, and we published this in one of our journals. And that's an approved option. And then you can also combine it with elotuzumab, which is the other antibody. Response rate was 53%, instead of 26% was the control arm which just got pom-dex, and the remission duration was 10.3 months.

So, if you recall, pomalidomide, those of you who have been on a similar schedule to Revlimid, three weeks on, one week off. One thing to pay attention to is the blood counts with this; patients sometimes need Neupogen (filgrastim). And we want to just, again, report those symptoms of infection like fevers, cough, anything that may be occurring.

Moving to more heavily treated. So, what if somebody's already had first, second, and third relapse, what do we do? Obviously, clinical trials are appropriate throughout the continuum, but if for some reason somebody's not eligible or there's not an available study, these are some standard of care options that are FDA approved or available.



And so, we'll look at VDCEP (Velcade (bortezomib), dex, cyclophosphamide (Cytoxan), etoposide, platinum), VDTPACE (VDCEP, thalidomide, doxorubicin), salvage transplant and selinexor. So, what is this VDCEP, VDTPACE? Well, it sounds like alphabet soup mumbo jumbo, but what it is is a bunch of drugs. And VDCEP I've written out the drugs there, and the VDTPACE has a couple more. But basically, the idea is that these are drugs that are going to be given at a low dose every day, all day, for four days in a row. So, it's an infusional 24-hour chemo. Many of you may not have heard this. It's not used extensively, but we at Mount Sinai have used it, and in a recent study with 141 patients who'd had four prior treatments, the response rate was 54% and the remission duration lasted 3.1 months.

Now, this regimen is almost like a leukemia regimen, meaning it's more intensive than your everyday chemo that we've talked about. Not quite as intensive as a transplant, but hair does fall out with these regimens, the blood counts do go down, people do need blood and transfusion support. And you might think, well, why go through all that if the remission is 3.1 months? And I would say the main reason we do this is to get patients from being ineligible for a study to being eligible.

So for example, if somebody has had a lot previous treatments and we want to try to get them to an exciting new treatment like CAR T (chimeric antigen receptor T cells) that we're going to talk about shortly, or the bispecific drugs, but their counts are too low, we can give this as a way to bridge them to that next treatment. And then that way when their numbers go up, we can go on.

Salvage Stem-Cell Transplant

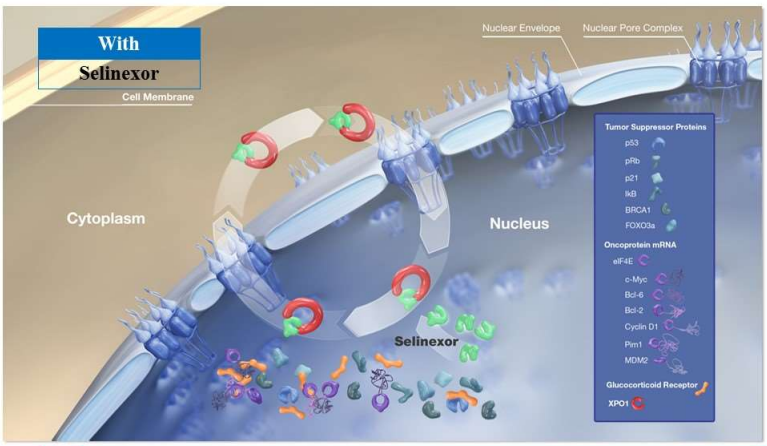
- 72% of thrombocytopenic (N=36) patients recovered to >75,000/µL
- 64% of neutropenic patients (N=14) recovered to ANC >1,500

Ref	N	Dates of SCT2	Lines of Prior Therapy	ORR	PFS (mo)	OS (mo)
2	83	Before 2006	NR	NR	15.6	34.8
4	106	1990–2002	NR	63%	NR	37
8	81	1992–2009	1	97.4%	16.4	53
9	200	1992–2010	2	80.4%	15.2	42.3
10	83	1994–2011	NR	NR	15.5	31.5
11	187	1995–2008	NR	NR	11.2	30
12	98	1994–2009	3	85%	10.3	33
14	75	1995–2012	1	82%	10.1	22.7
15	111	2000–2013	NR	92%	18	48
Current study	74	1998–2016	4	68%	6.1	19.3

ANC = absolute neutrophil count; µL = microliter ; BCNU = carmustine.
Tremblay D, et al. *Bone Marrow Transplant.* 2017;52:1468.

Similarly, we can do another transplant. And we published a study, and this is a study at the bar at the very bottom, in people who had four prior treatments, the response rate was 68% and remission duration 6.1 months. Again, when this might be helpful is shown at the top. When we looked at patients who had very low platelets or very low neutrophils and we couldn't get them to a clinical trial, 72% and 64% after transplant were able to recover their blood counts so that they could enter the clinical trial. Instead of having say light chain of 1,000, the numbers would go down, maybe go down to light chain of 100. And when that light chain goes up to 200, they're now eligible for a study, but with a lot less disease than they would've had.

Selinexor Inhibits XPO1 and Induces Cancer Cell Death



XPO1 in MM

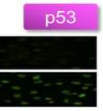
- Transports >200 proteins from the nucleus to cytoplasm
- Expression increased in MM vs normal PC/MGUS/SMM
- Correlates with shorter survival and increased bone disease

Selinexor

- Inhibits XPO1 through reversible covalent modification

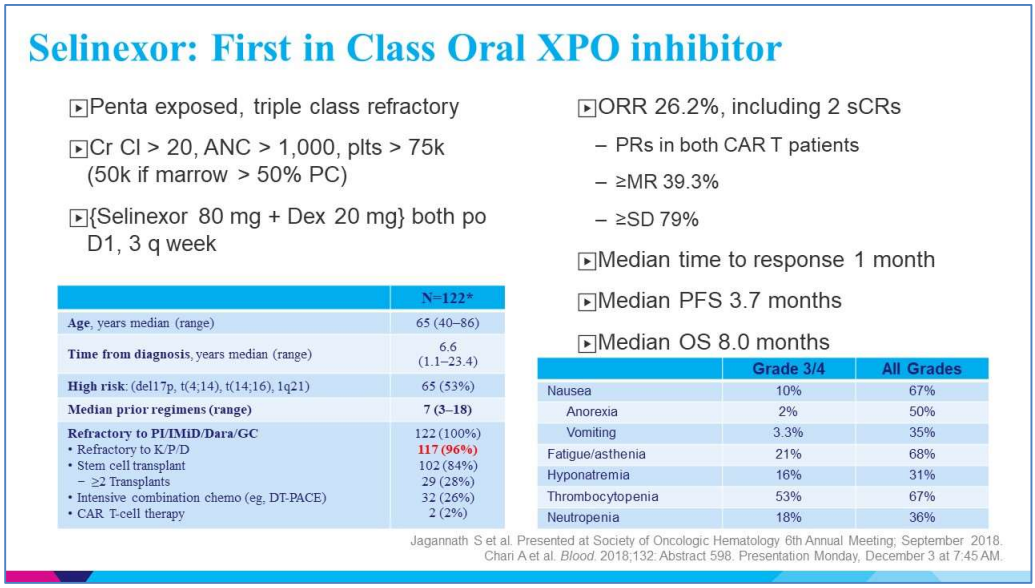
Selinexor Mechanisms of Action

1. Nuclear retention/activation of tumor suppressor **proteins** and **glucocorticoid receptor**
2. Reduction of oncoproteins through nuclear retention of their **mRNAs**

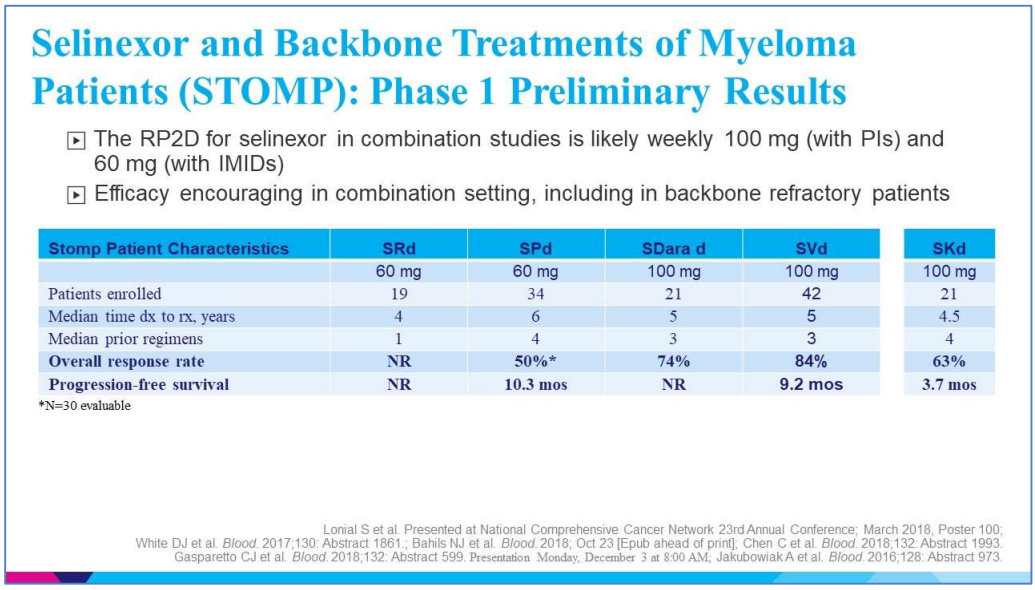


And, finally, selinexor, basically, there's a pump that moves things from the nucleus, which is the brain of the cell, into the cytoplasm. And what selinexor does is it blocks this pump. And I heard a

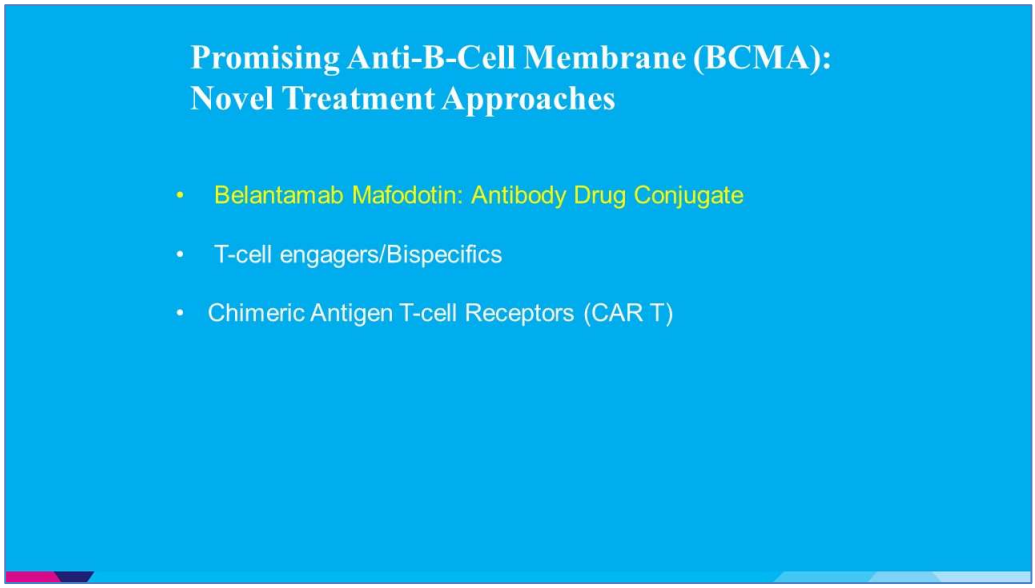
good analogy that this is like basically like a security guard, and the stuff inside the cell is like a rave party that's getting out of control and going out. And what the security guard does is prevents all of this chaos from leaving and keeps it contained. And by doing this, this drug has shown activity.



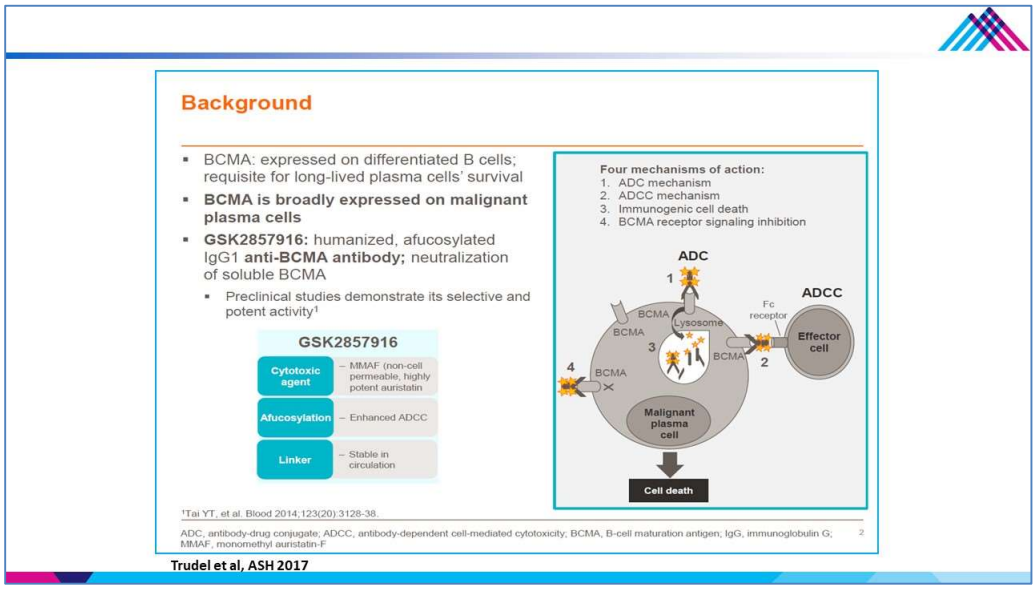
And this next slide, you see that in heavily treated patients, people who had failed seven prior treatments and no longer worked for them, with low blood counts, 96% had been refractory to carfilzomib-pomalidomide and dara. Even in this heavily treated population, we got a response rate in the upper right of 26%, and the remission duration was 3.7 months. Now it does have side effects, mainly GI, so nausea, anorexia, fatigue and blood counts. But I can tell you that at Mount Sinai we've been very aggressive with supportive care thanks to our outstanding nurses. It's just another plug for the importance of a healthcare team. When patients had symptoms, our nurses are really closely involved in giving supportive care to help with these blood counts and side effects. And at our site, the response rate was 56%, remission duration was longer, and our patients lived double what was seen in the overall study.



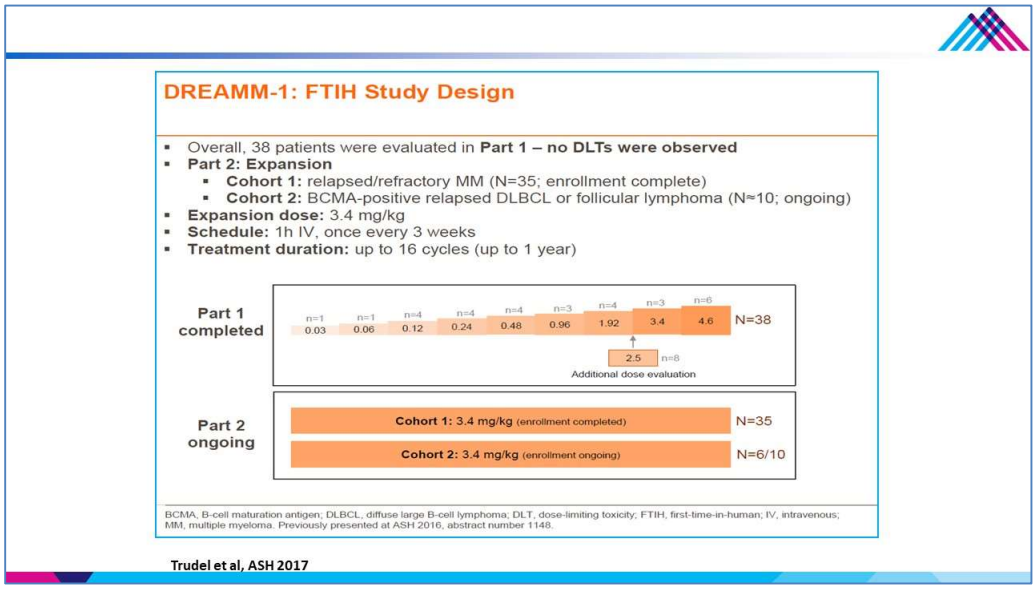
And you can also give it in combination with other drugs now that it's FDA approved.



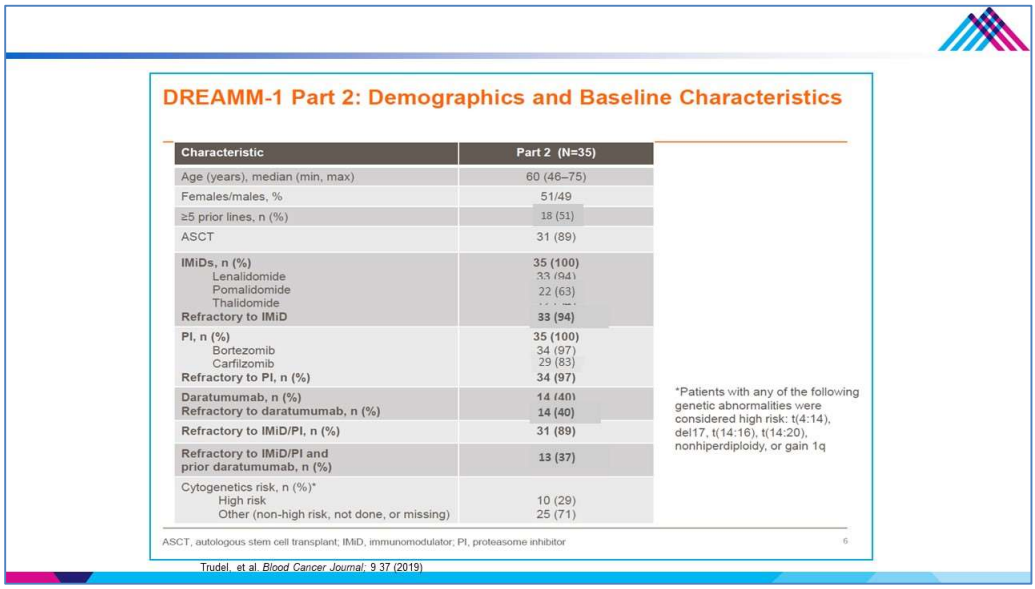
Lastly, I just want to spend a few moments on the newest category of drugs, which are anti-BCMA (B-cell mutation antigen) treatments. There's belantamab, the T-cell engagers, and CAR T. The first drug, belantamab, it's an antibody with a poison.



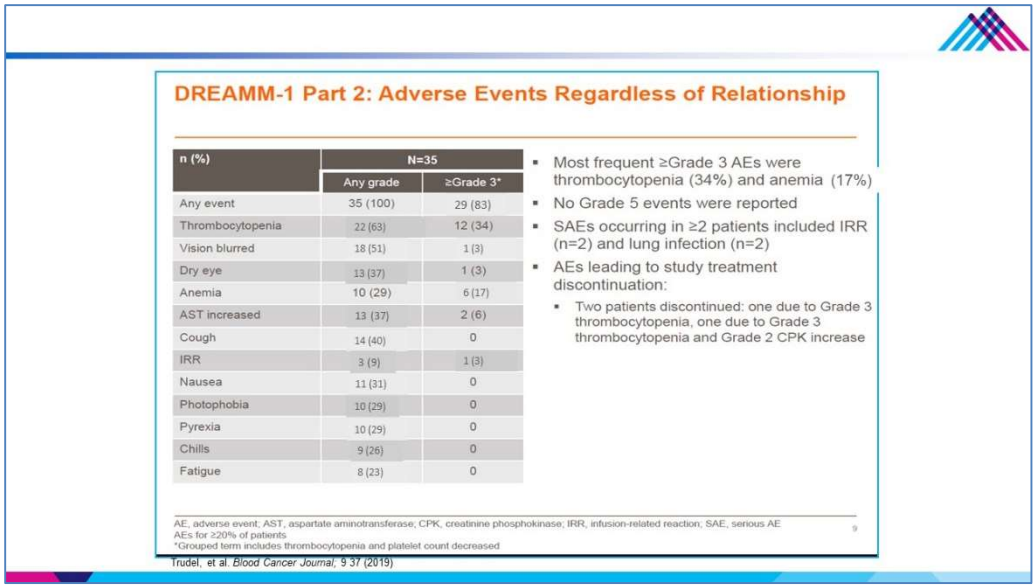
So basically, what we like about antibodies is they are targeted therapy. The antibodies go and bind to a particular protein. Here the protein they're attacking is BCMA, which is specifically expressed on a myeloma cell. But what you can see here in this picture is this antibody has these gold things attached to it, and those are basically poisons.



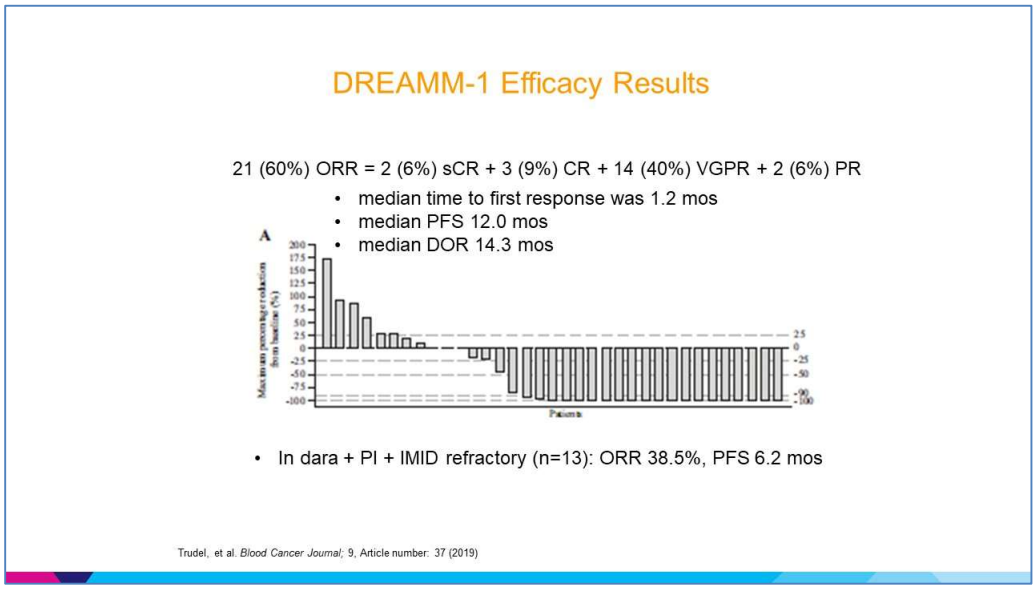
And what this antibody does is, it delivers the poison directly to the myeloma cell and the poison gets internalized and causes the cell to die. And it's a cool way of kind of killing myeloma with sparing, ideally, the rest of the body.



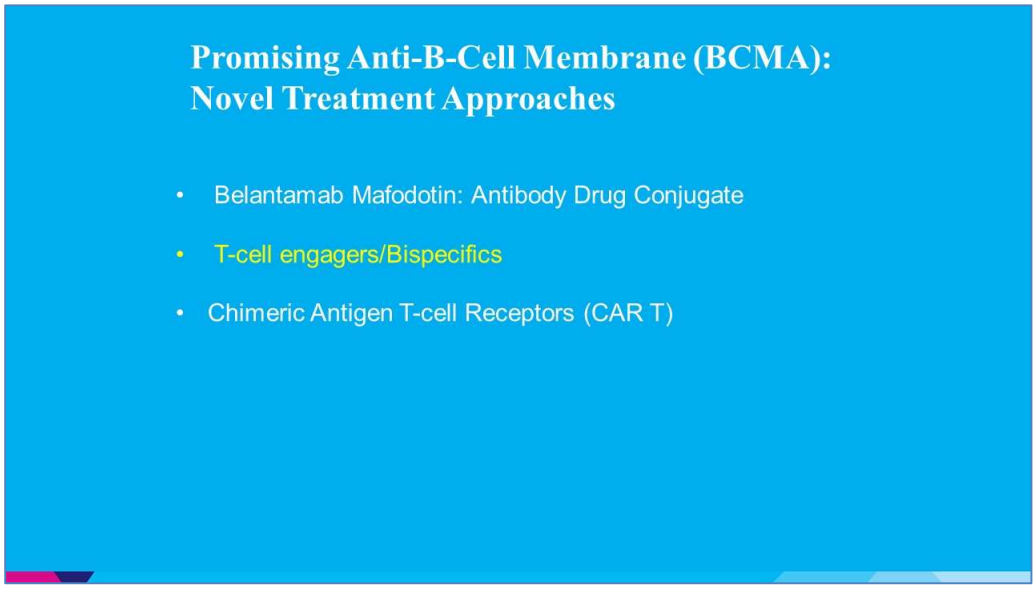
And in this initial study, this was a dose increasing study with 35 patients.



And in the interest of time, I'm going to get to the heart of the matter, which is the side effects first mainly are lowering of platelets and the other kind of hassle with this study is the eye issues. For some reasons, drugs that have this poison tend to cause ocular issues like dryness, blurriness, corneal issues. Fortunately, they're reversible, but it is an important side effect that needs to be addressed and requires regular eye exams.

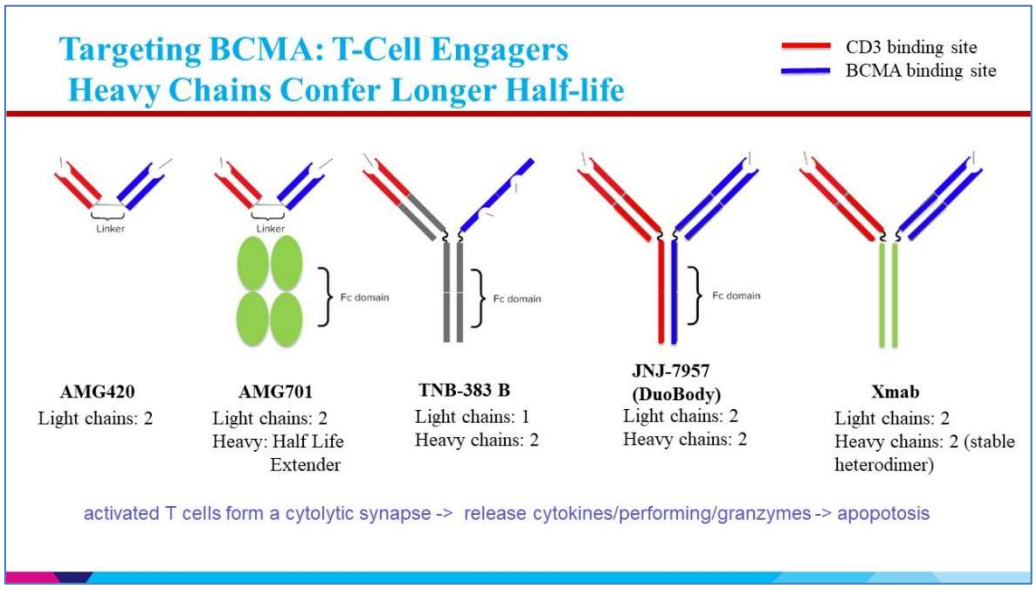


But what this drug showed is a 60% response rate. So that's pretty impressive in a heavily treated population. And in those who had had dara before, so they were kind of like that selinexor population, preliminary response rate 35%, remission duration of 6.2 months. This drug is given over one hour and is given every three weeks. So, it's a pretty easy infusion, but I think just we've got to follow those eye issues.

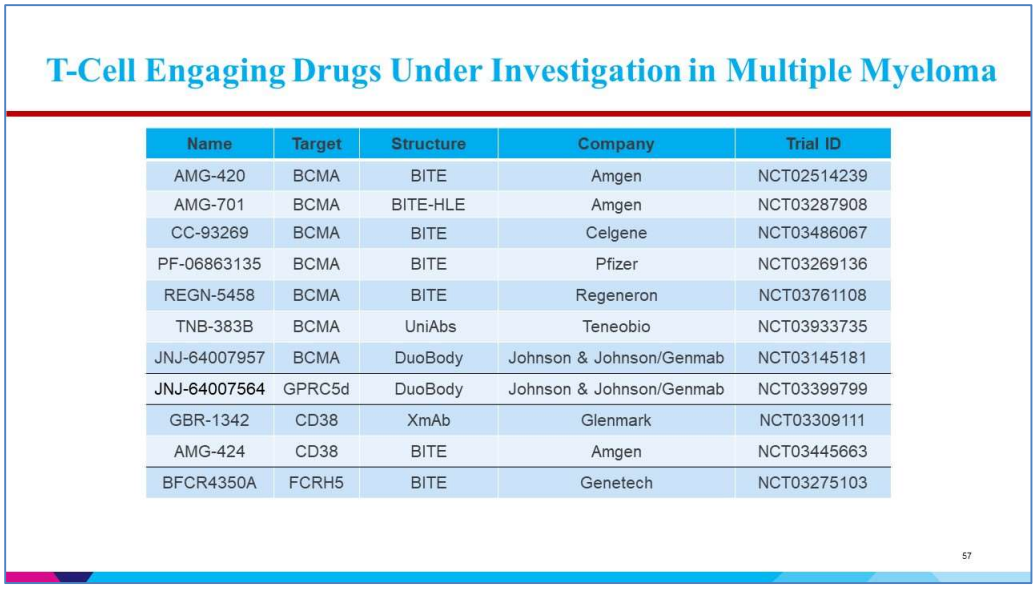


Next category is T-cell engagers, or bispecifics.

TRANSCRIPT



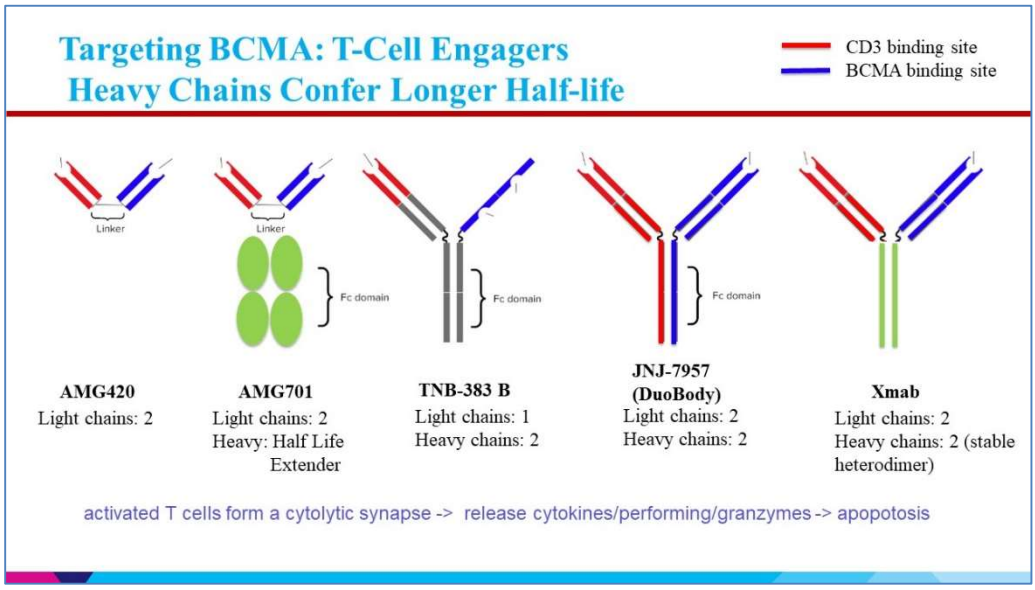
They come in a lot of different flavors. The compound that we've heard the most about is the one on the left on this slide called AMG 420, which is a very small molecule, which means that to give this drug and keep it at a right level in patients to kill the myeloma, you need to give it continuously. Rather than doing that because that's going to require a port and a pump, there's newer structures that you see on here that last in the body longer and then, therefore, can be given as a standard outpatient not continuous IV.



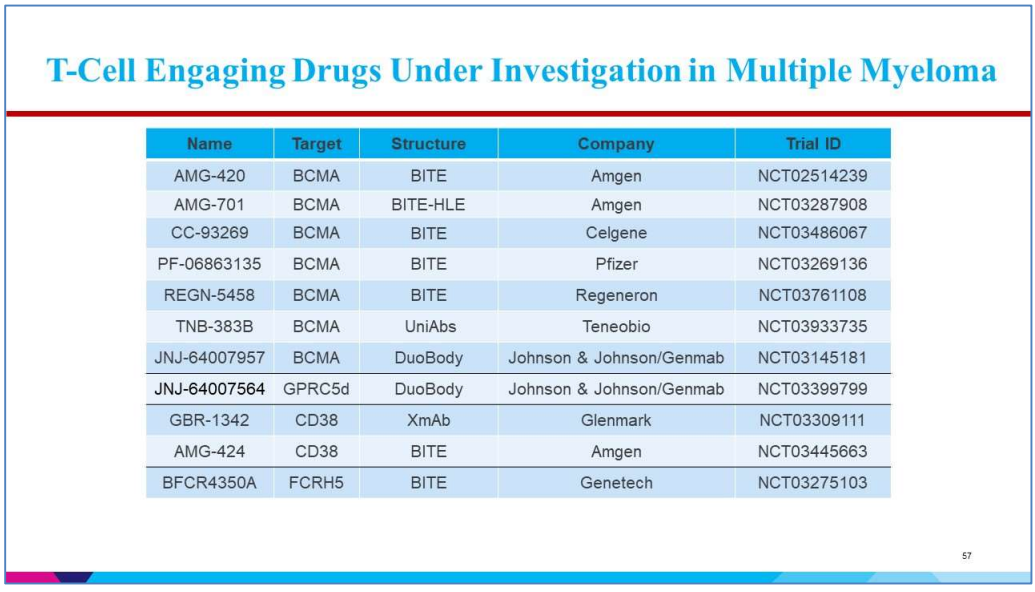
Name	Target	Structure	Company	Trial ID
AMG-420	BCMA	BITE	Amgen	NCT02514239
AMG-701	BCMA	BITE-HLE	Amgen	NCT03287908
CC-93269	BCMA	BITE	Celgene	NCT03486067
PF-06863135	BCMA	BITE	Pfizer	NCT03269136
REGN-5458	BCMA	BITE	Regeneron	NCT03761108
TNB-383B	BCMA	UniAbs	Teneobio	NCT03933735
JNJ-64007957	BCMA	DuoBody	Johnson & Johnson/Genmab	NCT03145181
JNJ-64007564	GPRC5d	DuoBody	Johnson & Johnson/Genmab	NCT03399799
GBR-1342	CD38	XmAb	Glenmark	NCT03309111
AMG-424	CD38	BITE	Amgen	NCT03445663
BFCR4350A	FCRH5	BITE	Genetech	NCT03275103

This next slide shows a lot of different, these T-cell engagers. And I should mention the way these drugs work is, going back to the previous slide.

TRANSCRIPT



They have two warheads. So, you can see in the red, one of these warheads is going to bind to CD3, and that's the T-cell. And then the other part binds BCMA. So, what does this do? It actually brings the antibody and brings—It brings the T-cells on the one side right up against the myeloma. And that's important because we can think about myeloma in a way as a failure of the immune system. And if we can spank these cells into working better, this is one way of doing it. CAR T is another way. But here, the antibody is basically forcing these lazy T-cells to recognize that there's a myeloma sitting here. And then when the T-cells are brought up right up against it, they recognize that they've been lazy, and they release chemicals causing damage to the myeloma. And that's the kind of principle of these bispecifics.

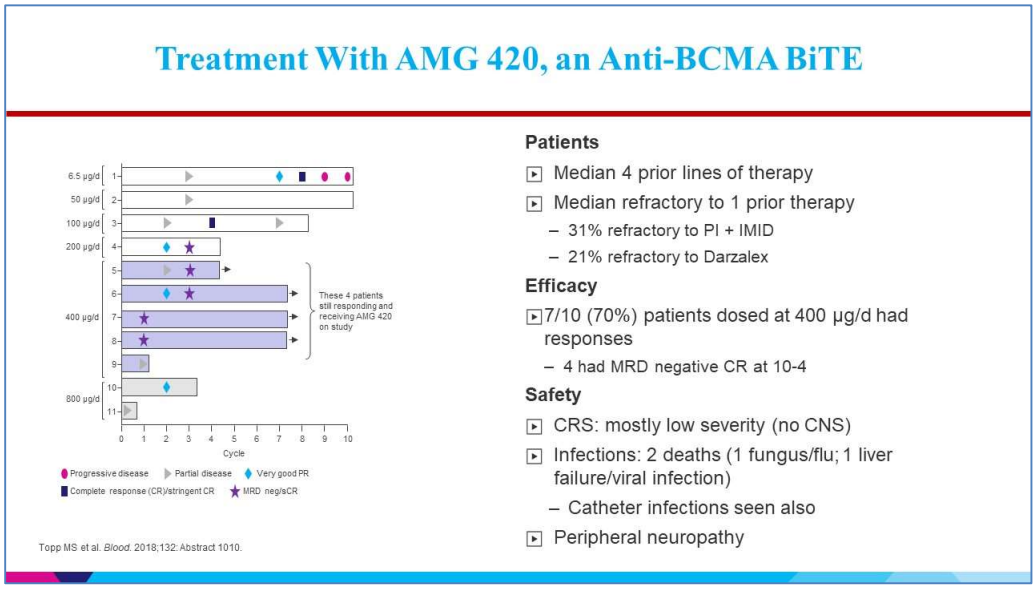


Name	Target	Structure	Company	Trial ID
AMG-420	BCMA	BITE	Amgen	NCT02514239
AMG-701	BCMA	BITE-HLE	Amgen	NCT03287908
CC-93269	BCMA	BITE	Celgene	NCT03486067
PF-06863135	BCMA	BITE	Pfizer	NCT03269136
REGN-5458	BCMA	BITE	Regeneron	NCT03761108
TNB-383B	BCMA	UniAbs	Teneobio	NCT03933735
JNJ-64007957	BCMA	DuoBody	Johnson & Johnson/Genmab	NCT03145181
JNJ-64007564	GPRC5d	DuoBody	Johnson & Johnson/Genmab	NCT03399799
GBR-1342	CD38	XmAb	Glenmark	NCT03309111
AMG-424	CD38	BITE	Amgen	NCT03445663
BFCR4350A	FCRH5	BITE	Genetech	NCT03275103

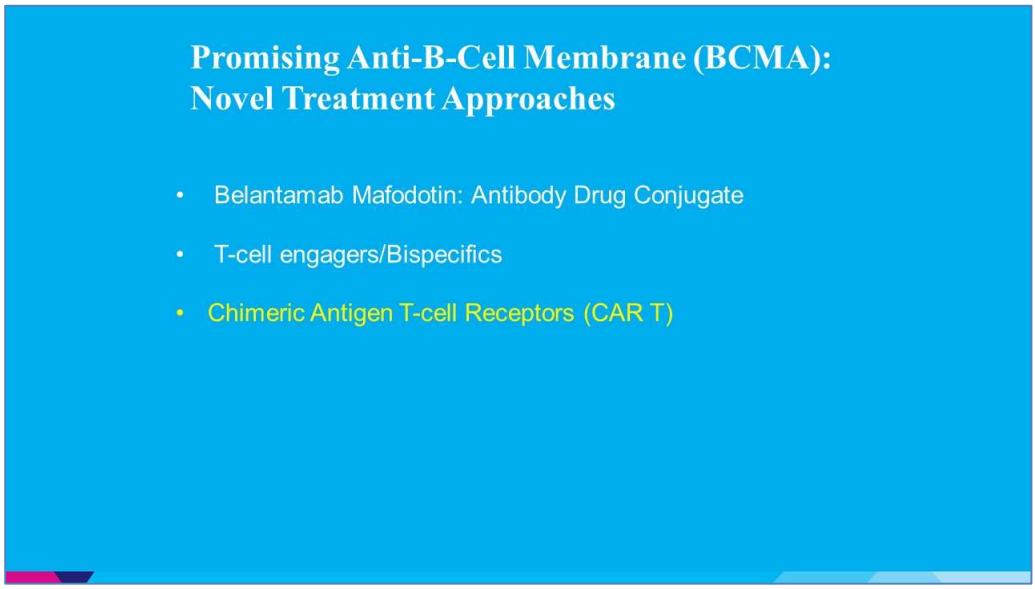
TRANSCRIPT

And the targets they're all engaging the T-cell and that's one half of these antibodies. The other half in column two here is the target. Many of them are targeting a protein called BCMA. Also, very exciting interesting data about GPRC5d, another protein. And then two others are CD38 and FCRH5. So, a lot of work. A whole new way of treating cancer.

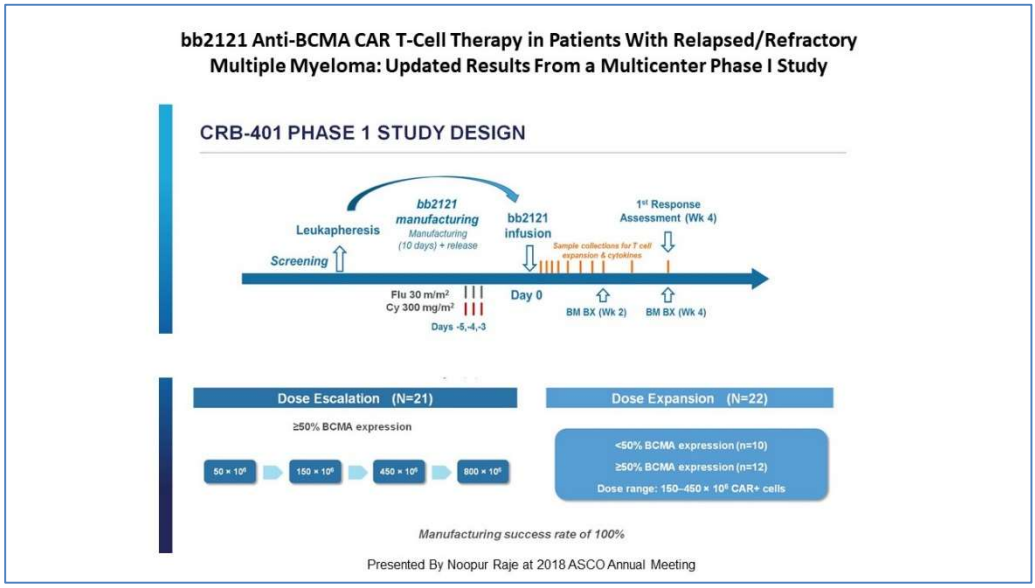
There is a drug that's already approved for another cancer called leukemia that has this structure.



And preliminary data from the AMG 420, which is that small version, was 70% response rates, but these are not as heavily treated as those other patients, so stay tuned for more data and really more sick patients. And then the side effect here was CRS (cytokine release syndrome). We're going to talk more about that with CAR T, so I'll defer that, but there were some infections and peripheral neuropathy. So, we're going to have to get more data on this and other compounds in this.



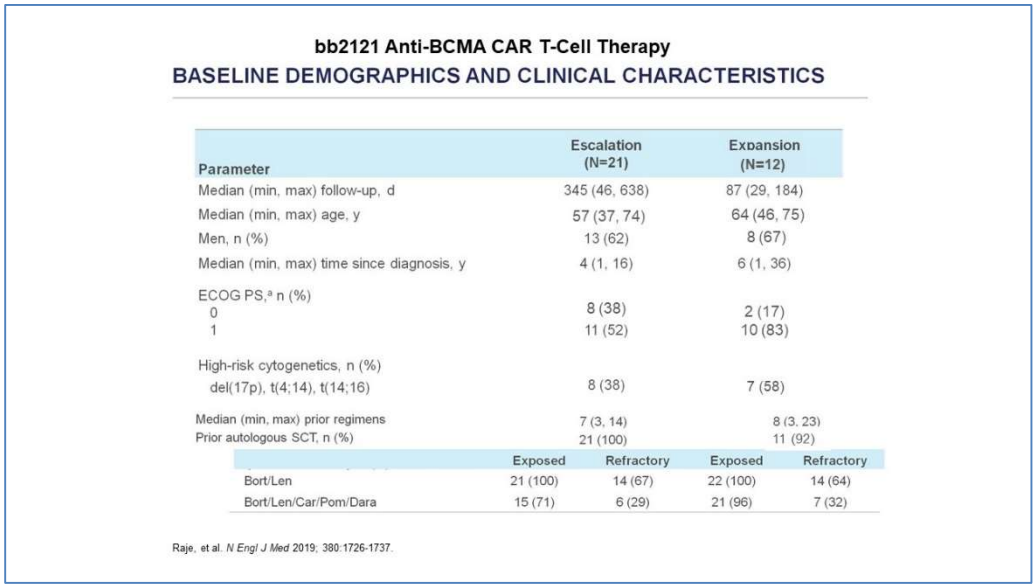
And last but not least, CAR T. I'm sure a lot of you have heard about it. What does CAR T stand for? As shown on this previous slide, it's chimeric antigen T-cell receptor, so we abbreviate that with CAR T.



This is the study that has gotten published already in *New England Journal* [o*f Medicine*]. But basically, what we do here in patients—this is the Bluebird study—if somebody's interested in CAR T, they first undergo leukapheresis, which means we collect their white cells similar to what we did for transplant. But this is typically a one-hour collection over one day as opposed to multiple days that are needed for a stem cell transplant. So, there's the collection, and then the T-cells are genetically modified. That's the manufacturing. And then they're eventually put back in. And this is basically, like I -alluded to, the bispecific is a premade structure. Here, the way we wake up these T-cells is we

modify them genetically to make them attack the myeloma, again, that BCMA protein that's specifically there.

So, at the bottom, you get a little bit of chemo, flu/Cy (fludarabine-cyclophosphamide), and then the infusion is done and then we watch for recovery. From a patient perspective, everything can be done as an outpatient until the actual infusion, and then typically patients are monitored approximately two weeks because of the side effects. And what are the side effects? We'll see that coming up, but that's the cytokine release.



bb2121 Anti-BCMA CAR T-Cell Therapy

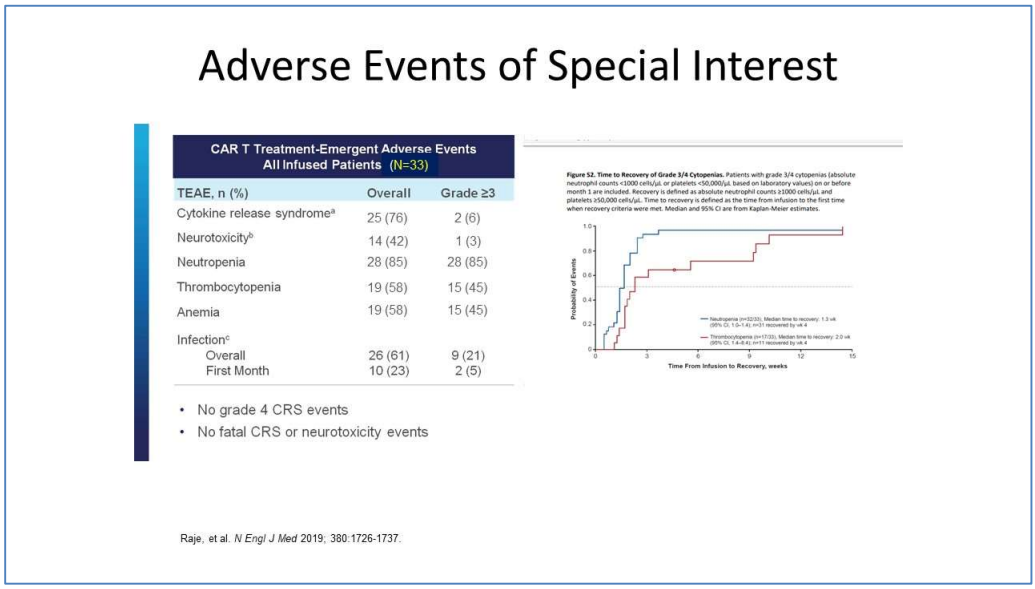
BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Parameter	Escalation (N=21)	Expansion (N=12)
Median (min, max) follow-up, d	345 (46, 638)	87 (29, 184)
Median (min, max) age, y	57 (37, 74)	64 (46, 75)
Men, n (%)	13 (62)	8 (67)
Median (min, max) time since diagnosis, y	4 (1, 16)	6 (1, 36)
ECOG PS,[a] n (%)		
0	8 (38)	2 (17)
1	11 (52)	10 (83)
High-risk cytogenetics, n (%)		
del(17p), t(4;14), t(14;16)	8 (38)	7 (58)
Median (min, max) prior regimens	7 (3, 14)	8 (3, 23)
Prior autologous SCT, n (%)	21 (100)	11 (92)

	Exposed	Refractory	Exposed	Refractory
Bort/Len	21 (100)	14 (67)	22 (100)	14 (64)
Bort/Len/Car/Pom/Dara	15 (71)	6 (29)	21 (96)	7 (32)

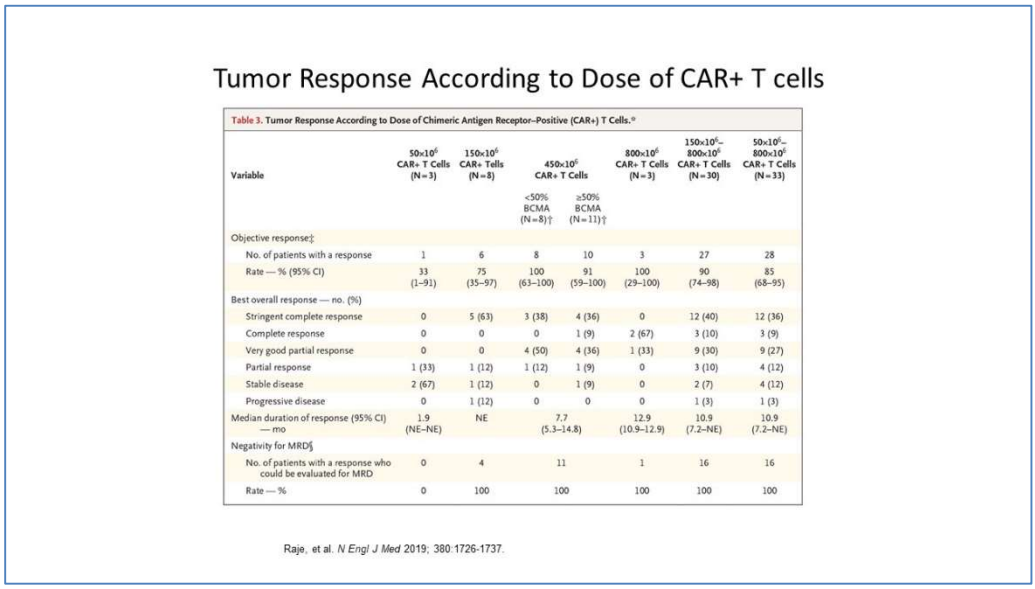
Raje, et al. *N Engl J Med* 2019; 380:1726-1737.

These were heavily treated patients. And in the interest of time, I'm not going to go through this slide, but just that there was a total of 21 patients in the escalation and 12 in the expansion, but very heavily treated. Typically, these patients had had seven- to eight-prior therapies.



And as I've been alluding to, cytokine release syndrome is basically when these T-cells, whether it's a bispecific drug or a CAR T, when they attack the myeloma, they can release chemicals called cytokines that can cause symptoms like fever, low blood pressure, low oxygen, confusion. And so, for now CAR T has primarily been done in transplant-eligible patients. So, if you look, most of the patients getting CAR T tend to be below the age of 70. And the reason for that is, we need to make sure that the safety profile is better understood before we expand it to sicker, more fragile patients.

The neurologic side effects, which can be concerning, are typically quite rare. There is a bit of lowering of blood counts. It can take anywhere from one to three months for the blood counts to recover. It's not from the chemo. I know a lot of patients feel like, "Oh, is this another transplant?" The chemo being given for CAR T is much gentler. It doesn't cause hair loss, doesn't cause nausea or vomiting, but the combination of the disease, the chemo, and then the CAR T can result in low white counts and platelets and red cells, so patients may need frequent blood checks even after they're discharged from the hospital to ensure that their counts are good.



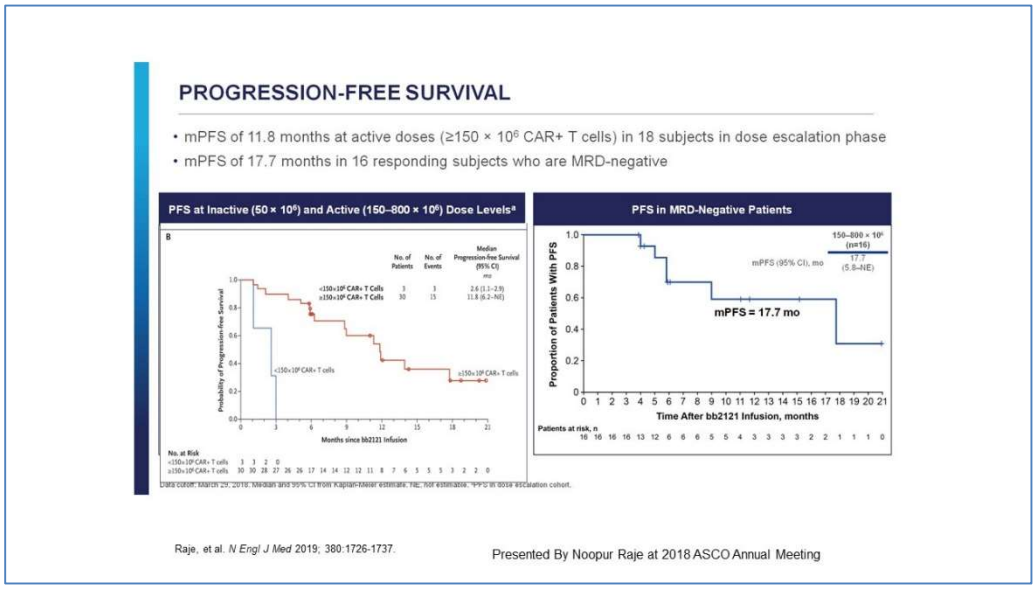
Tumor Response According to Dose of CAR+ T cells

Table 3. Tumor Response According to Dose of Chimeric Antigen Receptor–Positive (CAR+) T Cells.*

Variable	50×10⁶ CAR+ T Cells (N=3)	150×10⁶ CAR+ Tells (N=8)	450×10⁶ CAR+ T Cells		800×10⁶ CAR+ T Cells (N=3)	150×10⁶–800×10⁶ CAR+ T Cells (N=30)	50×10⁶–800×10⁶ CAR+ T Cells (N=33)
			<50% BCMA (N=8)†	≥50% BCMA (N=11)†			
Objective response‡							
No. of patients with a response	1	6	8	10	3	27	28
Rate — % (95% CI)	33 (1–91)	75 (35–97)	100 (63–100)	91 (59–100)	100 (29–100)	90 (74–98)	85 (68–95)
Best overall response — no. (%)							
Stringent complete response	0	5 (63)	3 (38)	4 (36)	0	12 (40)	12 (36)
Complete response	0	0	0	1 (9)	2 (67)	3 (10)	3 (9)
Very good partial response	0	0	4 (50)	4 (36)	1 (33)	9 (30)	9 (27)
Partial response	1 (33)	1 (12)	1 (12)	1 (9)	0	3 (10)	4 (12)
Stable disease	2 (67)	1 (12)	0	1 (9)	0	2 (7)	4 (12)
Progressive disease	0	1 (12)	0	0	0	1 (3)	1 (3)
Median duration of response (95% CI) — mo	1.9 (NE–NE)	NE	7.7 (5.3–14.8)		12.9 (10.9–12.9)	10.9 (7.2–NE)	10.9 (7.2–NE)
Negativity for MRD§							
No. of patients with a response who could be evaluated for MRD	0	4	11		1	16	16
Rate — %	0	100	100		100	100	100

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

And the response rate you can see on the right column, the overall response rate here is very good. It was actually 95% for all patients. And you can see that in the right most column, 85% in patients getting lower doses, but in the active doses, it's 90 to 100% because patients are getting different amounts of CAR T in the study. The remission lasted typically about a year.



PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]

PFS in MRD-Negative Patients

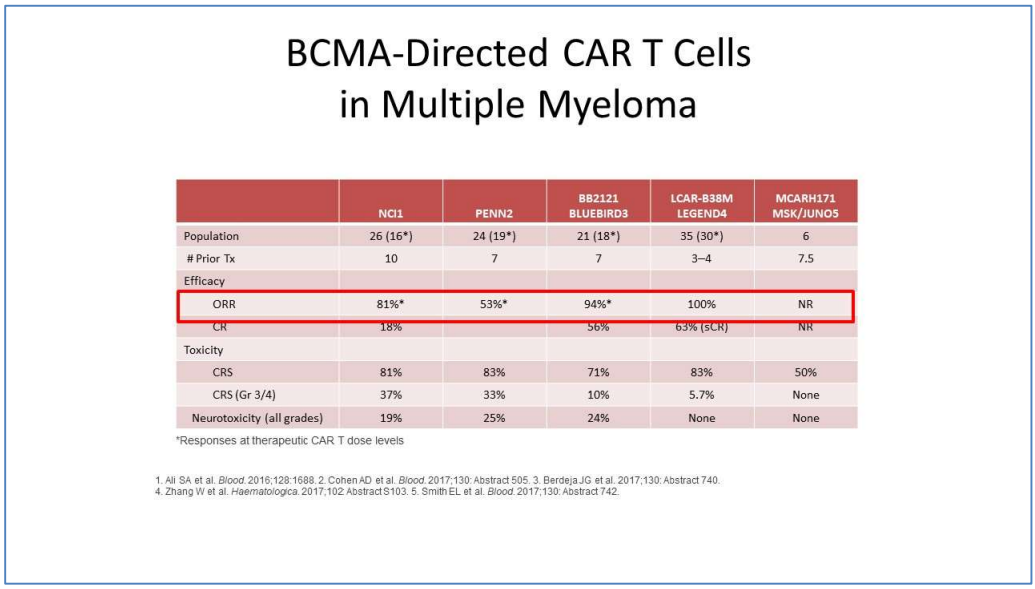
mPFS = 17.7 mo

Time After bb2121 Infusion, months

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

Presented By Noopur Raje at 2018 ASCO Annual Meeting

A lot of MRD negativity was being attained, but we're still [in the] early part of this. Some of these patients even if they were MRD negative relapse, so although much better, 17.7 months.

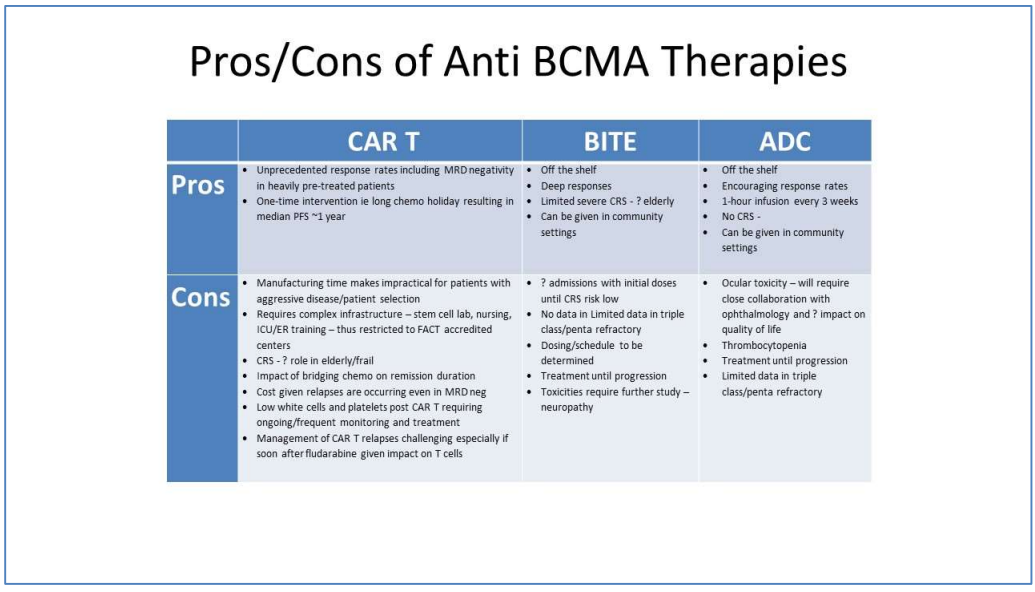


	NCI1	PENN2	BB2121 BLUEBIRD3	LCAR-B38M LEGEND4	MCARH171 MSK/JUNO5
Population	26 (16*)	24 (19*)	21 (18*)	35 (30*)	6
# Prior Tx	10	7	7	3–4	7.5
Efficacy					
ORR	81%*	53%*	94%*	100%	NR
CR	18%		56%	63% (sCR)	NR
Toxicity					
CRS	81%	83%	71%	83%	50%
CRS (Gr 3/4)	37%	33%	10%	5.7%	None
Neurotoxicity (all grades)	19%	25%	24%	None	None

*Responses at therapeutic CAR T dose levels

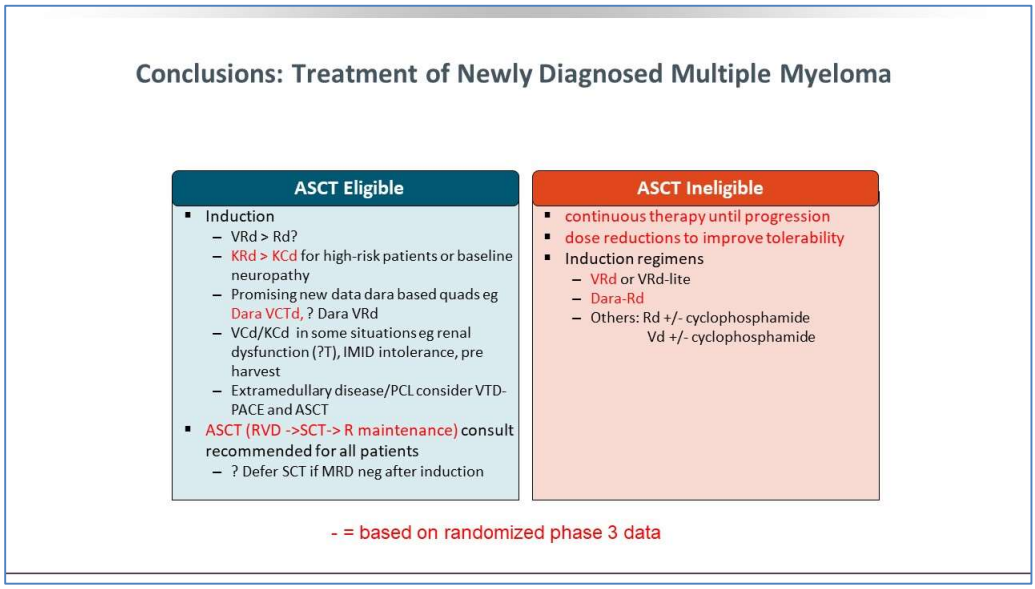
1. Ali SA et al. *Blood*. 2016;128:1688. 2. Cohen AD et al. *Blood*. 2017;130: Abstract 505. 3. Berdeja JG et al. 2017;130: Abstract 740. 4. Zhang W et al. *Haematologica*. 2017;102 Abstract S103. 5. Smith EL et al. *Blood*. 2017;130: Abstract 742.

Many CAR Ts are being studied. Seems like every day a new company is looking at this, so [it's] a hot area of research. Response rates range from 53 to 100%.



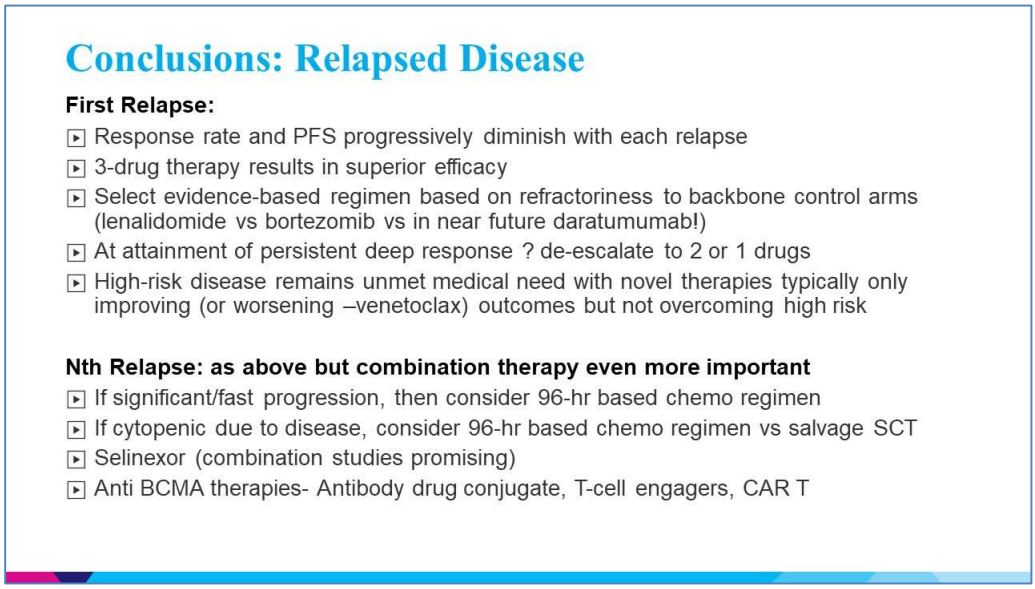
	CAR T	BITE	ADC
Pros	• Unprecedented response rates including MRD negativity in heavily pre-treated patients • One-time intervention ie long chemo holiday resulting in median PFS ~1 year	• Off the shelf • Deep responses • Limited severe CRS - ? elderly • Can be given in community settings	• Off the shelf • Encouraging response rates • 1-hour infusion every 3 weeks • No CRS - • Can be given in community settings
Cons	• Manufacturing time makes impractical for patients with aggressive disease/patient selection • Requires complex infrastructure – stem cell lab, nursing, ICU/ER training – thus restricted to FACT accredited centers • CRS - ? role in elderly/frail • Impact of bridging chemo on remission duration • Cost given relapses are occurring even in MRD neg • Low white cells and platelets post CAR T requiring ongoing/frequent monitoring and treatment • Management of CAR T relapses challenging especially if soon after fludarabine given impact on T cells	• ? admissions with initial doses until CRS risk low • No data in Limited data in triple class/penta refractory • Dosing/schedule to be determined • Treatment until progression • Toxicities require further study – neuropathy	• Ocular toxicity – will require close collaboration with ophthalmology and ? impact on quality of life • Thrombocytopenia • Treatment until progression • Limited data in triple class/penta refractory

And then this slide is there if you want to kind of pro-differentiate the different things. And we can talk more about this in the Q&A portion if people are interested. But basically, the one important difference is that CAR T needs to be manufactured, whereas the BiTe (bispecific T-cell engager) and ADC (antibody drug conjugate), which is the first medication we discussed, the latter two are ready to go, so they don't require this manufacturing.



And so, our conclusions for a transplant-eligible patient newly diagnosed, we believe in triplet therapy, probably with addition of dara. I would still recommend having everybody collect stem cells, and if somebody is averse to doing a transplant, if they're MRD negative, that may be a reasonable consideration. But if you want to do the transplant, it's certainly not a bad idea. The reason our improvements in overall survival have occurred up till now is probably because of, in part, transplant for especially the standard risk patients.

For transplant ineligible, I think you can do three-drug therapy as well, but we need to just monitor those doses and make sure it's the right setting.



And in relapsed disease, we want to try to use our active drugs early because responses can diminish with each relapse. And so, try to hit it hard with three-drug cocktails. And when you've used up the big five, which is dara, Velcade, Revlimid, Pomalyst and carfilzomib or Kyprolis, clinical trials are important. And 96-hour infusional regimens, transplant, second transplant, selinexor, or these three really promising anti-BCMA therapies.

So, with that, I will stop and hand it back over to the LLS team. Thank you for your attention.

Lizette Figueroa-Rivera, MA

Thank you so much Dr. Chari for updating us on the treatment options in myeloma.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

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

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the first question from our Web audience. Doctor Claude is 70 years old and has been on maintenance therapy for four years. Recently, he asked his doctor about a cure for myeloma, and he said treatment of myeloma has been so successful that it is somewhat being treated as a condition rather than a disease. Do you agree?

Ajai Chari, MD

Great question. I think myeloma, we call it multiple myeloma for a variety of reasons. The initial reason was because it's in more than one spot of the body, so to distinguish it from a solitary plasmacytoma. But I think other interpretations of myeloma is, there's different clones in a given patient and also there's different types of myeloma. And as I alluded to, for example, the 11;14 myeloma with the venetoclax, we may not be able to lump everybody into one basket.

What we know if we look at the data, our former colleague who's retired, Dr. [Bart] Barlogie, did an intensive therapy called Total Therapy 1 and 2 and a lot of maintenance, but he published that approximately 10% of patients with myeloma have been cured. And I have some of these patients in my own clinic. People who've had initial therapy, transplant. And although most patents are getting maintenance like Claude is, for some reason didn't tolerate it and for some reason these patients have gone 10 years without a relapse. So, we are curing now some patients already with myeloma.

The problem is, if the percentage of cure is that low, less than 10%, and we don't really know how to identify them, because cure requires two parts. One is that we can't detect any disease and the second part is ideally people are off therapy. So, if you're on preventative therapy, can we really say that it's been cured? And so, each of those has its constraints. First is to detect any disease, your technology has to be very good. And now we're getting to these MRD negativities, right, so we can pick up one in 10^{-6}, one in a million cells. And so, if we can find that little myeloma, we can be perhaps becoming more confident in the future saying, "You know what, this patient is MRD negative at two consecutive timepoints. Is this the kind of person maybe we should consider stopping therapy?" I'm not saying go out today, run out and get an MRD test and do that, but this is where studies need to go because if we know we're curing 10% and we want to try to identify them, the first step would probably be for those patients who are low risk or standard risk who are MRD negative for two consecutive timepoints, we need to start doing studies saying, "Can we actually discontinue chemo in this person?" And so, I think, for some of these patients then, we've achieved a cure. The

vast majority I would agree that it is a chronic disease, a condition like blood pressure and diabetes, where, hopefully, people are in very minimal therapies and having a great quality of life, but just making sure that they're getting checked our regularly.

Lizette Figueroa-Rivera, MA

Thank you. And along the same line, Phil is asking, "How many years remission can a patient expect their risk of recurrence to be lower?"

Ajai Chari, MD

So, what we can tell, you know, based on the studies, that first transplant, if somebody's transplant-eligible, they get initial therapy, transplant maintenance, those remissions are approaching four to five years now. And then the first relapse can be two to three years. So that gets us to now about seven to eight years for the first two lines of therapy. Now it's always important to remember, though, that those are standard risk myeloma and that's with RVd. Now if we do dara on the frontline, might we go from four to longer number of years for initial therapy and, therefore, these numbers will improve? And then the other important consideration is that all of these numbers, whenever we talk about numbers in medicine, they always apply to large groups of patients, so this is a bell curve and it's never a prescription for an individual patient. So, we don't have a crystal ball, but we can just say if we take 1,000 patients with myeloma, the numbers I just cited might be appropriate. But a high-risk patient would be typically on the lower end of those curves, and then a low-risk patient might be on the higher end of those curves. And that's why [we] need to start treating people differently going forward and perhaps low-risk patients not be treated forever, high-risk patients using these novel therapies like CAR T and bispecifics very early on to, hopefully, try to overcome the high risk.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Benita of Wisconsin. Please state your question. Your line is now live.

Benita, Wisconsin

Three years out from the transplant and the light [chains] start to go up again, when do you start treatment on something like that?

Ajai Chari, MD

That's a great question. First, it's important, I always talk about those CRAB symptoms because the blood test that we use, whether it's an M spike, light chains, urine protein, they're tumor markers, but they have to be thought about in context with the CRAB. So, if somebody has high calcium kidney, anemia, or bone disease, then that should be treated regardless of what the numbers are showing because it means that myeloma is acting up. Of course, the caveat would be let's say somebody has a bleed from an ulcer, that's why they got anemic; or if somebody took a lot of Motrin® and Advil® (ibuprofen), which, of course, we always counsel patients not to, and that's why they got kidney. But if the CRAB symptoms are not due to anything else and it's due to the myeloma, I would treat regardless of what the light chains are doing.

But then if you don't have that, which is typically—although before I talk about that last part, I wanted to also mention that the "B" also gets missed because calcium, renal, and anemia, you can check the labs. But I always encourage people to have at least periodic monitoring to make sure that the bone disease isn't recurring. And that would typically be either with an MRI of the spine and pelvis or whole-body MRI if it's available, or a PET-CT because bone disease is not something you can check by labs. And so, if somebody has new bone lesions, again, I would treat.

But let's say they don't, then usually what we use in myeloma clinical trials is that the light chains go to either 10 milligrams per deciliter or 100 milligrams per liter. Those are considered measurable. And the reason we do that is because, the best analogy is like if somebody wanted to do a diet, if you were trying to lose one pound, it's hard to know if a diet's going to work. But if you're planning on losing ten to 15 pounds, there's a reasonable amount of weight so that you know that if you're making a change, it's going to have an improvement or not. And when you're dealing with a very small amount like one pound, you could have fluctuations in that. And the same thing with light chains. If the light chains are barely above normal and you change the treatment, it could be going down just because it would've gone down anyway. But it would be very unlikely for somebody's light chains to be much higher than that and then just go down spontaneously or change with renal function.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Donald. Donald asks, "What is high risk? Also, once you've been taking a drug and then move to another, can you ever return to that drug or to another drug in that class?"

Ajai Chari, MD

So, risk can be defined in different ways. Typically, what we talk about risk is called molecular or cytogenetics or FISH (fluorescence in situ hybridization). And on slide four of the deck that you have, there are the current definitions of high risk, which is that deletion 17p, translocation 4;14, 14;16, amplification of chromosome 1. However, we're also recognizing now that there's a new term called functional risk. And a good example, there's actually clinical trials now that people are eligible for not because of their genetics but because of how long their remissions lasted. So if somebody had a transplant and the remission duration, we said typically should be four years with maintenance, and if

they relapsed in less than three years or if it's a nontransplant eligible who relapsed within 18 months, we call that functionally high risk, right, because that's more important than what we predict at the beginning. And I always say that what happens to patients is more important than what we predict. That if somebody's predicted to have high-risk disease but they remain in remission a long time, great. Maybe that's not really high risk or maybe our treatments are really good for that patient.

Conversely, if somebody had standard risk disease but they presented with unusual symptoms or very early, that could be high risk. And to that point, extramedullary disease, which is myeloma outside of bone marrow, myeloma in the blood, those can also be features of high risk. So, a lot of ways of defining risk, but at the end of the day, the most important is remission duration, I would say.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Richard of New Jersey. Please state your question. Your line is now live.

Richard, New Jersey

Hello, I've been fighting multiple myeloma now 11 years, and I've relapsed three times. And right now, I'm on a Pomalyst and Ninlaro-dex regimen. And the side effect is a little tough. I'm very weak, tired and woozy all the time, mouth sores and this and that, but I'm putting up with everything. Is that normal for the treatment?

Ajai Chari, MD

Yes. So first, 11 years, congratulations, but it sounds like you're fighting through and you're having some symptoms. So, I think rather than any specific, we'll talk about, in general, symptom management. So, fatigue is a big one. We want to think about. what are the causes of fatigue? Anemia can do that; the thyroid dysfunction, which can be affected by drugs like IMiDs—Revlimid, thalidomide—so somebody should have their thyroid function checked; adrenal insufficiency, which is something that's not well appreciated but we've reported on. Sometimes when we keep getting steroids over time and then what happens is that patients feel great for a day or two, but they sometimes have a crash if the steroid leaves their body, and that can present with wooziness, light-heatedness when you stand up so with a lowering your blood pressure or weight loss. So that's an easy test to check and get treated for.

The other important thing I would say in symptom control is, you have to balance the risk and benefit. And it's not just for this particular regimen, but all regimens. At the beginning of a particular patient's

relapse, the disease's burden is higher, right. So, they may have CRAB symptoms, they may have more marrow involvement, more light chains, etc. So, we went to hit the disease hard. And this is a war, so we want to stay ahead of our enemy. So, you want to pummel this enemy down and then keep it down. And so, the regimens and the doses and frequency and intensity that you use in somebody who's first starting out, versus somebody who's gotten a good disease control, is going to be different.

So, what I try to do is, as you heard, three drugs are typically better than two drugs. So, we usually use three-drug cocktails in patients, try to hit the disease hard. But once we've achieved optimal disease control, then we can start weaning off some of those medications, either eliminating steroids, for example, which patients hate, and then maybe lowering the drugs of the other medications to try to keep it under check without compromising the disease control. But we don't want to start off with very low amounts of drugs. I always say the reason why is oncology a specialty in and of itself? And it's because you saw that there's seven classes of drugs. It's hard to keep up with all of this information if you're a primary care doctor. And then the other reason is that in drugs in oncology, there's what we call a narrow therapeutic index. If you don't give enough of the drug, you're not going to kill the cancer, and if you give too much, you may cause side effects. So, you've got to figure out for each particular patient what is that sweet spot. And so, I would just encourage you to work with your doctors and healthcare team, including nurses and nurse practitioners, to try to find the right dose for you depending on how well your disease is controlled.

And certainly, the last point I would say is, we have seven different classes of drugs, so if there is a particular drug that is really not tolerable, I always tell my patients, "You know, you don't get extra points for suffering." And one of the things is, the privileges of treating myeloma is, you're helping people live longer and better. And ideally, we want to find regimens that are going to not compromise patients' quality of lives.

Lizette Figueroa-Rivera, MA

Thank you. We'll take the next question from our Web audience. Kamal is stating that after stem cell transplant, since the gut or abdominal lining is being rebuilt, what is the best foods and exercise to maximize chances of long periods of myeloma remission?

Ajai Chari, MD

Well, the principle here is that the high dose of chemo, as I alluded to, the transplant is really high-dose melphalan with stem cell rescue. And so the toxicities we see with transplant are really based on that same principle that these conventional chemos, when given in high doses, kill anything in the body that grows quickly, which is primarily bone marrow and, hence, the need for the stem cells. But the other two big ones are the hair, which grows back obviously, and the GI tract. So, what we usually see with GI is now people can have mouth sores, nausea, vomiting, or diarrhea. Most of the time, the nausea is in the hospital and then when the counts recover, the nausea diminishes. And, of course, some patients are also, I should mention, getting outpatient transplants, which we offer at our center

to people who are below the age of 60 and within commuting distance. But the nausea typically improves. The diarrhea tends to be most prominent when the counts are low and that also tends to improve. The taste can take anywhere from one to three months to recover, even after the transplant. So, I would say that if somebody's having a lot of GI symptoms after having the blood counts recover, it should be discussed with the hematologists and oncologists to make sure that there's nothing being missed. But if it's persistent, a GI eval-, gastrointestinal evaluation may need to be done.

And in terms of the, so what can we do as patients and caregivers? So, I think most of the time it's just a time issue. Like during the 10 to 14 days after the high-dose chemo, that's usually when we see it. So, if it's after 14 days usually when the counts recover. Lately there's been a lot of liberalization of the diet. Before there used to be a lot of neutropenic diet restrictions, like avoiding fresh foods and really being very conservative. And the data on that are conflicting. But once the counts are recovered, I tell all my patients, "As far as I'm concerned, you can eat whatever you want. The only thing I wouldn't recommend, going to a salad bar with food that might've been out there a long time." And people also think they need to be cooped up at home recovering. It's fine to go out. The main restriction we recommend is for three months posttransplant avoiding large crowds—so like in contained spaces things like planes, movie theaters, buses—because that's where in somebody in your vicinity is coughing and you don't have the ability to leave.

But in terms of the diet itself, it's really what you can tolerate. If some people do have heartburn or are still recovering, maybe avoid the spicy foods, caffeine, avoid lying down quickly after eating. If somebody's having taste issues, sometimes ginger and other things have been shown for particular patients. But there's not really an officially well studied regimen that has been shown to be helpful. But there's some, perhaps if somebody did get a lot of antibiotics and their gut floor has been affected by the antibiotics in the hospital, there may be a role for like probiotics as well, but I would discuss that with your healthcare team because you want to make sure that the white count has recovered before doing anything like that.

Lizette Figueroa-Rivera, MA

Thank you. And with a lot of patients who have a lot of bone pain, are there some restrictions in exercise?

Ajai Chari, MD

So, we do recommend for patients with myeloma, not because of great data but just kind of conventional wisdom if you will, to avoid lifting more than 10 to 15 pounds. And the reason for that is, even MGUS (monoclonal gammopathy of undetermined significance) and smoldering myeloma patients we know have a higher rate of osteoporosis and osteopenia than healthy controls. There is something about the plasma cells that destroys the bone. I would rather patients do frequent reps than if they're going to do weights than massive weights with fewer reps.

And to the point of bone disease, which we didn't talk about a lot, but in every patient in my clinic, we have in our problem, in our note, we address the following things about bones: (A) when was the last imaging? It is important, as I alluded to, to make sure imaging is being monitored. Obviously, in somebody who's been in remission for six years off chemo, I don't necessarily need regular imaging. But in somebody who's just attained their first risk remission and presented with relapsed bone disease, we want to make sure that we've eradicated all that disease. And so, imaging is important. I do try to get bone densities at least once on patients because if they have osteoporosis, I want to make sure I'm improving the bone strength to prevent future fractures. And then we check vitamin D levels. Once the myeloma is well controlled, there's very low risk of getting high calciums, so vitamin D supplementation. Particularly with drugs like Xgeva® (denosumab), which is a recently approved drug for myeloma bone disease where you can get profoundly low calcium levels, it's important to keep the vitamin D level adequate.

The last part of bone health is the bisphosphonates, or anti-bone damaging drugs. So whether it's zoledronic acid, Zometa; or Aredia, also known as pamidronate, or Xgeva known generic as denosumab, those are important and has been shown in studies to not only decrease pain, prevent fractures, improve bone strength, but also improve myeloma remission duration or how long people live. So important to go through all of those components to maintain optimal bone health for patients.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Tamala of South Carolina. Please state your question. Your line is now live.

Tamala, South Carolina

Yes. I've been dealing with myeloma; I was diagnosed in 2010. And I think I had stem cell in '11. And I think I was clear for about two years, and then I went into remission. I went into remission for two years. I was in remission for two years, and then I started back on the Darzalex® (daratumumab) in 2016. And I'm, you know, on it now and they said that my body's working well with it, but it was like one of the other patients that said, you know, the first day after—I had chemo yesterday—you know, I'm still high a little bit from the steroid. And then today I'm kind of like that and then tomorrow I have to push myself and Saturday usually I have to push myself. And then I deal with like the neuropathy in my hands only when the temperature is low. And other than that, well I have a nephew, sorry to say, has it too and he's had the CAR T. And it didn't really do that much for him so he's on a brand-new drug, a trial drug right now seeing what it does for him. And he's 33 years old.

Ajai Chari, MD

Yes. So, I think we talked about some of the kind of cyclical pattern that people have with chemo with respect to steroids, you know, that high and crash. I think many people will get a high, but if the crash is more than normal, we should make sure that your team rules out the adrenal problem, which is when your body doesn't–it's fine when you take steroids, but when it's become so lazy with making steroids that if the steroids leave your body, then you get that crash. So that's something that's fixable.

That said, with dara there's kind of an interesting—One of the easiest studies I've ever had to convince patients to participate in is the sub-Q dara. So when you compare IV and skin dara because, you know, the safety profile when you give dara over intravenous versus in the skin, the risk of allergic reactions, which is 50% on the first dose with IV dara, drops to less than 20%. And in some studies, as low as 7% for allergic type of things. So, it seems to be safer. In terms of the efficacy, how well it works, it seems to be comparable. But in terms of convenience, we're taking the first dose dara from median of six to eight hours, to now five minutes injection in the skin. And in the later treatments, it's getting to three to four hours is now it's still five minutes. And where a lot of centers are doing rapid dara over 90 minutes, so if you haven't had that yet, you could talk to your team about getting the IV dara over at least 90 minutes to make it faster. Because all the allergic stuff tends to happen in the first couple of doses and after that, it's really a nonissue.

For patients who have neuropathy when that's worse with cold, I would recommend that the teams evaluate patients for what's called cryoglobulinemia. Some patients with myeloma and lymphoma, the proteins that we detect in the blood can cause clotting in the small vessels of the fingers and toes and sometimes they can even become blue. And the treating of that is really getting rid of the myeloma protein, but it's also helpful, obviously, to stay warm if you can. Some patients move to warmer climates who have this as a very prominent symptom. But that's something that could be checked and ruled out. And, yeah, I think so those are the things to kind of consider. But typically, dara by itself does not cause neuropathy and typically does not cause fatigue and crashes.

And the last point I would mention is that we've actually, in patients who are on very long-term dara, we've been weaning off the steroids because, again, most of the allergic stuff is the first few cycles, and so when somebody's on a very long-term treatment, if they're not having any allergic problems, you can even take off the steroids, which we all know that is least liked by patients.

Lizette Figueroa-Rivera, MA

Thank you. And now that you mentioned CAR T cell therapy, Barbara, as well as many of our other participants, are asking when will CAR T be a standard treatment for multiple myeloma?

Ajai Chari, MD

Right now, it's been submitted to the FDA, and my guess is within the next year. And the first CAR T that will be approved is Bluebird, the one that we saw the data for. The questions are going to be— I mean I have patients who had all the other drugs, and nothing worked, and now they're in remission. And, of course, we talked about the cytokine release syndrome and the blood counts, but what's great about CAR T when it works is that really, it's a one and done thing. Once the CAR T is done if somebody achieves a remission, they're off all drugs, which is almost unheard of for patients with myeloma who have had it for a long time after seven previous therapies, which are typically continued until they stop working, to now get this one and done treatment where you're completely off and having a great quality of life, assuming the blood counts have recovered.

So that's a great thing. However, not everybody, of course, is going to stay in remission. And I think one of the big things, which we haven't talked about but it's going to be an important issue, we've had all of these drugs approved and each drug is quite expensive. And CAR T in other cancers for which it's been approved has been $500,000 to $600,000. And so, I think one of the questions will be if and when CAR T is approved, which we think is going to be in the near future, when will insurance companies agree to pay for it? In what setting?

And so, I think if CAR T cannot be obtained, that's why I would still encourage patients to do clinical trials. There are actually a lot of studies doing CAR T not just in heavily treated patients but in earlier and earlier relapses, particularly for high-risk patients. For example, at our center, we have a study for CAR T for first relapse in a high-risk patient because, as we alluded to, those patients typically go through all the regimens, but the remissions don't last long. But if we have a novel, innovative way, that might be worth considering. But I think stay tuned. It should be available, best guess is within the year.

Lizette Figueroa-Rivera, MA

Thank you. And I know we didn't mention smoldering myeloma, but Paul is asking if there's anything new with smoldering myeloma?

Ajai Chari, MD

That's a great topic. I think we know that when you take people with newly diagnosed myeloma, because one of the questions that comes up, "How long might I have had it?" And most people aren't running around getting these esoteric blood tests like SPEP (serum protein electrophoresis), light chains, etc. But the veterans who participated in the study kindly had donated their blood and so what was interesting is, in this publication, when you take newly diagnosed patients with myeloma, and you go back in time to see how long they may have had it, if you go back one year, 100% of patients have detectable myeloma proteins. And if you go back eight years, it's about 80%. And so, what this means is that the vast majority of patients probably have a premyeloma state, whether it's MGUS or smoldering. And the question is when do you intervene and treat?

So, there's two different camps, right. So one camp is, we have treatments that are very well tolerated and if we can identify these patients who are going to be at very high risk of progressing from smoldering to myeloma requiring chemo, why do we need to wait for CRAB symptoms? Why not just intervene early and prevent those side effects and give these well tolerated regimens and get rid of it and just get people into remission and go for a cure?

The other side of the equation is you have healthy people. Smoldering myeloma, by definition, have no symptoms. And we don't yet have perfect risk stratification models. For example, I personally take issue with the new myeloma-defining events like free light chain greater than 100. I always tell people, you know, that we shouldn't treat numbers, we should treat patients. And if you diagnose somebody with smoldering myeloma and they have a concerning lab, more important than the photograph of that patient at that moment in time is their movie. How did those labs change over the next year to two years? Because high-risk smoldering myeloma, by definition, is somebody who's going to progress within the next two years. And so the response to the early treatment group is we can't even agree on who's truly high risk because all of these models, the initial free light chain ratio rate greater than 100, people had a risk of progressing by approximately 90% at two years, which all, of course, sounds concerning.

But newer studies where patients are followed prospectively it's as low as 30%. So, unless we get the right population correct for really who's high risk, and then the second thing is the right treatment, we may be overtreating a lot of patients. And, also, what treatment? Because the recent study that was just presented this year and actually just got published was the use of Revlimid in smoldering myeloma, and it showed that the remission duration was increased. The problem is it only really helped in high-risk patients of which there were only 16 patients in each arm. Also, 50% of patients discontinued the drug for side effects. The response rate was only 50%. We don't have any information whether CRAB symptoms were prevented. So, yes, we can treat people, but we have to, at the end of the day, be able to show that our treatments are actually helping them live more time without CRAB symptoms and live longer overall. So, there's a bit of a data gap right now and kind of what happens to smoldering kind of depends on patient and physician perspectives.

Lizette Figueroa-Rivera, MA

Thank you. And our last question for today is a very timely question. Leona is asking about vaccinations: Are they okay, and do you recommend getting the flu shot?

Ajai Chari, MD

The second one is easy. We do recommend flu shots because the vaccine may not prevent all flus, but the very population where it's intended is typically the older population with cancer on chemo, which pretty much applies to almost all myeloma patients. And so not to mention the biggest complication in myeloma, in terms of what leads to issues and even death, is infection. And so if we can give these flu shots, even if it doesn't completely prevent it, the hope is that it would prevent the

complications, which means a secondary bacterial infection because we know flu is a virus, but it can be associated with a secondary bacterial infection which can then result in hospitalization or ICU care. So, I think a flu shot is a no-brainer. Ideally, try to do it in your week without steroids or without chemo. Revlimid-type drugs are actually fine. There are some studies that it boosts a response, but steroids can blunt them. And also, patients who are getting IVIG you may want to do it in your non-IVIG week.

In terms of the other vaccines, basically for nontransplant patients, we recommend pneumonia 13 once followed by the pneumonia 23 a couple months later. And that pneumonia 23 should be repeated every five years.

The Shingrix vaccine is also available now, but although it's not yet approved for myeloma patients, there's two types of shingles vaccines, Zostavax® (zoster vaccine live) and Shingrix® (recombinant zoster vaccine). Zostavax is a live vaccine which we do not like in blood cancer patients, but Shingrix is a killed vaccine. It's a two-shot vaccine given a couple months apart. If you can get it approved, you can get it possibly at your local pharmacy. There's no risk in getting that. However, it's important to remember that drugs like dara and Velcade and carfilzomib, they can reactivate shingles in patients. And even if somebody got a Shingrix shot, I don't know that the shot works as well, will work well enough to stop the shingles preventative drugs like acyclovir or valacyclovir.

And then the last part of the vaccination discussion would be for posttransplant patients we do recommend a more complete schedule which usually will be handled by the transplant center. That includes things like *Haemophilus influenza B*, tetanus, diphtheria, pertussis, the pneumonia, etc. So, you can check with your local doctor.

Lizette Figueroa-Rivera, MA

Well, thank you. And thank you, Leona, for that question. And thank you all for your questions. Dr. Chari, thank you so much for your continued dedication to patients and for staying on a few more minutes. We had so many questions for you. Thank you.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

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If you weren't able to get your question in today, please call a Leukemia & Lymphoma Society information specialist at 1-800-955-4572. Information specialists are available to speak with you from 9 AM to 9 PM Eastern Time, or you can reach us by email and infocenter@LLS.org.

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Again, we'd like to acknowledge and thank Celgene and Takeda Oncology for partnering with us to support this program. Thank you so much again, Dr. Chari, for sharing your knowledge with us today

and to all patients, caregivers and professionals participating in today's program. And on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us.

Goodbye, and we wish you well.