Transcript

Slide 1. Welcome & Introductions

Operator:
Greetings and welcome to Emerging Therapies for Multiple Myeloma telephone and web education program.

It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera. You may begin, mam.

Lizette Figueroa-Rivera:
Hello, everyone, on behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

We have over 1,000 people participating from across the United States and several countries around the world including Austria, Canada, Germany and the United Kingdom.

Special thanks to Dr. Ajai Chari for volunteering his time and expertise with us today.

Before we begin I'd like to introduce Andy Coccari, The Leukemia & Lymphoma Society's Executive Vice President and Chief Product Officer, who will share a few words. Andy, please go ahead.

Andrew Coccari:
Thank you, Lizette. I'd like to add my welcome as well to the patients, caregivers and healthcare professionals attending this program today. I'm very excited to be able to address you all at the beginning of this wonderful program.

You know, The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For over 60 years, LLS has helped pioneer innovation in targeted therapies and immunotherapies that have improved survival rates and quality of life of many blood cancer patients. To date we've invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will be relentless to fund promising research from the bench to the bedside.

In addition, as this program demonstrates today, we are a leading source for free blood cancer information, education and support. You know, many of you might not know, but we touch patients in their communities where they live, through our 56 chapters across the United States.

LLS also, in addition to those chapters, acts as a voice for all blood cancer patients. We advocate for patients, survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care, very important.

We're fortunate today to have with us a great presenter, Dr. Ajai Chari, one of the nation's leading experts on myeloma. We appreciate his dedication to supporting our mission and his commitment to caring for patients who are living with blood cancer.

I'd like to represent all the executive leadership team from The Leukemia & Lymphoma Society, and everyone at the home office in Rye Brook, New York, in the United States, in thanking him for joining us today and providing us with this important information on emerging therapies in multiple myeloma.

Thank you to all, enjoy the program, and now I'd like to turn it back to Lizette.

Lizette Figueroa-Rivera:
Thank you, Andy.

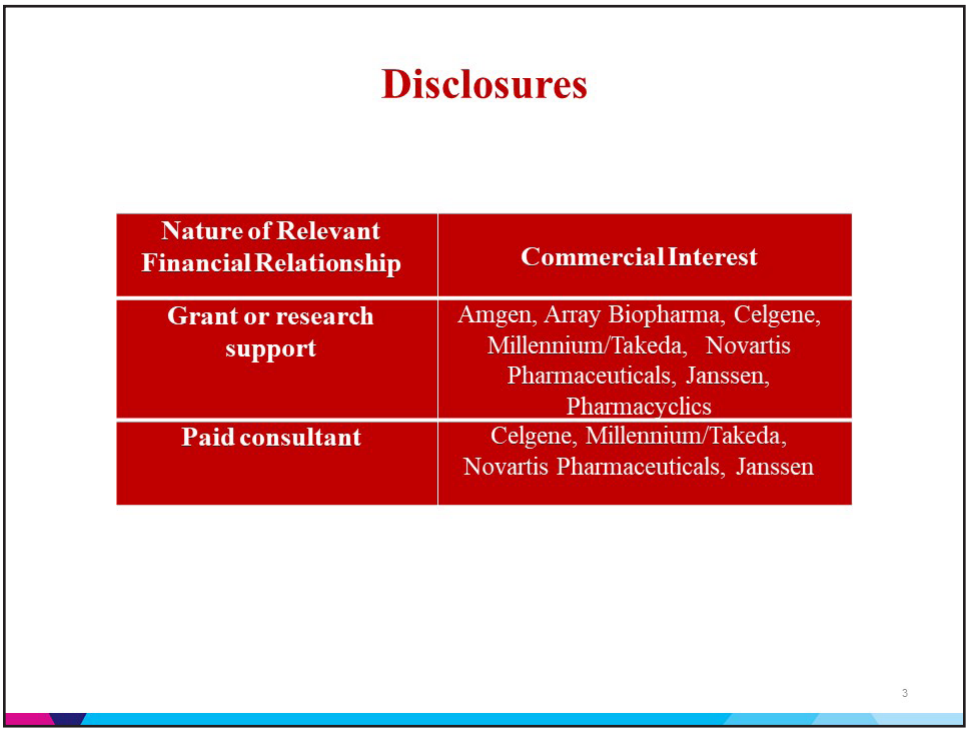
And support for this program is provided by Amgen, Bristol-Myers Squibb, Celgene Corporation, Sanofi Foundation of North America, and Takeda Oncology.

I'm now pleased to introduce Dr. Ajai Chari, Associate Professor of Medicine, Director of Clinical Research, at the Icahn School of Medicine at Mount Sinai Hospital in New York, New York. Dr. Chari, I'm privileged to turn the program over to you.

Slide 2. Emerging Therapies for Multiple Myeloma

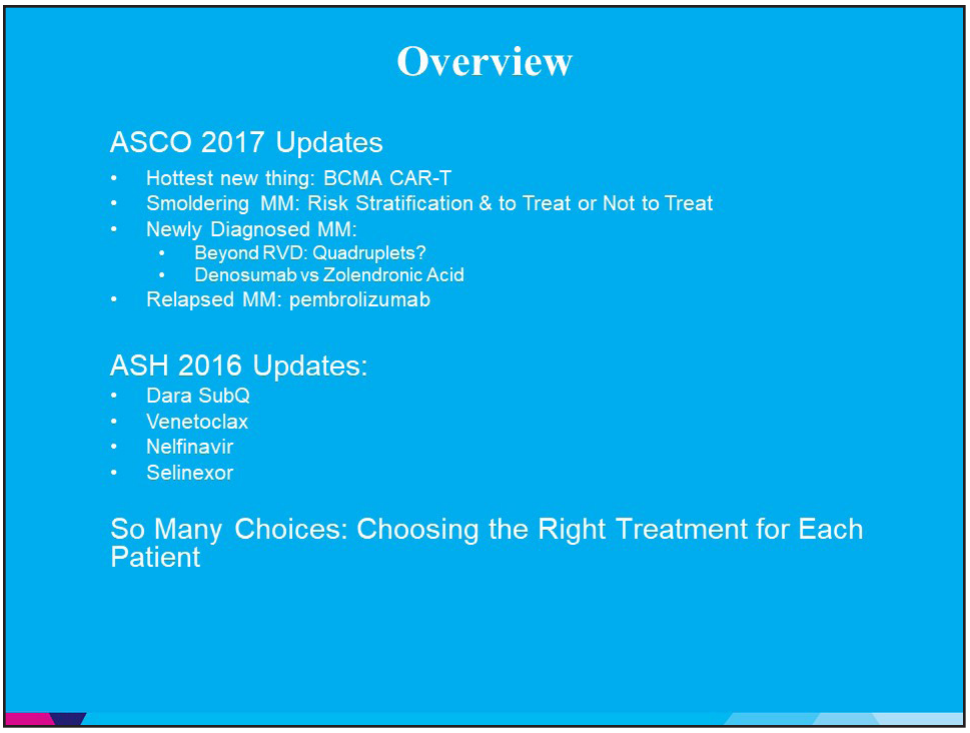
Dr. Ajai Chari:
Thanks, so much Lizette and Andy and LLS. This is a great opportunity for patients and caregivers to catch up on myeloma. There's so many new and exciting developments, so it's my pleasure to be here, and let's get this going.

So, as we mentioned, the topic will be Emerging Therapies for Myeloma, including updates from the ASCO meeting that just happened in June in Chicago.



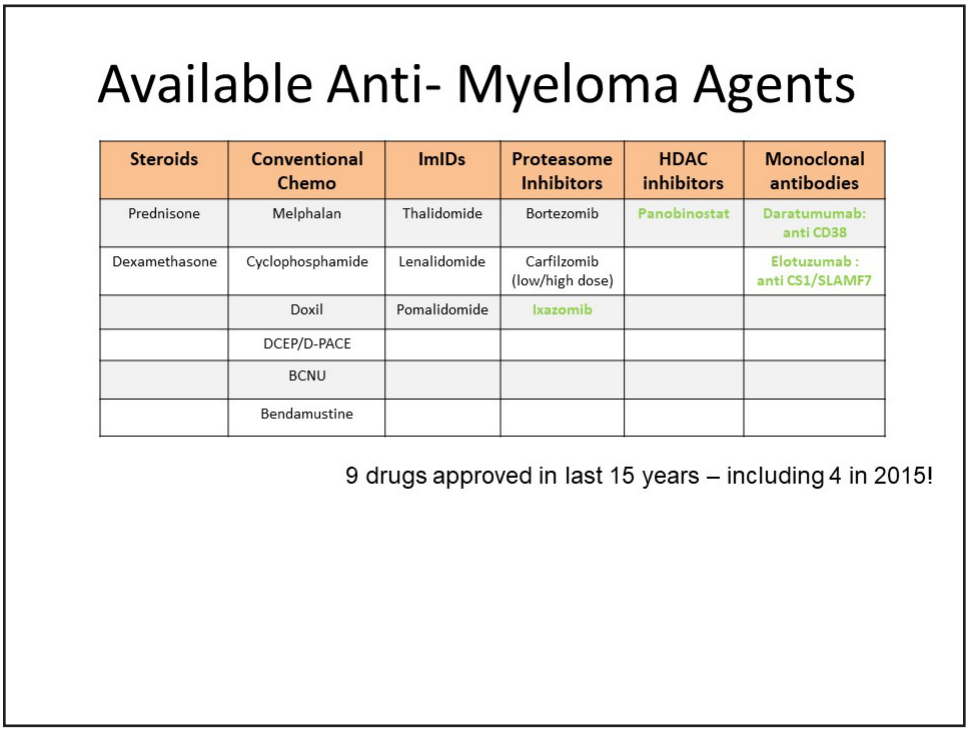
Slide 3. Disclosures

So, these are my disclosures. I've received grant and research support from the companies listed, and also served as a consultant. All of these are doing a lot of exciting work in the field of myeloma.



Slide 4. Overview

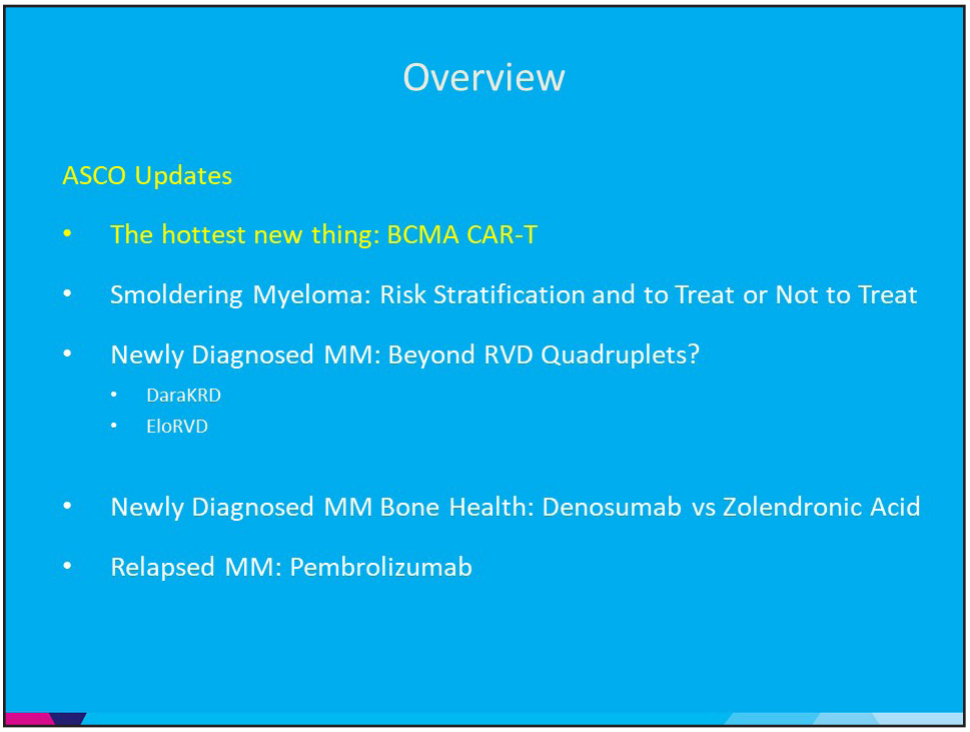
So, today we'll be going over basically three high level topics. The first is ASCO updates, second will be the America Society of Hematology 2016 updates, and finally, when we have so many choices, how do we put this together and figure out the right treatment for the right patient?



Slide 5. Available Anti-Myeloma Agents

So, the next slide shows the currently available or FDA-approved agents for myeloma. And I think it's important to start with this so we know how these new treatments are being placed in terms of sequencing and combination therapies.

And essentially, we have 6 classes of drugs: steroids, conventional chemotherapeutics, immunomodulatory drugs, proteasome inhibitors, HDAC inhibitors and monoclonal antibodies. We'll come back to some patient-specific issues with each of them towards the end of the program, but I think it's a really exciting time in myeloma, which is a relatively uncommon cancer, but to have the four drugs shown in green, ixazomib, pano or panobinostat, daratumumab and elotuzumab, all 4 were approved in 2015, which is really an amazing accomplishment. And in combination with the other recent approvals, these are nine drugs that are approved in the last 15 years. And these have translated into significant improvements in patient outcomes. So, it's a really exciting time for myeloma research.

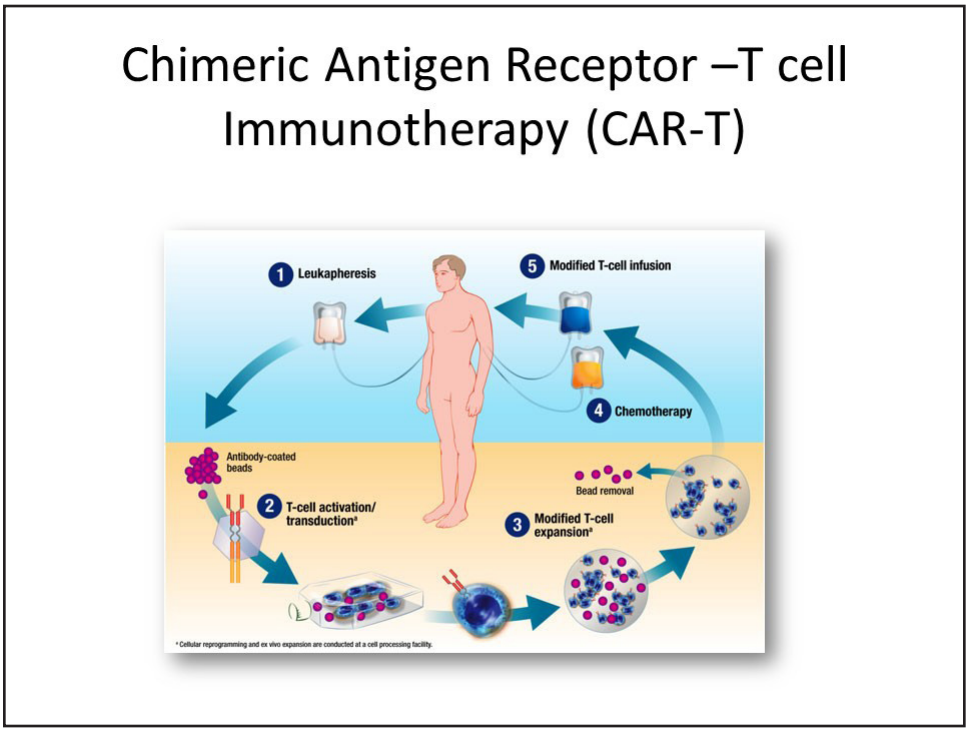


Slide 6. Overview

So, moving into now the first segment, which is the ASCO updates, the hottest new thing, everybody's heard about it, CAR-T.

Slide 7. First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results

And so we'll be talking about what CAR-T is.

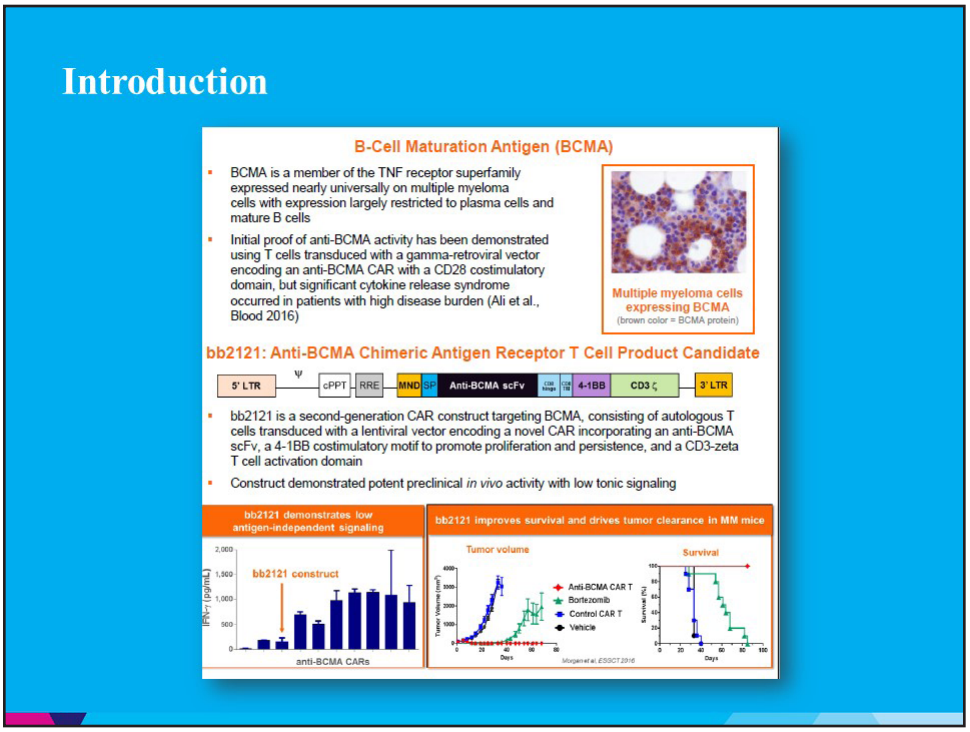


Slide 8. Chimeric Antigen Receptor –T cell Immunotherapy (CAR-T)

And the next slide, there's a schematic of what CAR-T essentially involves. And similar to stem cell collection, there's a process called leukapheresis where the white cells are removed from the body through a vein, and then those white cells are basically modified and they activate the T-cells, which is the important component of the immune system that helps kill cancer and also certain types of infection. These T-cells are genetically modified and then those modified T-cells are put back into the patient after they've undergone some chemotherapy. And so that's basically the CAR-T high level process.

Slide 9. First-in-human multicenter study of bb2121 anti-BCMA CAR T cell therapy for relapsed/refractory multiple myeloma: Updated results

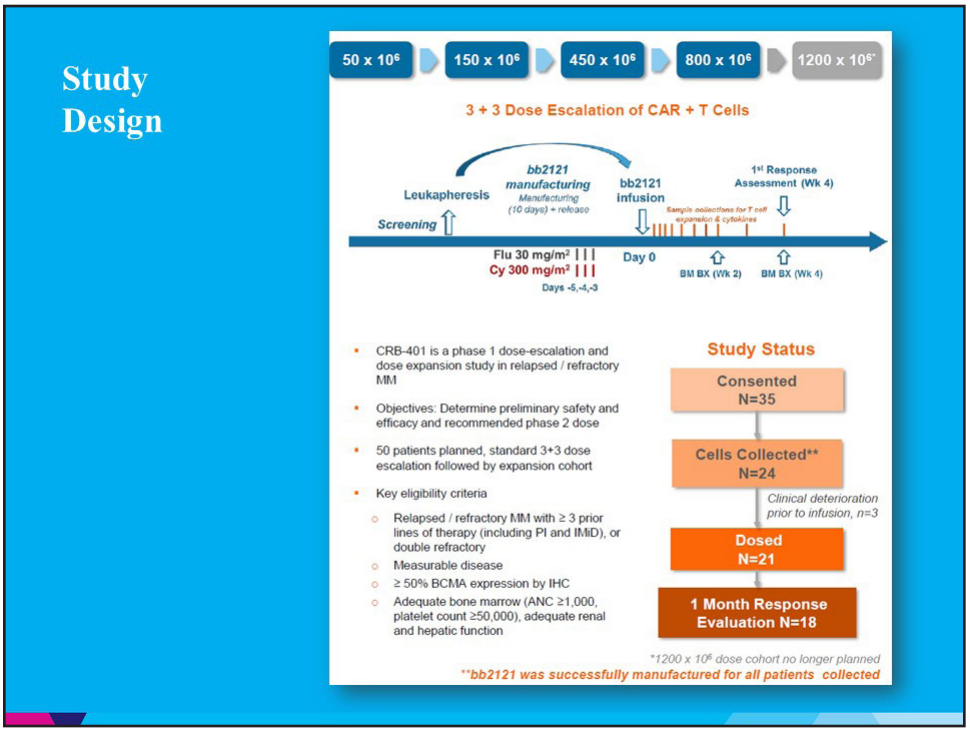
And there were 2 presentations at ASCO. One is this first one, is called bb2121. And this is from the Bluebird Company, which is partnered with Celgene. We did participate and we have this open at our hospital at Mount Sinai, and one of our patients is represented in this data.



Slide 10. Introduction

So, what is BCMA? Well, basically those T-cells that we just talked about that have to be modified, they need to be attacking a specific target because you want the T-cells to attack cancer, but spare the rest of the body, which means that you have to find proteins that are expressed primarily on the cancer cells, but not on the other normal cells that we all have. BCMA is an excellent candidate for this because it is highly expressed on plasma cells. And then what they do is they make this chimeric antigen receptor, which is what the CAR-T stands for. And basically, this construct or this molecular combination is used to target the BCMA, and what it involves is those T-cells have a genetic component that targets the BCMA.

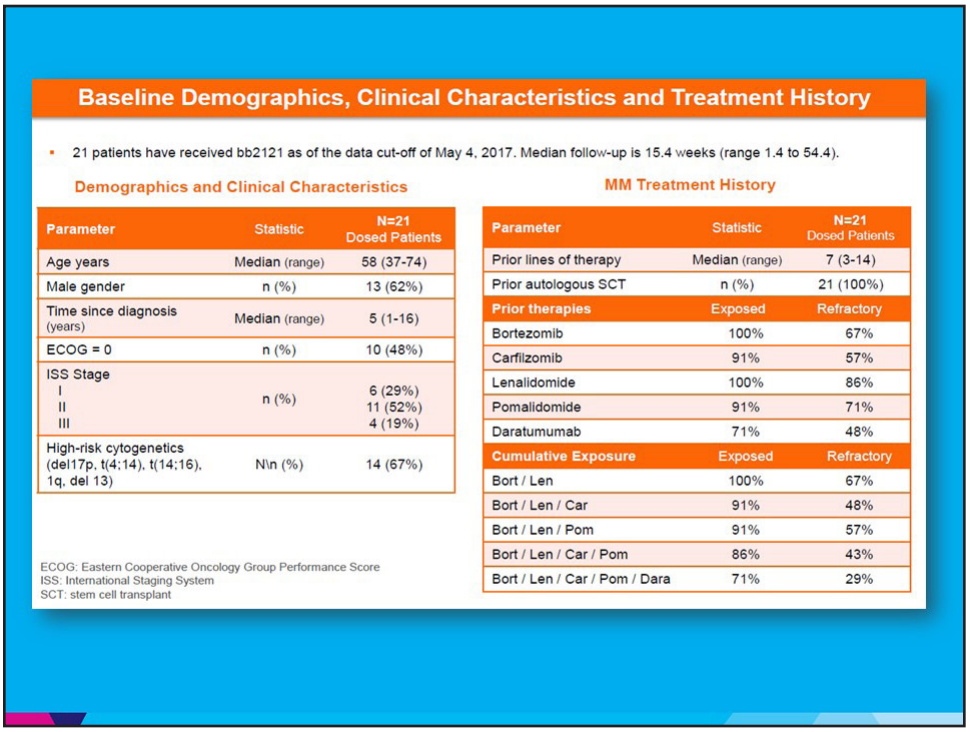
And what you see, it's small on this slide, but on the lower right hand portion of the slide you see that when cells are basically untreated myeloma cells in the lab, they just keep growing in mouse models. The blue line shows that as the mice get – if they're not treated with anything, that's the control. Now when you use an approved myeloma drug such as bortezomib or Velcade®, you do see that there's a delay in the cells growing, but eventually they do grow. What's really interesting is that with the BCMA CAR-T, that red line, not only is the growth of the tumor delayed, it actually never seems to occur. And that not only is it a growth issue, when you look at the curves of how the mice lived, you see that the flat line means that these mice never died, suggesting that we're actually able to cure this. And that's really what's so exciting about this technology, that it's not just a constant therapy, which most myeloma treatments are, but perhaps a one-time intervention to get definitive control.



Slide 11. Study Design

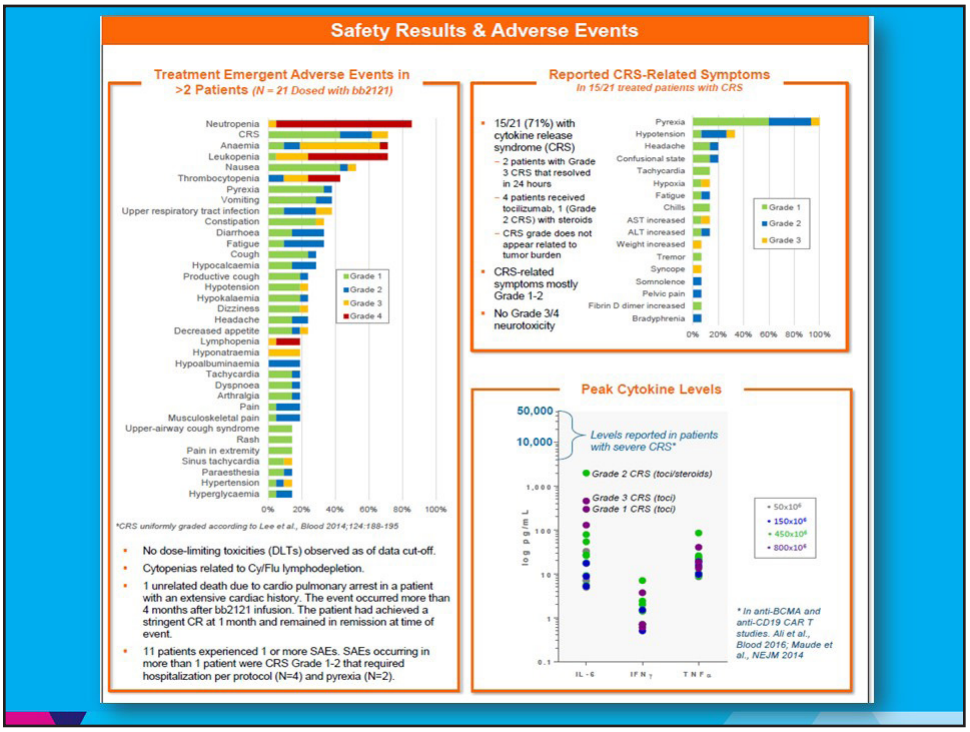
So, in this next slide we see the study design and it basically involves – patients have to be screened, and then their cells are collected by the leukapheresis product, as I alluded to, the bb2121, that's the specific manufacturing process. And those cells are infused on day 0. But prior to day 0, there's some chemo and that's called fludarabine and cyclophosphamide, and those are given 3 days prior to that. So, it's kind of a mini-transplant if you will. And then patients are followed after that.

In this Bluebird study, there were a total of 35 patients consented, of whom 24 had cells collected, so we do see a drop-off and that could be for a variety of reasons. Then 3 patients had a deterioration before they could be infused, so the results that we're going to be looking at are with the remaining 21 patients.



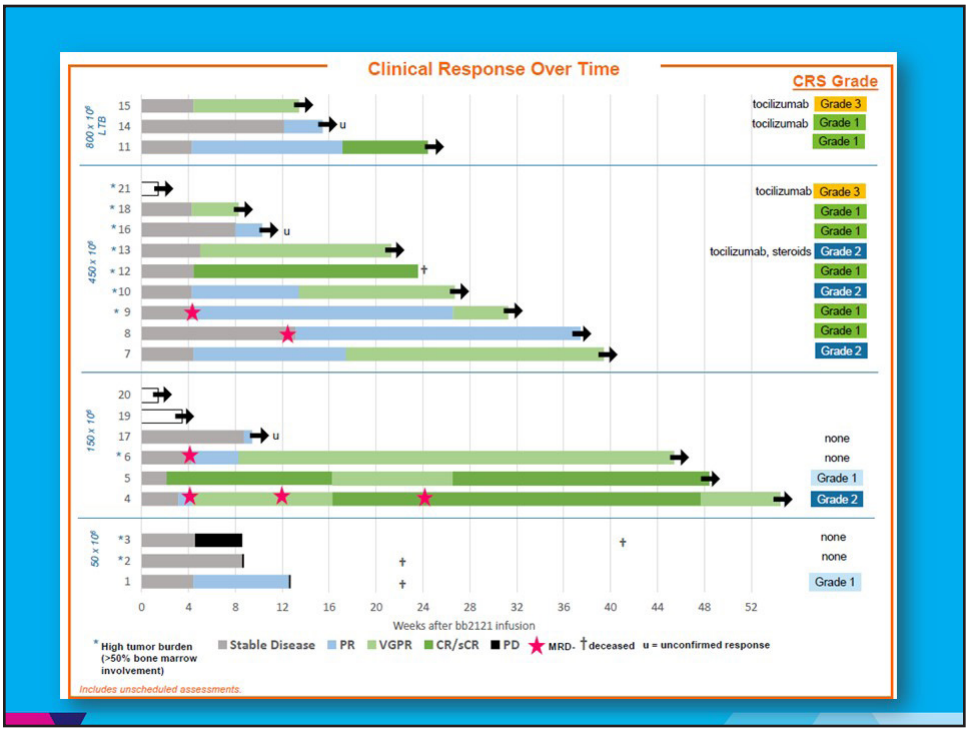
Slide 12. Baseline Demographics, Clinical Characteristics, and Treatment History

And the next slide shows the baseline characteristics. What's important to look at here is, were these people who had had just 1 or 2 therapies, or are these heavily treated, what were their other types of options? And what we see is actually quite heavily pretreated patients. They had a median of 5 years since their diagnosis, about 67% had high risk genetics. They had a median of 7 lines of prior therapy, and including many of them were refractory to the big five of bortezomib, carfilzomib, len, pom and dara, so this is a significantly treated population and there's not an easy standard of care.



Slide 13. Safety Results and Adverse Events

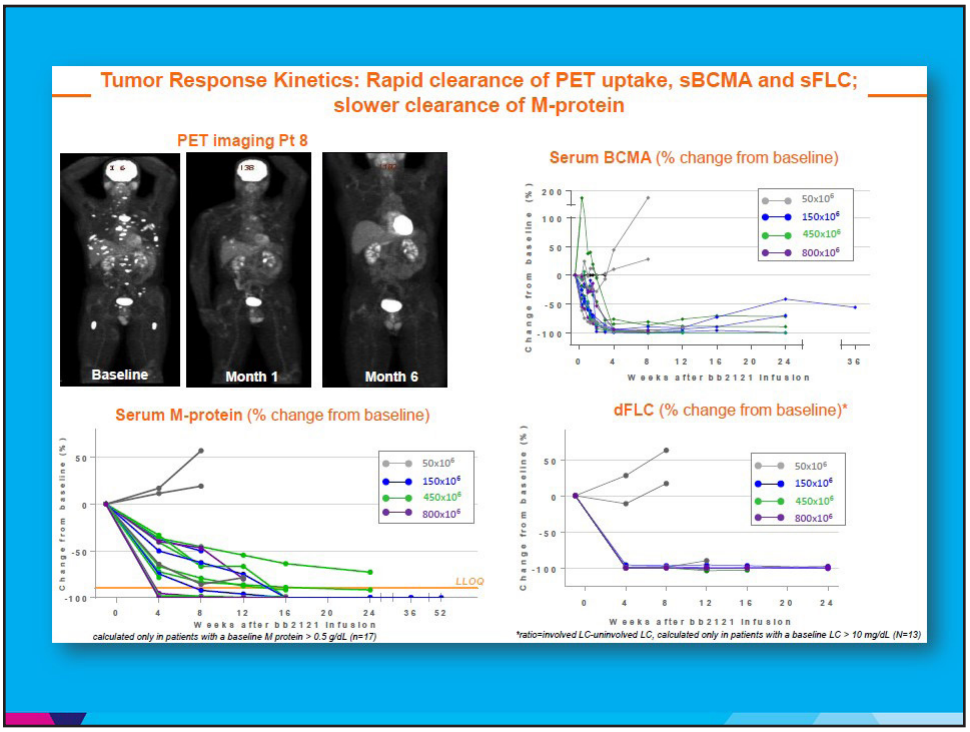
And what we see on the next slide is first the side effects on the upper left. And the first few are blood counts. And remember that the CAR-T infusion is preceded by chemotherapy, which is going to lower the counts, and so that's clearing up the marrow and allowing these CAR-T cells to also kick in, so those low blood counts aren't particularly surprising. But the important thing to pay attention to in all CAR-T is what's called CRS, cytokine release syndrome. And that's shown also in detail on the right. Cytokine release syndrome is basically – kind of the easiest way to think about it is immune havoc. You have these activated T-cells that are now being infused and they can create cytokines or chemicals that get released when they're doing this attack. And those things can be mild, moderate or quite severe. And our grading criteria in oncology, we classify things as mild, as grade 1-2, and severe is grade 3 and 4. And in this particular study, 71% of patients did have some level of cytokine release and you can see that it could be something like fever, low blood pressure, headache, fast heart rate, etc. But when it's serious, this is when we need to use medications to increase the blood pressure because fluids aren't adequate, or have to give oxygen support. And there's actually now also an intervention called tocilizumab, which is a medication that blocks one of the cytokines that can cause CRS. And so that is used in severe CRS. And this is the main thing that needs to be further clarified. Some of the other CAR-T formulations, not this one, have had more significant and serious side effects than have been seen in this one, but that's one of the things that needs to be better studied going forward in future CAR-T studies.



Slide 14. Clinical Response Over Time

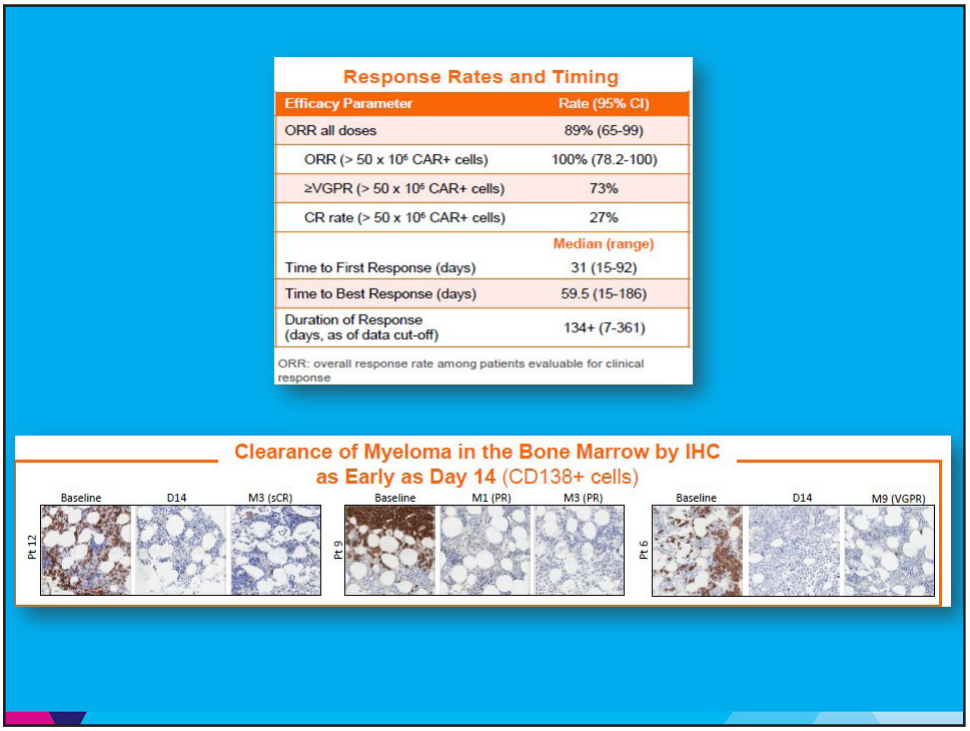
And what about the benefit? That's the really exciting part. On the next slide, we see that going from bottom up, the patients at the bottom got the lowest amount of cells, CAR-Ts infused, and as you go up they get higher doses. And basically, anybody who has an arrow means that they're still responding and doing well. So, you see that the vast majority of patients have arrows, meaning they're still in follow-up. The lower doses didn't have a durable response and so – and that's normal whenever we do these studies, we have to first make sure that this is safe and then keep increasing the dose until we see the safety and benefit balance that we like to see. Impressively, not only are patients still on therapy, you see by the depth of color response, blue is partial response, and as you go to the darker green you're getting to complete responses, patients are getting very deep responses and they seem to be sustained.

It's important to remember, though, that most of the patients have not gotten that much follow-up yet, so the bottom is showing weeks, so a lot of them are below 6 months of follow-up. But still, given the nature of the population that we saw, these are really outstanding results for CAR-T.



Slide 15. Tumor Response Kinetics: rapid clearance of PET uptake, sBCMA and sFLC: slower response of M-protein

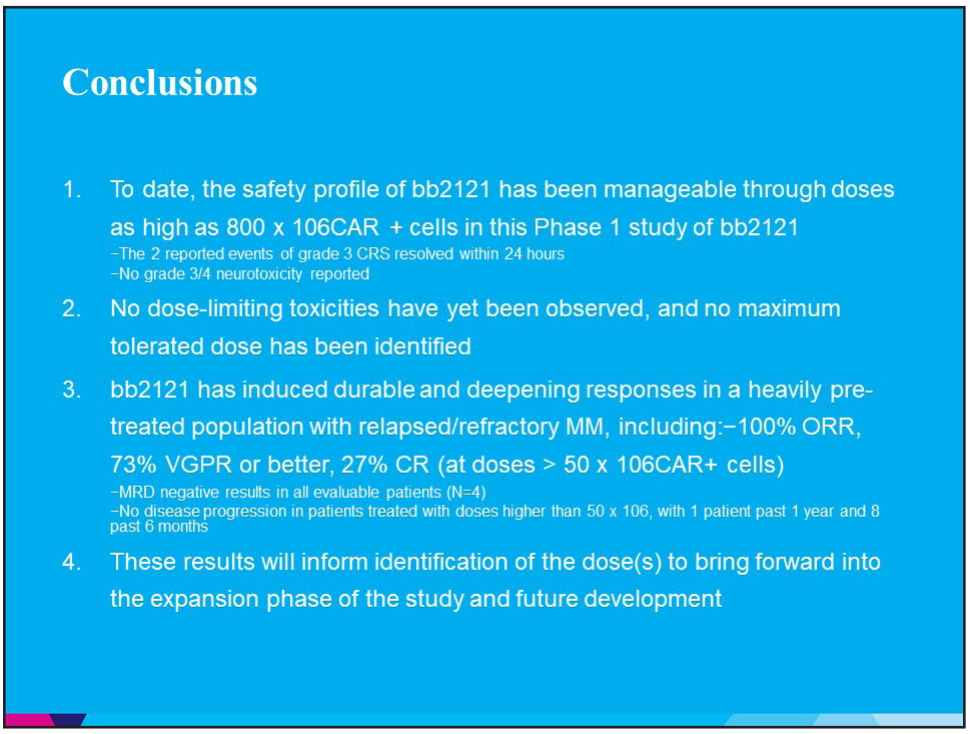
The next slide shows also what the PET scan looks like. And in the upper left you see the little white spots scattered all over the chest of the patient and those disappear very quickly, within 1 month, and remain gone in 6 months. And then the other 3 graphs are showing similar, that these are the protein levels of – the bottom 2 show the protein levels of the myeloma, the so-called M-protein, or free light chains, and we see that almost all patients had a drop. The few that didn't, the 2 patients that didn't, are the ones that had very low doses of the CAR-T infused. And then also the BCMA, which is the target of the CAR-T, that protein level decreases as well and seems to stay down. So, this is really very exciting for patients.



Slide 16. Response Rates and Timing

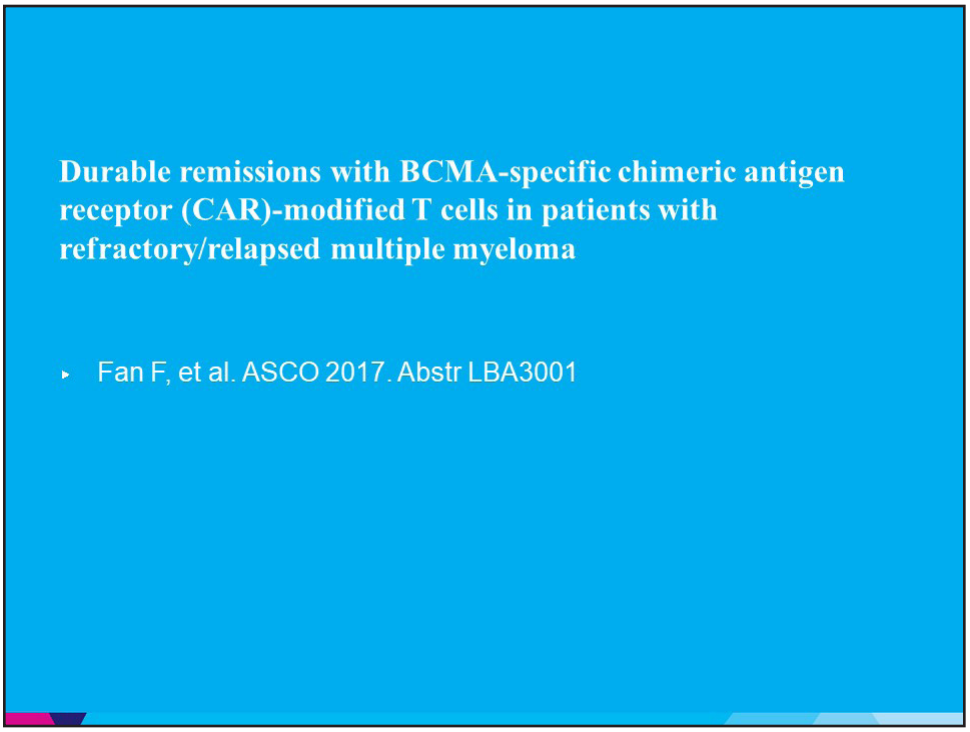
And the summary of the response was 100% response rate. So, every patient responded and they were deep responses. It took about a month to get that first response and by response we're talking about a 50% drop. Doesn't mean that patients weren't improving before that, but by myeloma criteria a response requires a 50% drop. And importantly, the duration seems to be continuing.

The marrows on the bottom show that the myeloma cells, even by day 14, you see a disappearance of the plasma cells, the cancerous plasma cells. So, this is really an exciting outcome.



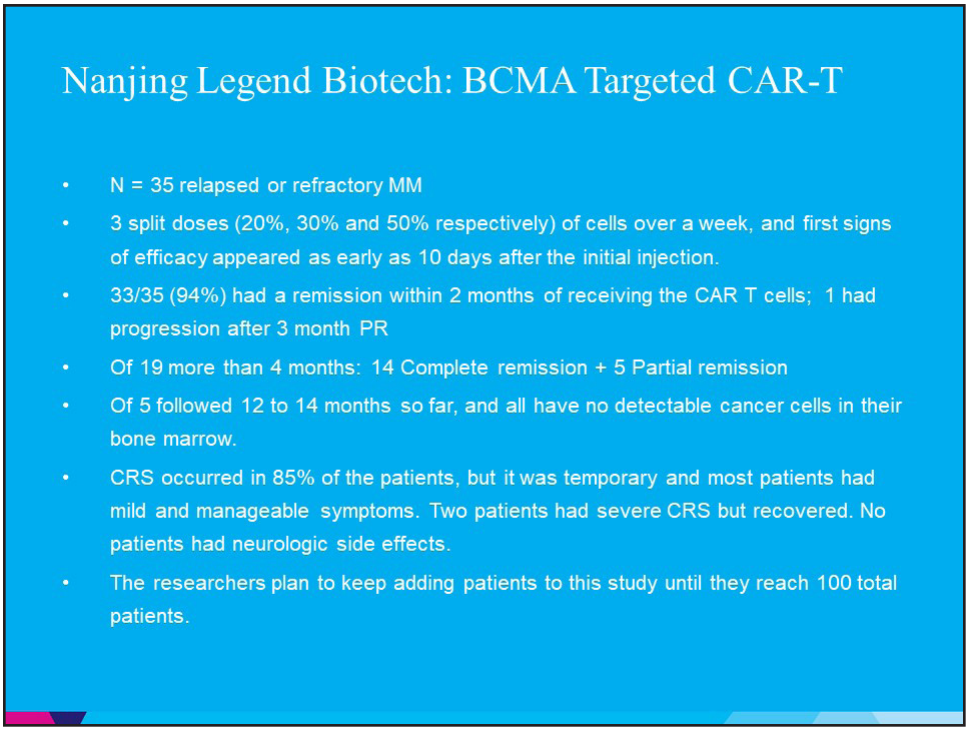
Slide 17. Conclusions

And I think this is just a summary slide saying that we see excellent responses and the toxicities seem to be manageable, but admittedly this is still 21 patients and we need longer follow-up.



Slide 18. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma

The next slide is also another CAR-T. This was considered a late-breaking abstract, which is usually reserved for again very high impact, important developments in oncology.



Slide 19. Nanjing Legend Biotech: BCMA Targeted CAR-T

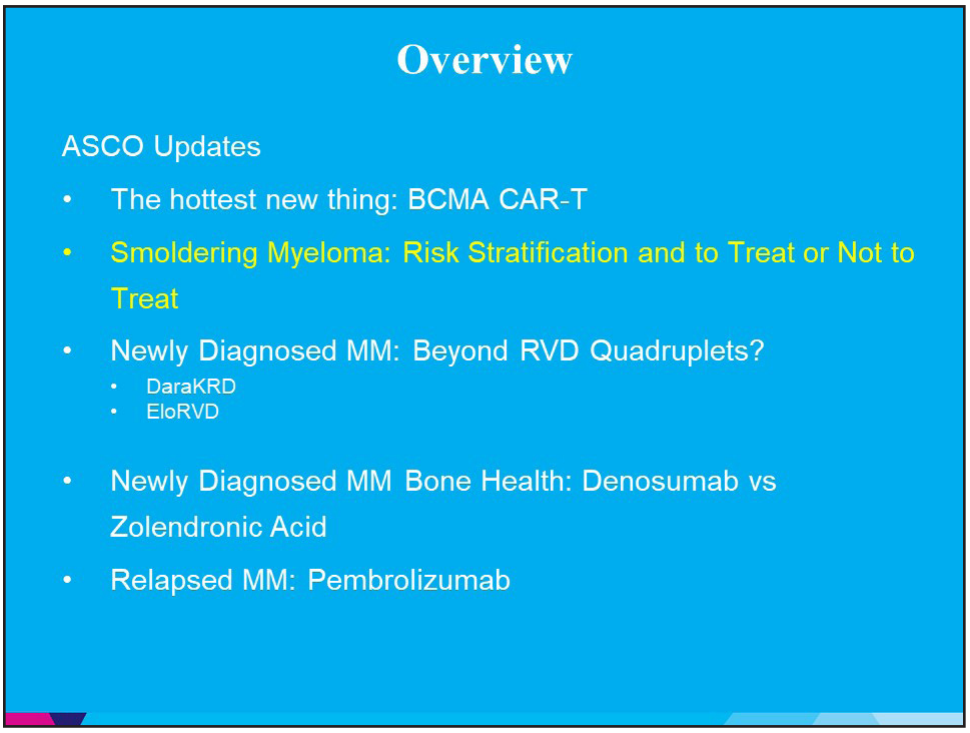
This is also a BCMA CAR-T. This is coming from China by a company called Legend, and this is Nanjing Legend Biotech, and it's another BCMA-targeted CAR-T.

So, a lot of the myeloma studies are looking at BCMA, but other tumor types are using different targets, but you'll see that BCMA seems to be the leading target in myeloma.

This is a 35-patient study, again, relapsed or refractory. There's very little published on the internet about this, but patients got 3 split doses. The first signs of response appeared quite early, as soon as 10 days. Ninety-four percent had a remission within 2 months of dosing. One person did progress after 3 months, however, of the people who've been followed for at least 4 months, 14 have been maintaining a complete remission, 5 have had a partial remission, and of the ones that were followed even longer, say, a year, 5 still have no detectable disease and are in a complete remission.

As is expected with all CAR-T, there is some cytokine release or CRS. This was seen in 85%. But it was temporary and in most patients, it was mild and manageable. Two patients did have that severe variant where blood pressure can drop or oxygenation drops, but those were manageable. And the plan is to expand this study.

So, I think if I had to pick one exciting development from ASCO, it was really the CAR-T. And there's a lot of excitement about this. There's different constructs or different products, if you will, and they're available around the country, but still it's relatively early. Patients do need to be heavily treated. And part of that is there is this risk of cytokine release and we need to understand that better. And so, there'll be a lot of opportunities for this I think and a lot of excitement about expanding this in the future, to not just heavily pretreated patients, but for now we need to get a better handle on risk-benefit in this heavily treated patient.

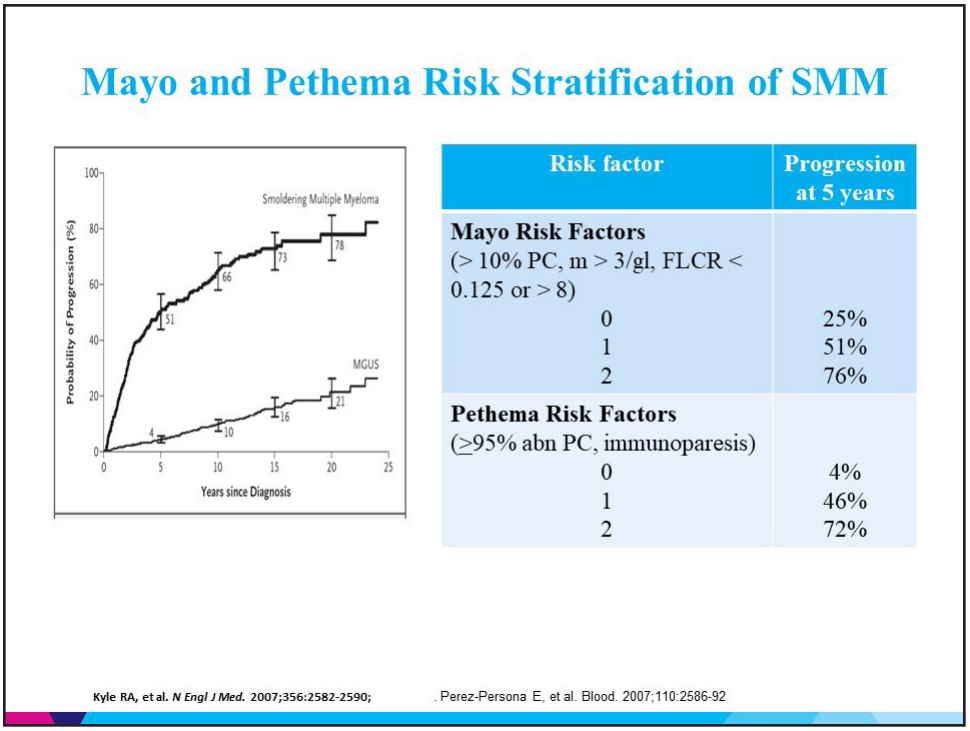


Slide 20. Overview

Then the next topic at ASCO, moving to the other end of the continuum, because from now, that was the hottest thing, but now we're going to go through smoldering myeloma and newly diagnosed, some bone strategies, and then relapsed myeloma. And so basically in the order of disease diagnosis.

Slide 21. Smoldering Multiple Myeloma (SMM): Predictive Value of Free Light Chains and Group Based Trajectory Modeling (GBTM)

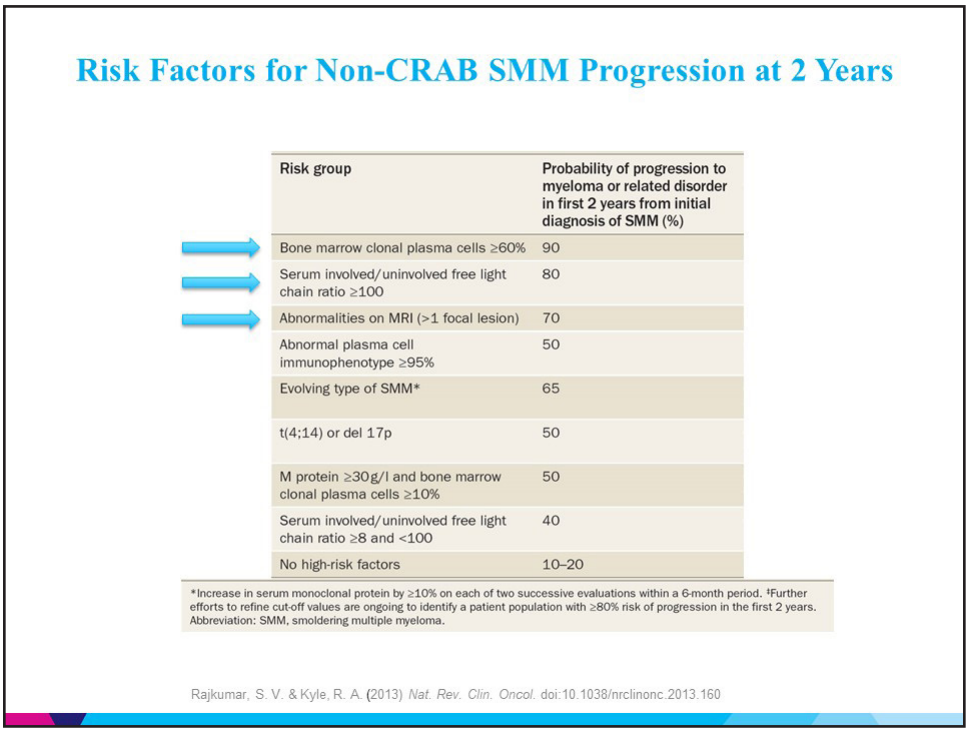
Smoldering myeloma, this is actually our group's presentation, and we were looking at the predictive value of free light chains and what's called group based trajectory modeling.



Slide 22. Mayo and Pethema Risk Stratification of SMM

And so, one of the differences between smoldering myeloma and MGUS, MGUS standing for monoclonal gammopathy of uncertain significance, is the rate of progression. Neither MGUS or smoldering myeloma by definition have any active end

organ problems. You've probably all heard about the CRAB symptoms, which stands for C for hypercalcemia, R for renal insufficiency, A for anemia, and B for bone disease. By definition neither MGUS or smoldering myeloma will have those. And these are basically asymptomatic patients. But the difference between MGUS and smoldering, as shown on the curve, is how quickly will they potentially convert to myeloma. And you see that smoldering myeloma patients have a higher rate of progression than MGUS. And so most of the work being done in terms of preventing myeloma or treating early is going to be in smoldering. But you can see that even in smoldering myeloma, by the Mayo model, the risk of progression at five years for some patients is as low as 25% and other patients at 76%. So, because these are healthy people, we need to make sure that if we're going to do any study, that we pick the patients who are most at risk for progression, so that if we do intervene, we have a reasonable chance of actually helping them.



Slide 23. Risk Factors for Non-CRAB SMM Progression at 2 Years

This next slide shows that there were 3 variables that were found to predict a very high rate of progression at 2 years, which is ranging from 70 to 90%, and these rates are so high that there was a consensus statement put out by the International Myeloma Working Group, that if a patient had more than 60% plasma cells in the marrow, if they had a free light chain ratio of more than 100, or if they had more than 1 lesion on the MRI, these patients were felt to be at high risk enough of progression to active myeloma that they should be treated early.

I can tell you, though, that in real world, many of us in myeloma centers are not sure what to do in particular with the free light chain ratio of greater than 100, because we've all had patients who've had them and not progressed, and the issue is, let's say, somebody's had a free light chain ratio for 3 years already and hasn't progressed, do we now need to treat these people just because of that ratio and this predictive value. And so, because that was never really clear, we decided to look at our data in more detail.

Current Definitions of MGUS, SMM and MM

	MGUS	SMM	MM
(1) Serum M-protein	< 3 g/dL	≥ 3 g/dL or BJP > 500 mg/d	Any paraprotein
(2) Bone marrow plasma cell %	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
(3) CRAB*	None	None	At least one
(4) Myeloma Defining Events**	None	None	Possible
For diagnosis	All 4 criteria must be met	Either (1) OR (2), WITHOUT (3) OR (4)	Either (2) + (3), OR (2) + (4)

*CRAB criteria:
(1) Serum calcium > 11 mg/dL or > 1 mg/dL above ULN,
(2) renal insufficiency (serum Cr > 2 mg/dL or Cr Cl < 40 mL/min),
(3) anemia (hemoglobin > 2 g/dL below the LLN, or < 10 g/dL), and
(4) bone lesions (one or more osteolytic lesions revealed by skeletal radiography, CT, or PET)

** Myeloma defining events:
(1) clonal bone marrow plasma cell % ≥60
(2) involved to uninvolved serum free light chain ratio ≥ 100
(3) > 1 focal lesions (each ≥ 5 mm in size) on MRI

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Slide 24. Current Definitions of MGUS, SMM and MM

That just kind of goes over the definitions of smoldering myeloma for those who need it.

Comparison of high risk SMM at various institutions

	Mayo Clinic	University of Athens	University of Pennsylvania	Denmark	MM GIMEMA-Latium Working Group	Mount Sinai
Years of investigation	1970-2010 (FLCR), 1996-2010 (BMPC)	-	2008-2012	2005-2013	1980-2010	2010-2015
Number of Centers	single	-	single	multi	multi	single
Inclusion Criteria†	yes	-	-	yes	yes	yes
FLCR						
n	586	96	118	209	-	185
FLCR ≥ 100 (n/%)	90(15%)	-	11(9%)	23(11%)	-	27(15%)
median TTP (mo)	15mo	13mo	20mo	-***	-	23mo
2 year progression (%)	72%	98%*	64%	30%	-	52%
Overall progression†† (%)	98%	100%	-	-	-	67%
BMPC						
n	655	96	121	-	397	273
BMPC ≥ 60 (n/%)	21(3.2%)	8(8%)	6(5%)	-	10(2.5%)****	22(8%)
median TTP (mo)	7mo	15mo	-	-	-	25mo
2 year progression (%)	95%	95.5%**	100%	-	100%	45%
Overall Progression†† (%)	-	100%	100%	-	100%	77%

Abbreviations: † stipulation that lab data be obtained within 3mo of diagnosis. †† progression during study follow up period which is median of 77mo for N=273 and median of 60mo for N=185. - data not available. *data at 14mo. ** data at 18mo. *** not enough patients progressed to calculate median TTP. **** N= 7 by bone marrow biopsy core, N=10 by bone marrow aspirate

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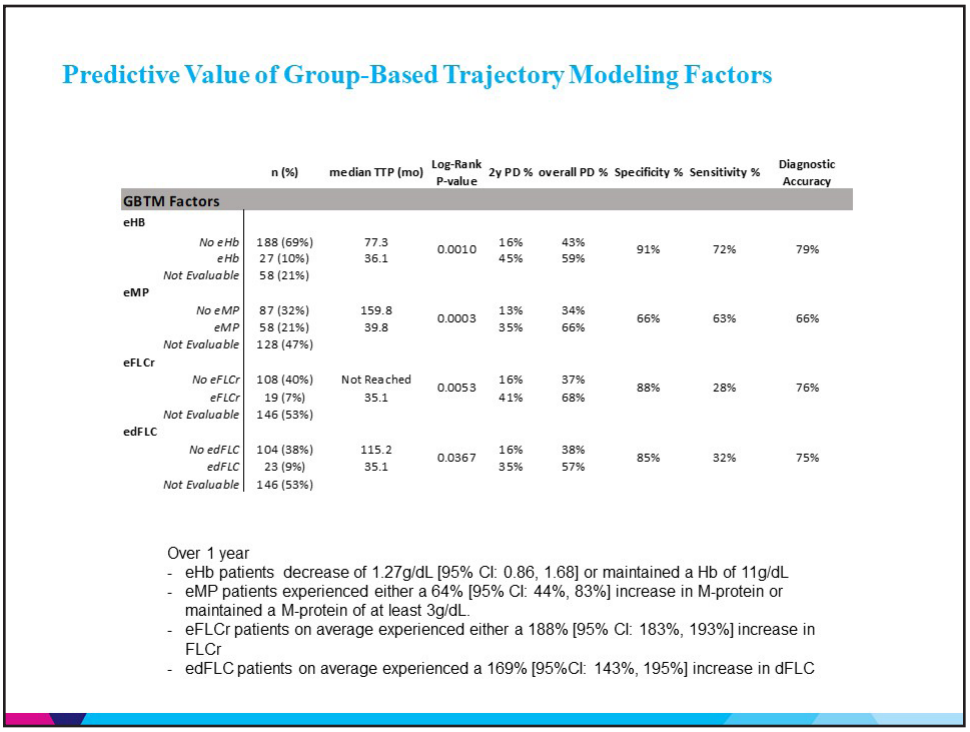
Slide 25. Comparison of high risk SMM at various institutions

And so, this next slide basically summarizes what we now know about these free light chains and also the marrow. So, at the very top of the slide are the basically now 6 different studies that have been done looking at predictive values of smoldering myeloma. And the first one is the Mayo group, which is a very large number of patients, 586, but the patients ranged from 1970 to 2010. So, as you can imagine, there's going to be a lot of heterogeneity in terms of particularly bone

imaging over that time frame. And then the other studies' sample sizes are listed here and our study, which was presented at ASCO here this year, was 185 patients. And when we looked for patients who had more than a free light chain ratio of 100, those numbers are indicated here. Again, relatively small numbers, but the initial studies did say that these patients had a high risk of progression at 2 years, ranging from 70 to nearly 100%. However, new studies have been lower, 64%, and importantly from the Denmark group, as low as 30%, and in our hands, in our population, it was 52%.



Slide 26. Predictive Value of Group-Based Trajectory Modeling Factors

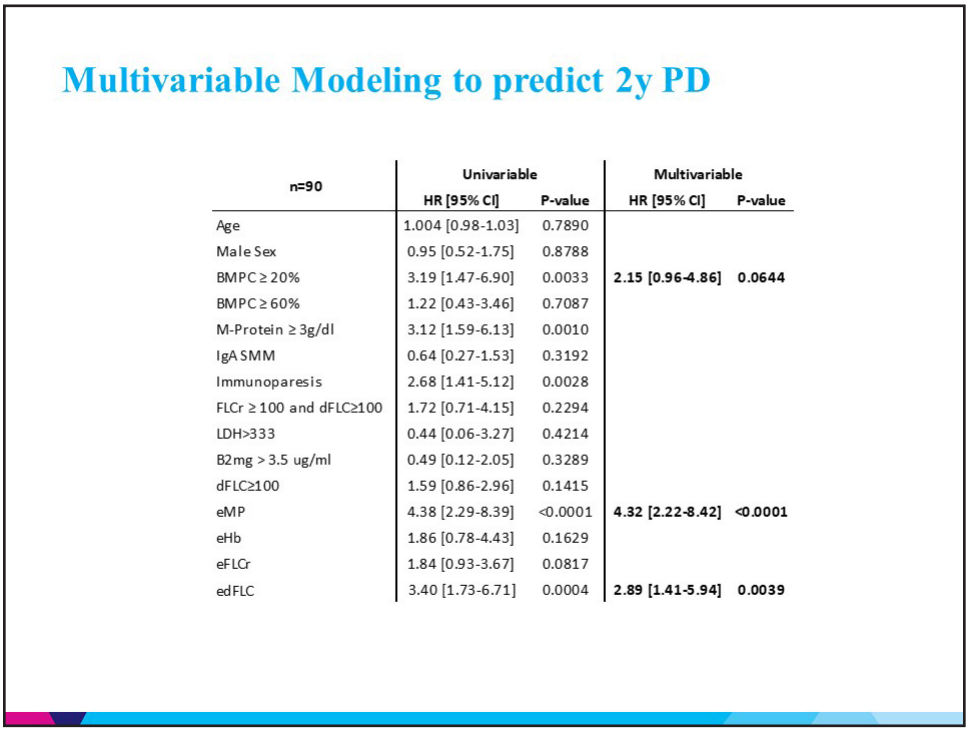
So, why is this important? Right now, as I alluded to, free light chain ratio greater than 100 has been classified as active myeloma requiring therapy because the initial predictive value was felt to be as high as 80%. I think what we're seeing now is it may not be that clear cut, and while certainly patients are at increased risk of progression if they have a high free light chain ratio, it may not be high enough to immediately warrant therapy and we probably need more information.

And then similarly for the bone marrow greater than 60%, intuitively kind of makes sense, when patients have a lot of disease in the marrow, there's probably a higher likelihood to progress to active myeloma by the usual CRAB symptoms, and you see that in these initial studies. There was about a 95% to 100%. In our sample, the risk of progression at two years was 45%.

I think what this slide shows is that if we're going to really make progress in smoldering myeloma, we need to combine all this data across all the institutions and that is being proposed right now through the International Myeloma Working Group, because we're seeing quite a disparity. In particular, the bone marrow greater than 60%, you see across all the studies, we're talking about a cumulative number of patients across all sites of 50 patients. So, it's always a little concerning to be making treatment decisions on the basis of such small numbers and on the basis of retrospective studies, meaning not patients who've been followed consistently from the date of their diagnosis, but rather the charts going backwards. So, I think we need a little bit more information about the true value.

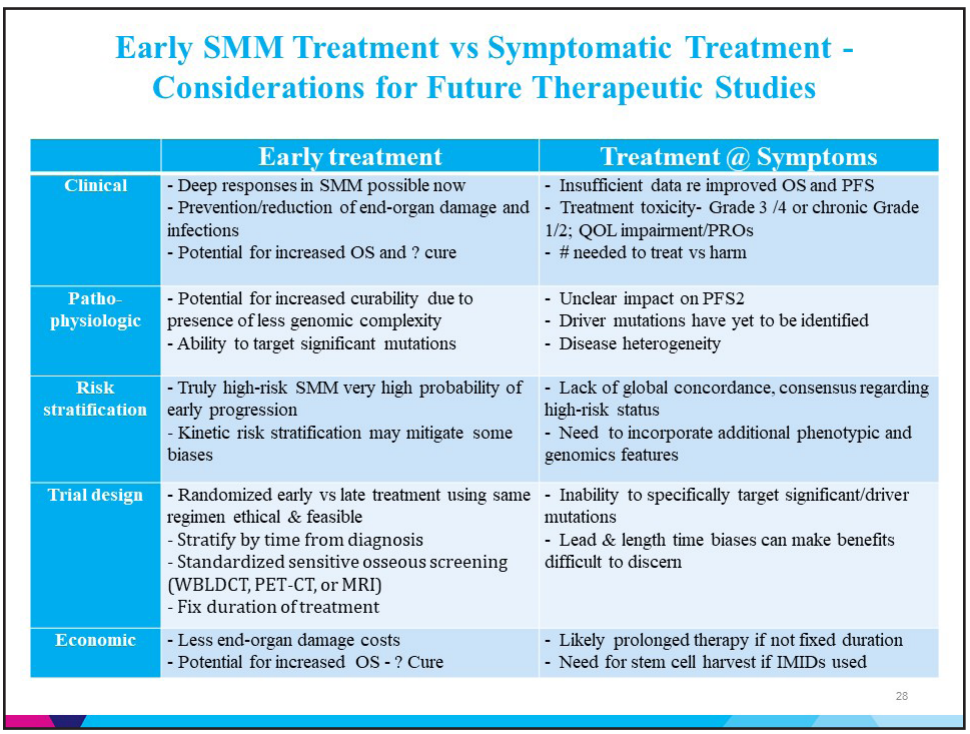
And then the last few slides on this topic are basically a new way of looking at this, which is rather than looking at the baseline, looking at how people do over time, so that maybe it doesn't matter as much what you start with, but how that changes over time. And these are the different labs that we looked at. The Mayo group had already published that the evolving hemoglobin and M-spike did seem to correlate with a higher rate of progression and that is what we found here as well. But interestingly, we also found that the free lights, when they evolved, seemed to also be important, and it wasn't just perhaps the baseline free light chain ratio, but the evolution. And we found that, for example, the patients who did have a

high free light chain ratio change, they had a time to progression of 35 months versus those who didn't have that change, they didn't even actually progress during the period of follow-up. So, suggesting that maybe the kinetics of the disease are equally important as the initial numbers.



Slide 27. Multivariable Modeling to predict 2y PD

And the next slide shows that when you look at all of these different factors and what's called multi-variable modeling, the 3 things that seem to be most important in our group was the marrow being more than 20%, the M-spike increasing over time, and lastly the evolution of the free light chains over time. So, that's basically what our model has shown.



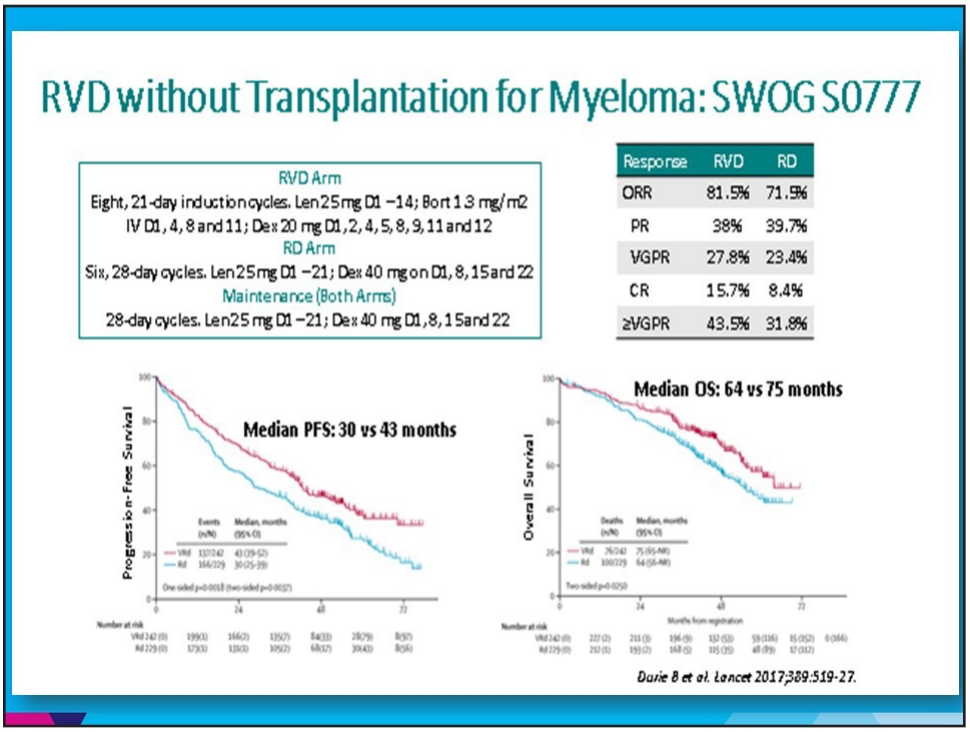
Slide 28. Early SMM Treatment vs Symptomatic Treatment - Considerations for Future Therapeutic Studies

And I think this slide, and we can certainly come back to this in terms of details if people have more questions about smoldering, but it summarizes the pros and cons of early treatment. Certainly, there's a lot of reasons why we are interested in treating early, before people become symptomatic, because we can get deep responses, we can avoid those CRAB symptoms, and potentially we're trying to see if we can get rid of the disease permanently. On the flip side, nothing is without side effect. We need to really make sure that we're going to be able to help these patients. Anybody who's treated myeloma has had patients who've remained asymptomatic for 7, 10 years, even people that you thought were supposed to be progressing. And so to be intervening on patients like that without what we call prospective randomized studies is challenging.

We also need to ideally target whatever is causing the conversion from smoldering myeloma to active myeloma. And as our work highlights, we really need to have a standardized risk classification, we need well-designed clinical trials, and so I think a very important area of clinical research, but probably not yet ready for prime time, where everybody should be being treated off-study, because we need the data.

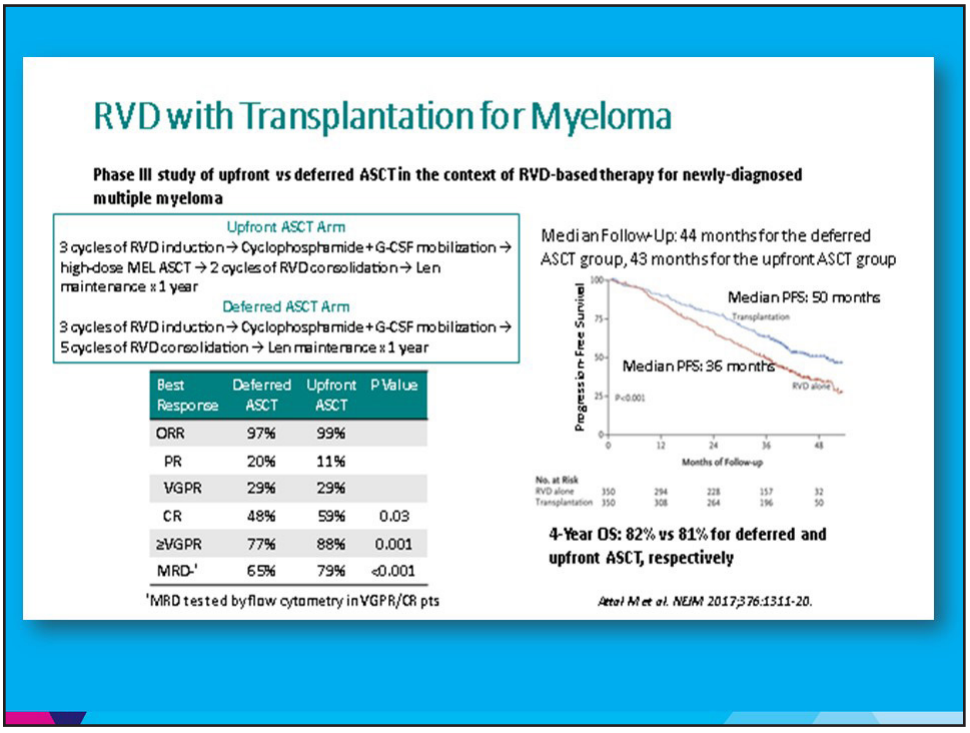
Slide 29. Overview

Moving now to newly diagnosed myeloma, there's a lot of interest in improving outcomes for these patients as well, although we've done a pretty good job for this population.



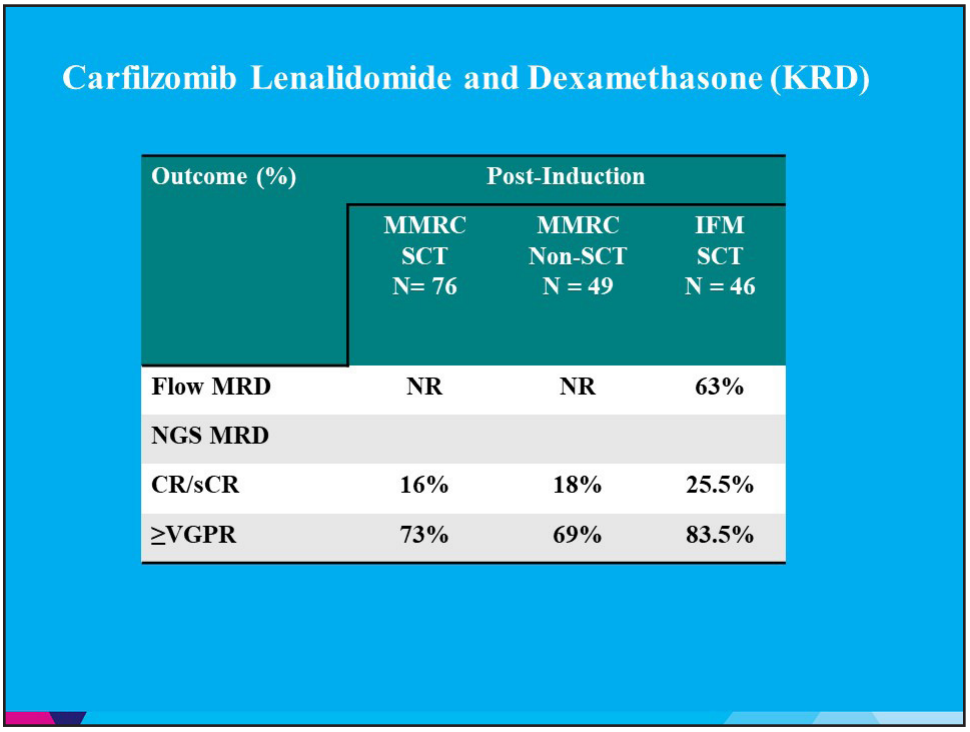
Slide 30. RVD Without Transplantation for Myeloma: SWOG S0777

Shown on the next slide is the SWOG study that was presented and has been published now in Lancet in this year, and this is called the SWOG 777 study. And it's basically something that's been done a lot in the US, but without actual proof data because we believed in so much of the single arm Phase II studies, we didn't really have the randomized studies to support it, but now we see that when you compare RVD, which is lenalidomide or Revlimid®, V is the Velcade or bortezomib, and dex, vs just lenalidomide and dex, we see that the red arm, which has the 3-drug regimen, had better progression-free survival and also lived longer, so overall survival. So, we now see that 3 drugs are better than 2.



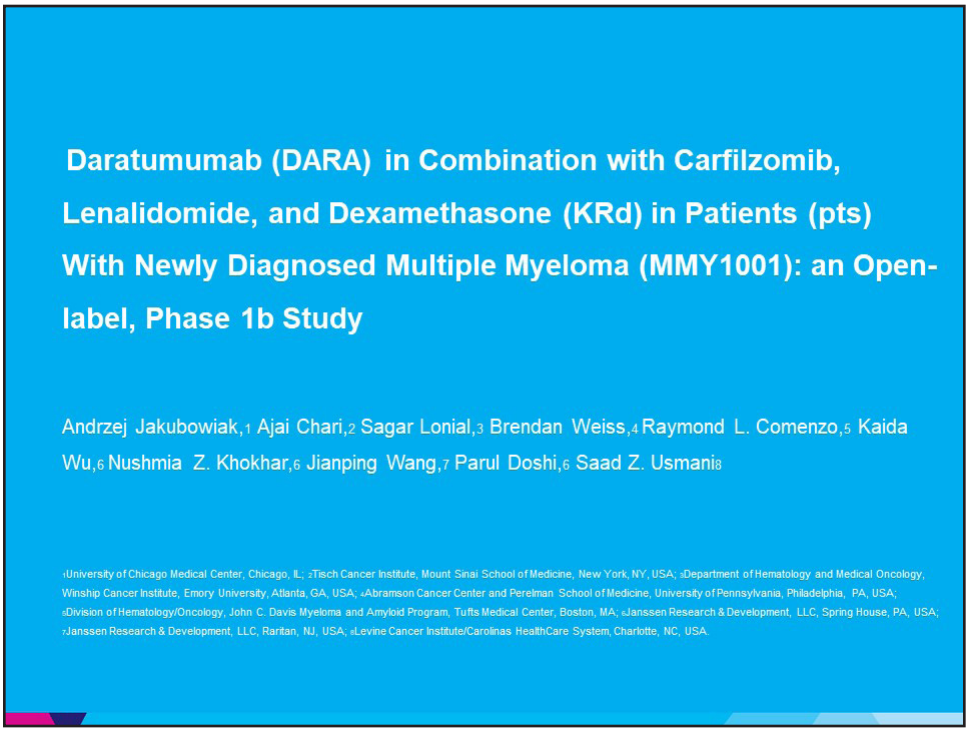
Slide 31. RVD With Transplantation for Myeloma

This was also supported in a clinical trial where not only did the patients get RVD, but they also got transplant early versus delayed transplant, and it looks like in this study so far, this was published in the New England Journal this year, that RVD followed by early transplant seems to be associated with longer survival, although we don't know yet whether it makes a difference, the patients lived comparably in terms of overall survival in both arms. So, remission duration may be longer with early transplant, but perhaps how long people live, we don't know yet because they haven't followed out the patients long enough.



Slide 32. Carfilzomib Lenalidomide and Dexamethasone (KRD)

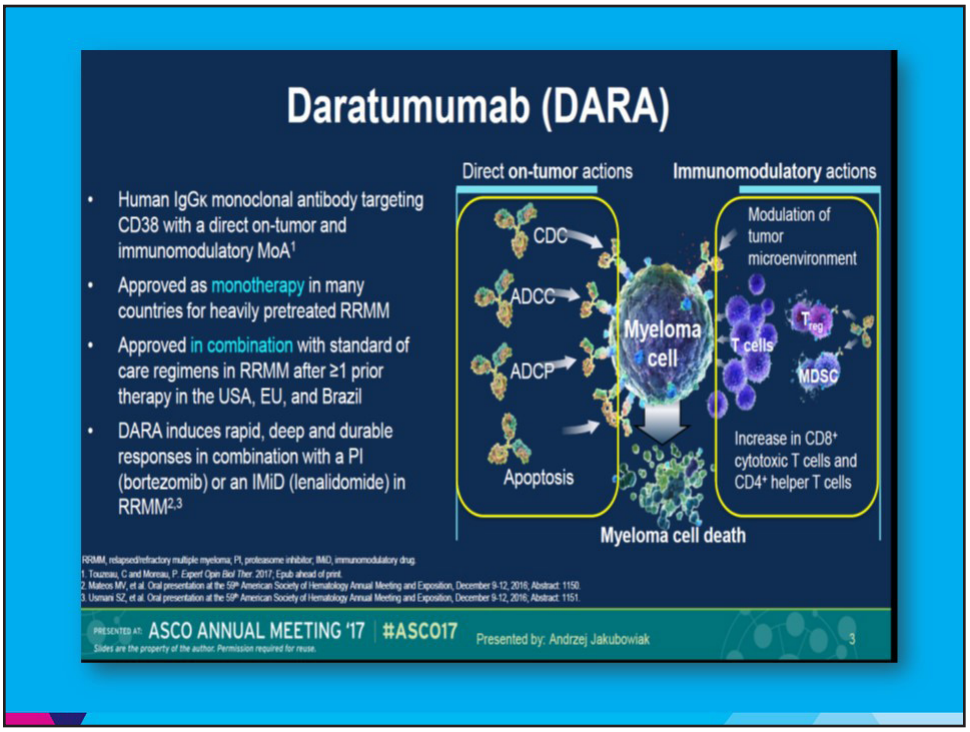
So, if that's our current standard of care, can we do better than that? And the next slide is basically a triplet regimen where bortezomib has been replaced with carfilzomib. Carfilzomib, lenalidomide and dex, or so-called KRd, and there've been 3 small studies that have been presented. And we see that their response rates after the initial induction therapy ranges from 16 to 25%, so this is an excellent response. And then very good partial response or better ranges from 70 to 84%. So, these are very important and very deep responses. What we're not seeing here is the overall response rate. Almost everybody responded and they're getting very deep responses.



Slide 33. Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients (pts) With Newly Diagnosed Multiple Myeloma (MMY1001): An Open-label, Phase 1b Study

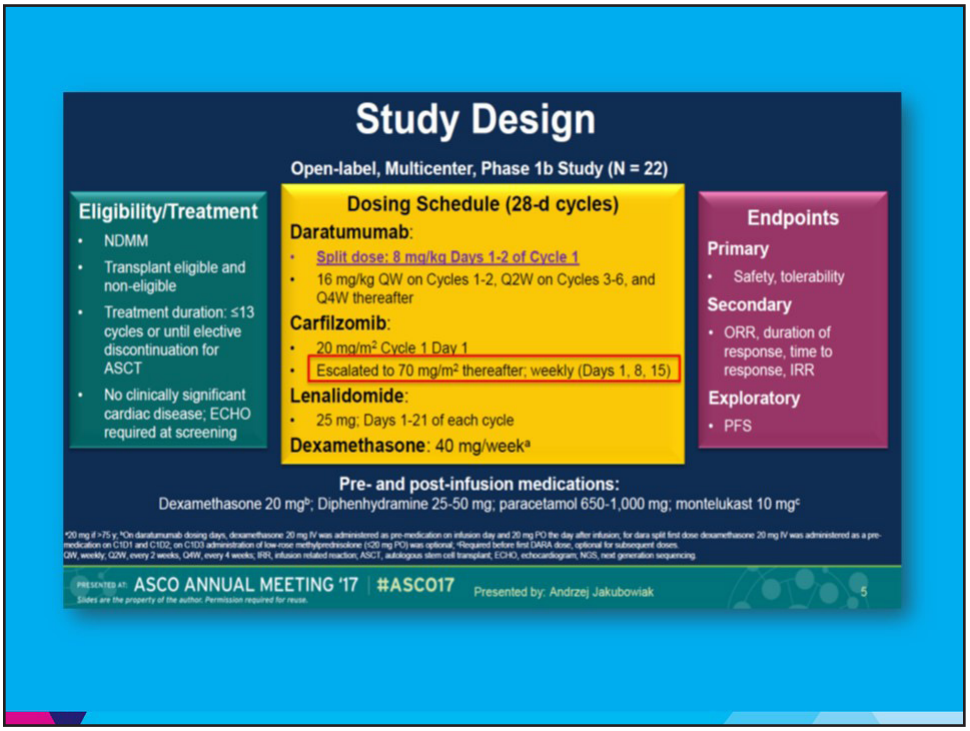
So, if that's the current standard of care, the question then becomes, on the next slide, what happens when you add another agent?

It's important when we add drugs that we don't just add randomly, but we pick drugs that aren't going to have overlapping side effects otherwise, even if there's some potential benefit of activity in terms of efficacy, we may be compromised with the safety side of things.



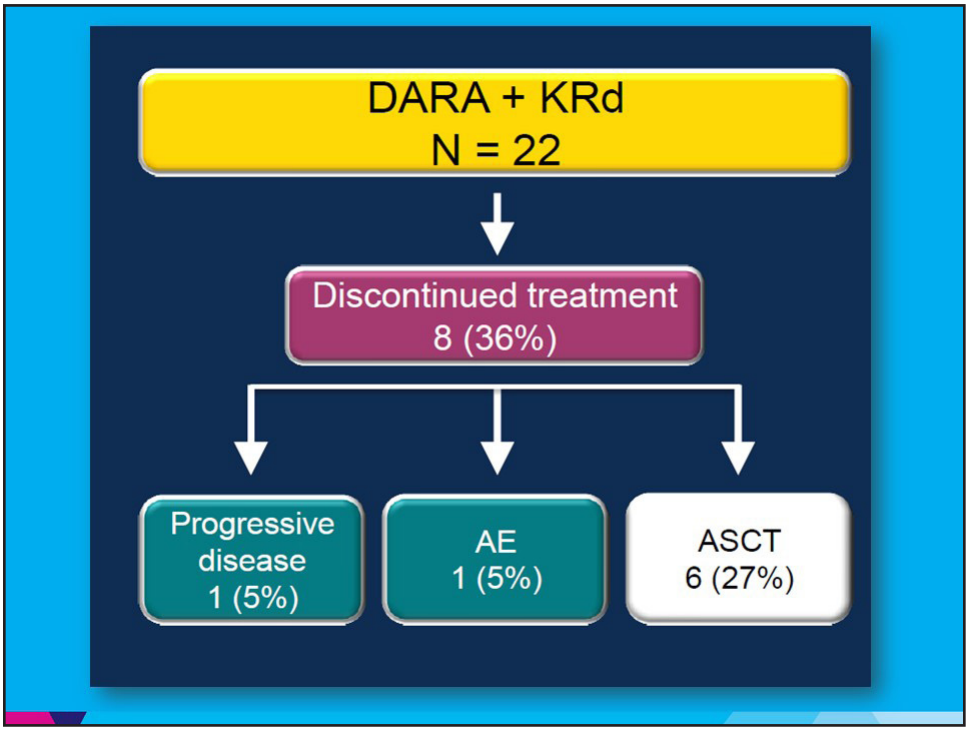
Slide 34. Daratumumab (DARA)

So, this study, which is a Janssen-sponsored study, is daratumumab, which is the new CD38 antibody that was FDA approved, in combination with KRd, for newly diagnosed patients. So, right now, daratumumab is not approved for newly diagnosed patients, but rather in relapsed and relapsed-refractory population. We actually recruited a fair number of patients to this study as well at our center at Mount Sinai. And dara is basically an immunotherapy, if you will, and the antibody attacks CD38. It works by many different actions. It works directly on the tumor, causing cell death, but it also uses the immune system, again, perhaps with the T-cell expansion, to help control the myeloma.



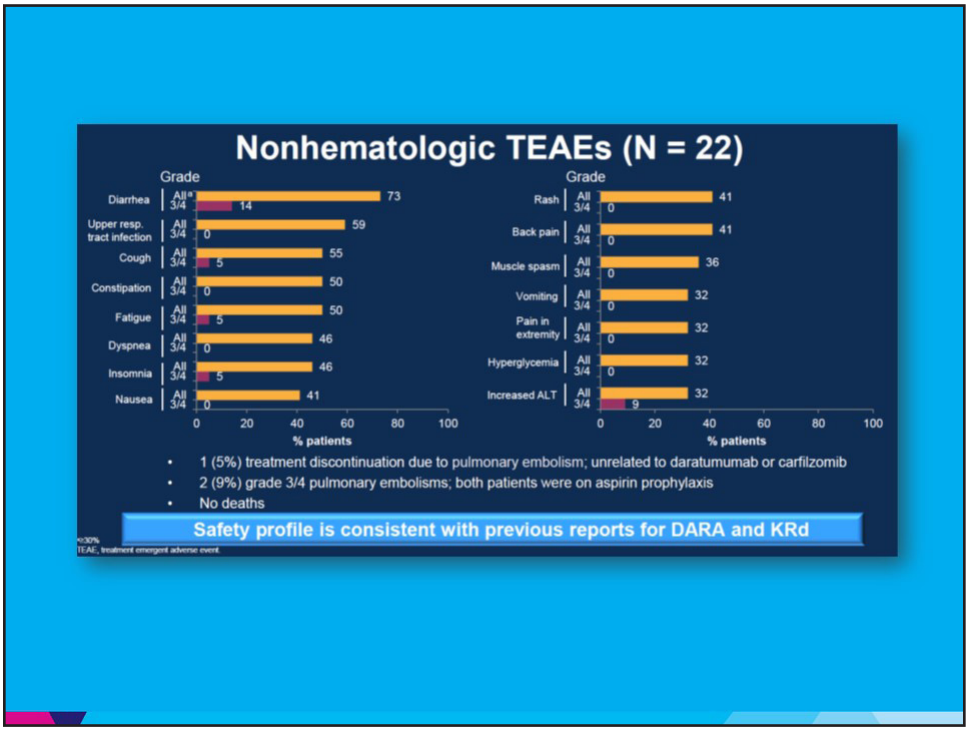
Slide 35. Study Design

On the next slide, we see the design of the study. It was basically newly diagnosed myeloma patients. Everybody got standard doses of carfilzomib, Revlimid or lenalidomide and dex. And daratumumab was also given at the standard dose and schedule. The one difference is that in the first week, the daratumumab was split into 2 days rather than giving it all on 1 day, because now we do have another IV drug, the carfilzomib, that's also given on the same day.



Slide 36. DARA + KRd

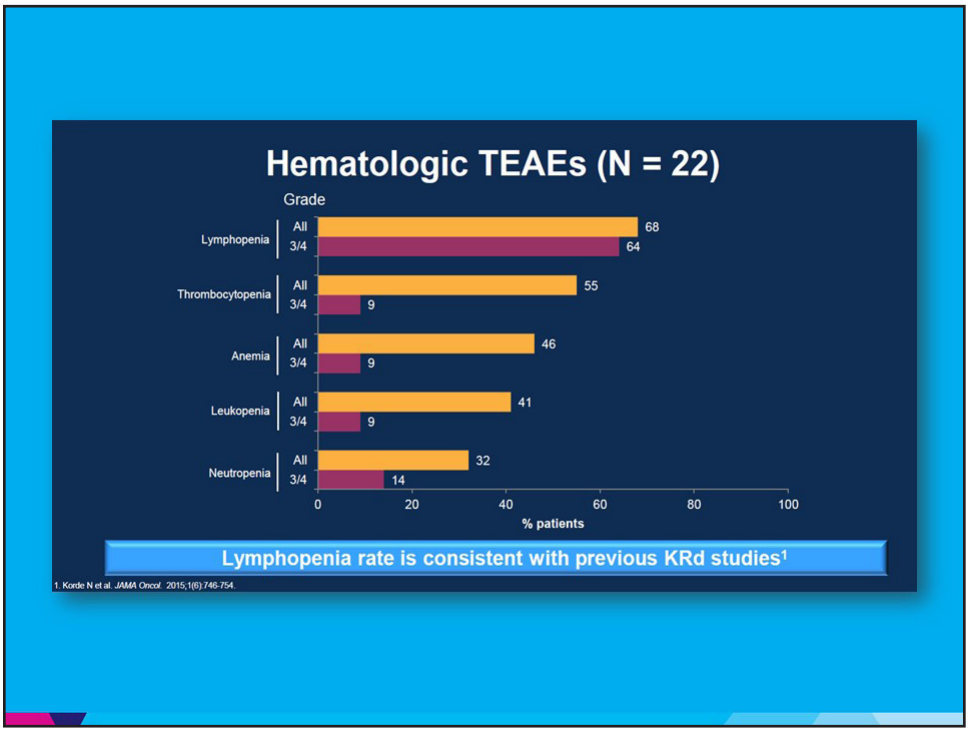
And so with this four drug regimen, it's again a small study, 22 patients, some – the vast majority of patients who discontinued treatment went on to transplant, one for progression of disease and one for side effect or adverse event.



Slide 37. Nonhematologic TEAEs (N = 22)

And the adverse events are shown here. Really the safety profile is pretty much what you would expect from each of the drugs. And again, so things – and you see that the yellow bars are low grade, meaning minor, so although it's diarrhea, but these aren't debilitating, severe, profuse volumes, they're more of considered an inconvenience from patients' perspective. But you see a little bit of upper respiratory, cough, etc. Really in terms of the severe stuff, which is shown in the red, everything is pretty uncommon. There is a little bit of diarrhea, also minor laboratory changes in liver tests, but generally very well tolerated.

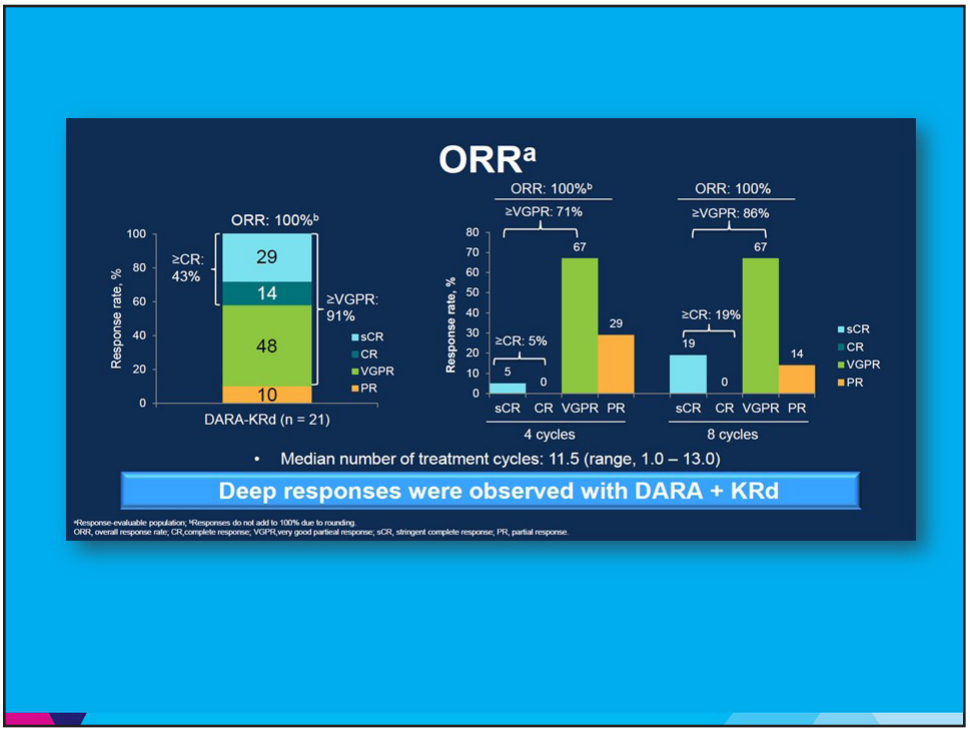
One of the questions always is whether there's any cardiac or pulmonary issues with these treatments because generally myeloma patients are older, so there's a background rate of cardiac issues, but then on top of that these drugs can have different effects. So, there was one discontinuation due to a blood clot and then there were two other blood clots, and even though they were on aspirin. So, we do need to remember that patients who are newly diagnosed and have a lot of myeloma burden and are getting treated, may have an increased risk of these types of complications.



Slide 38. Hematologic TEAEs (N = 22)

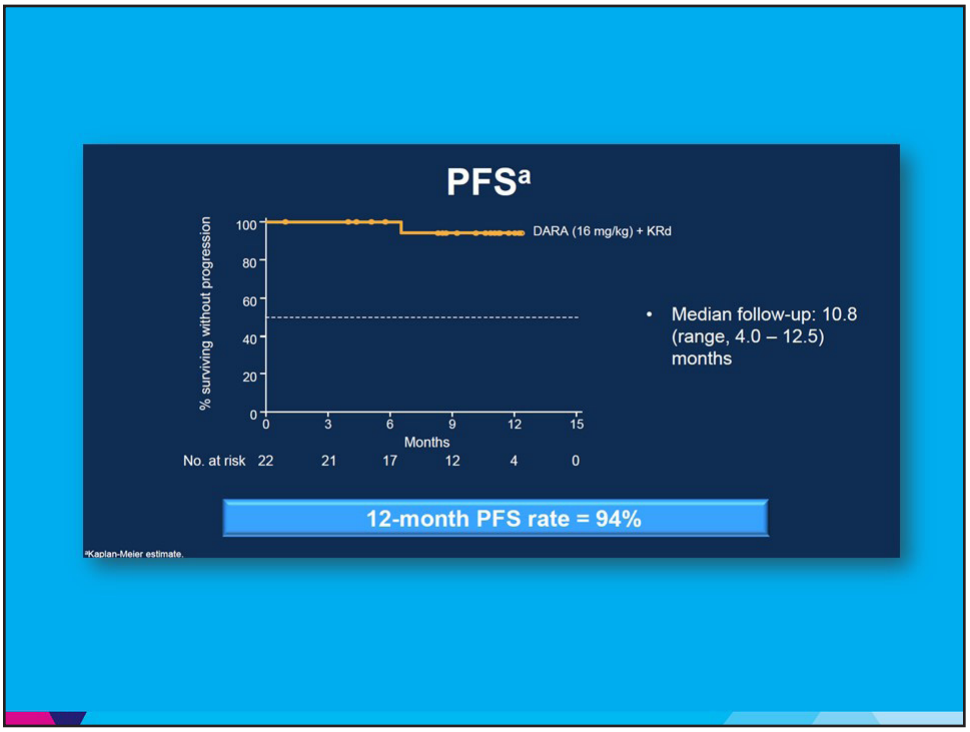
And then the blood counts are shown here.

The blood side effects are pretty straightforward for hematologists and oncologists to manage. Obviously, the marrow could be replaced with myeloma and then on top of that these drugs can lower the counts, but generally these were typical with what was expected, perhaps slightly higher neutrophil rates being low, which is important for preventing infection.



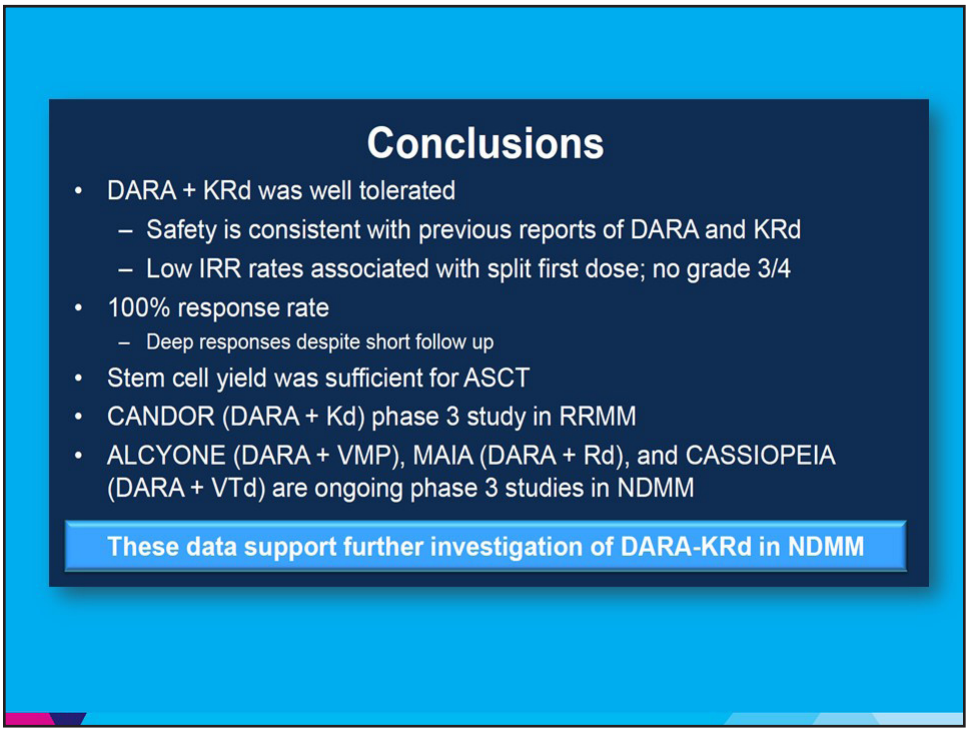
Slide 39. ORR[a]

Shown here is the responses, 100% response rate, meaning everybody had a benefit from treatment, and shown on the left are the depth of response. We had partial response in 10% and then 48% had very good partial response, followed by 14 with complete response, and then impressively, almost 30% with stringent complete responses. So, these are really deep responses overall. And then on the right side they're broken down by four cycles and eight cycles. And as you would guess, as people stay on therapy, the response depth does increase.



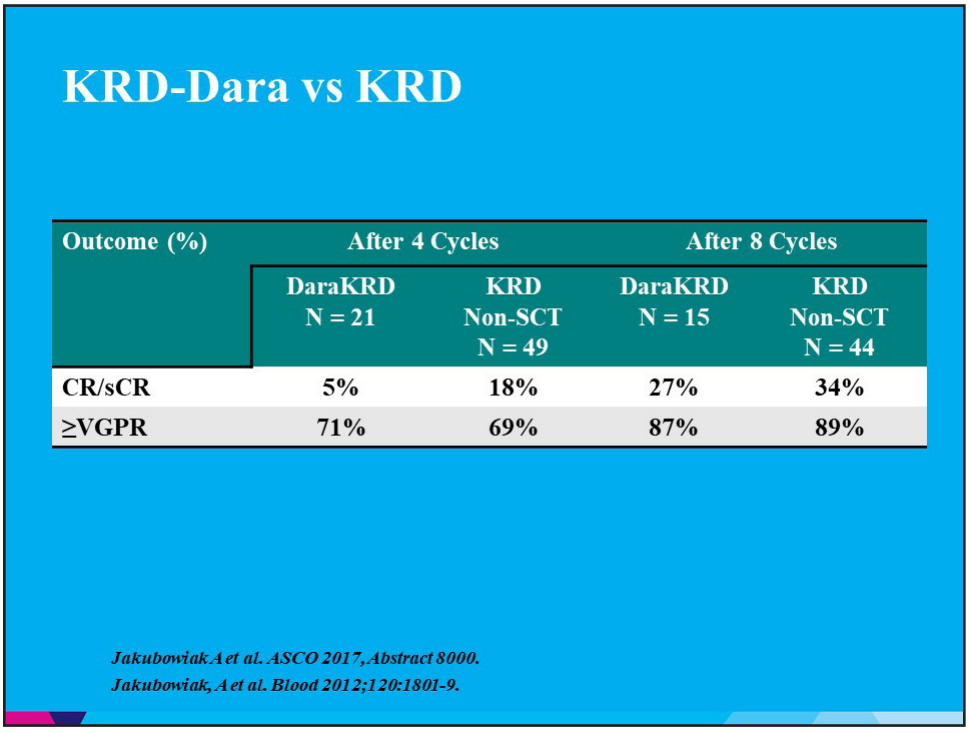
Slide 40. PFS[a]

And this next slide shows that the remission seems to be durable. Hardly anybody has progressed. There was just that one patient, so everybody remains in good remission.



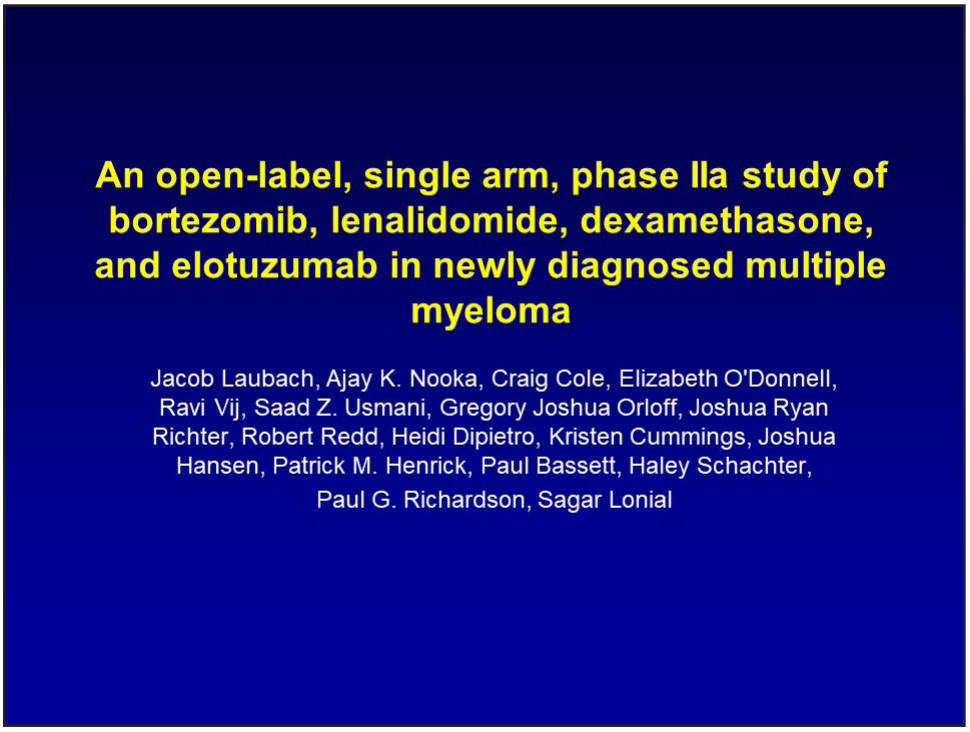
Slide 41. Conclusions

And so, to conclude, this seems to be well tolerated. The infusion reactions were actually lower than when dara is given all in one day, so typically that's associated with about a 50% minor infusion reactions, like tickle in the throat, runny nose, and here it was half that. Everybody responded. Most patients had an excellent stem cell collection. And there's randomized Phase III studies that are going on.



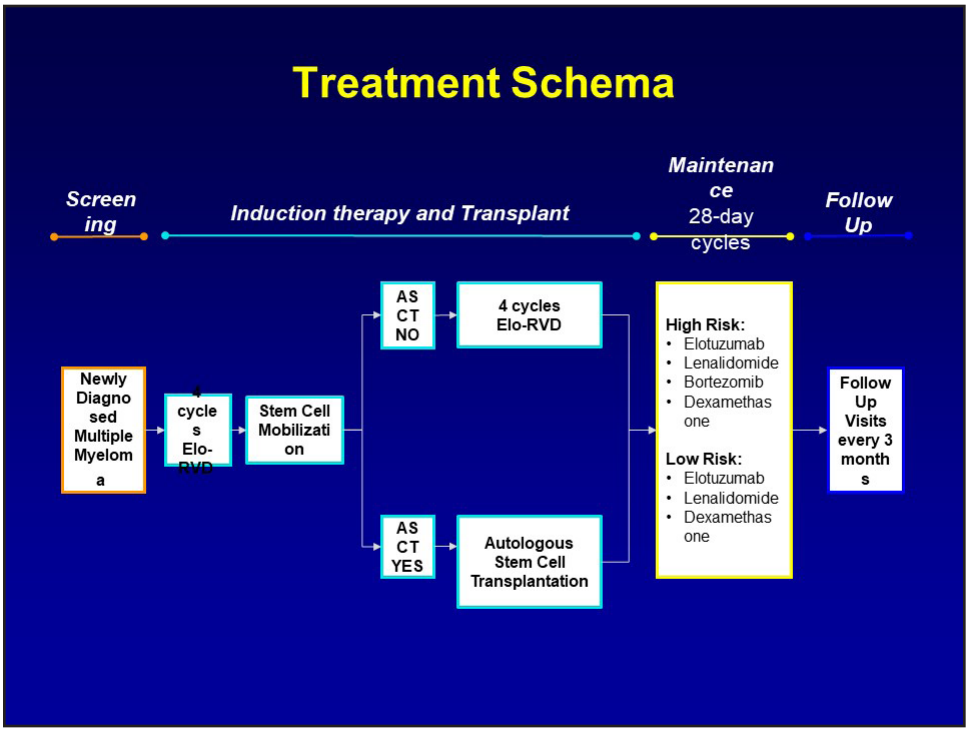
Slide 42. KRD-Dara vs KRD

To just put that into context with what we saw with the previous KRd, so what's unclear always from a single arm study is what is the fourth drug adding, so how much more benefit did we get with dara relative to what we would see with KRd. And so, this is from Dr. Voorhees's presentation with – he was the discussant for this – and basically the response rate with dara KRd after four cycles, 5 versus 18%, very good partial response, 71 versus 69, and then after eight cycles also seeming comparable. So, I think what that's telling us, that we don't necessarily see a clear difference between those two arms, and probably we need more follow-up to see what's the long-term difference in terms of depth of response.



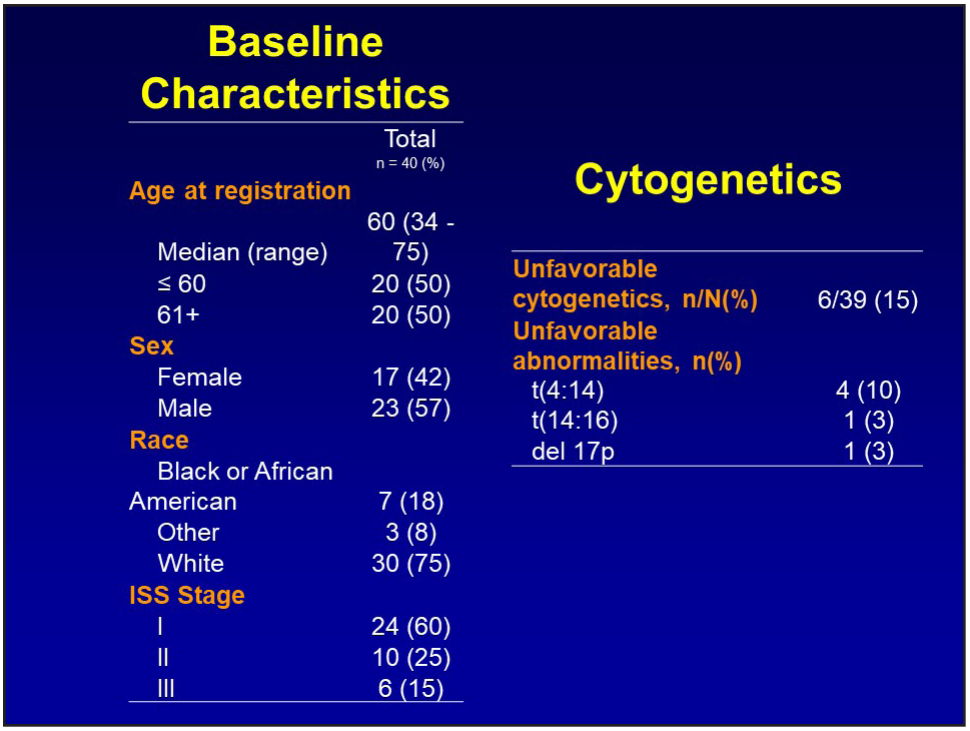
Slide 43. An open-label, single arm, phase IIa study of bortezomib, lenalidomide, dexamethasone, and elotuzumab in newly diagnosed multiple myeloma

This next slide tells us about a different monoclonal antibody called elotuzumab, also for newly diagnosed patients and also being added on top of a triplet regiment.



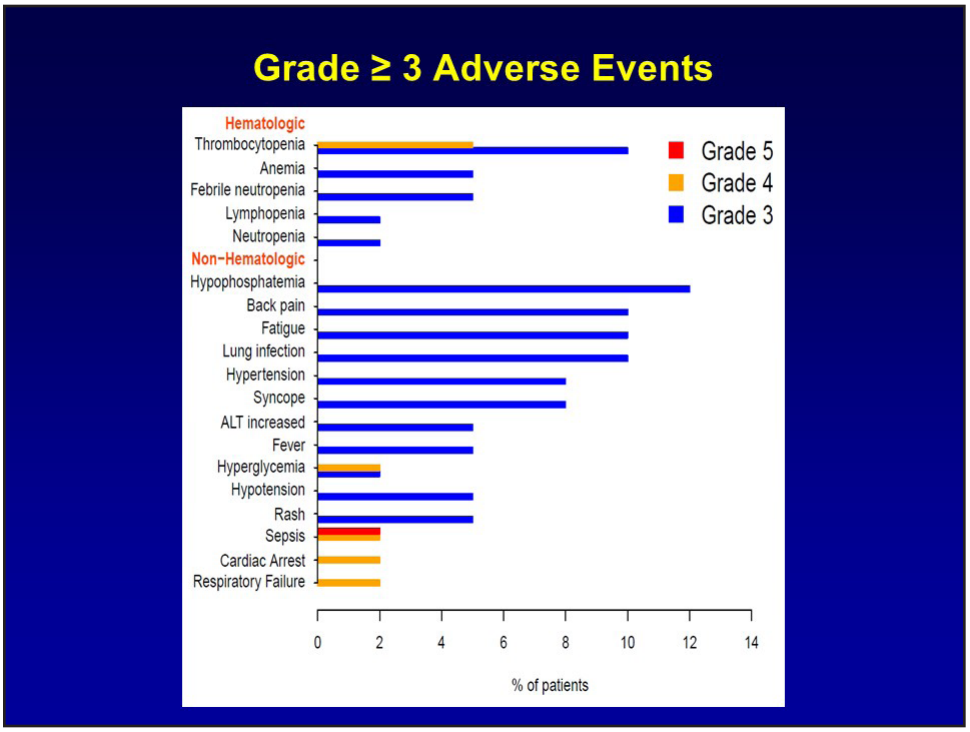
Slide 44. Treatment Schema

Here we're using bortezomib, len-dex, or VRD, RVD, plus elo. This is presented by Dr. Laubach from Dana-Farber. And the study design is shown here. Newly diagnosed patients, everybody got four cycles of the four-drug regimen, had cells collected, and then some went to transplant, some didn't. And then depending on what they got, they had different types of maintenance therapy.



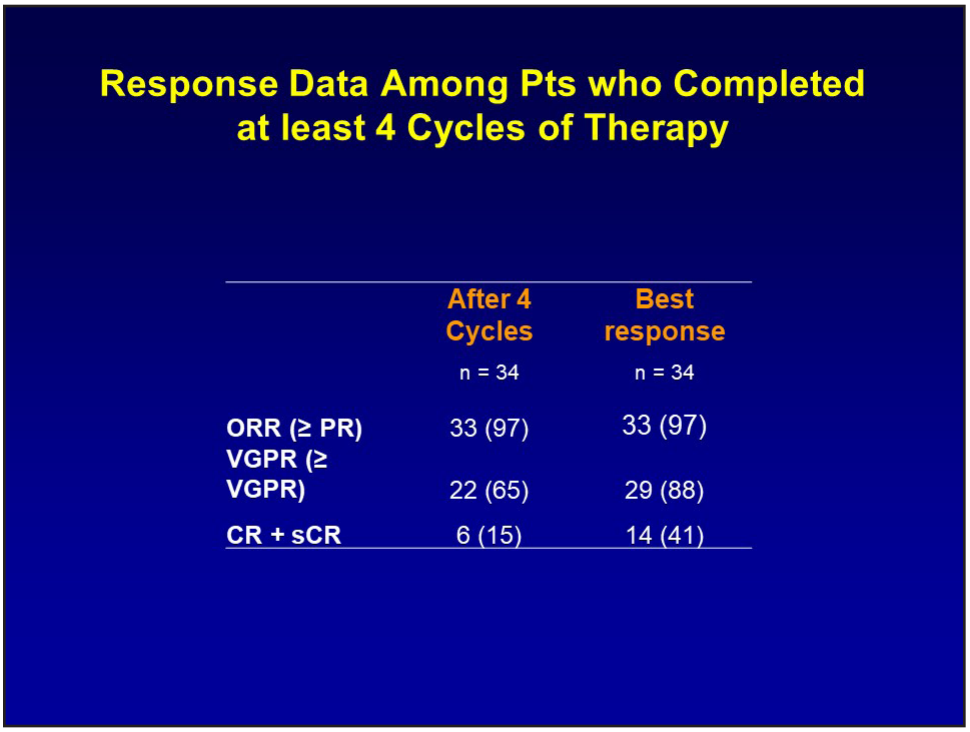
Slide 45. Baseline Characteristics

And this is a 40-patient study, usual characteristics of newly diagnosed patients. About 15% had high risk genetic findings.



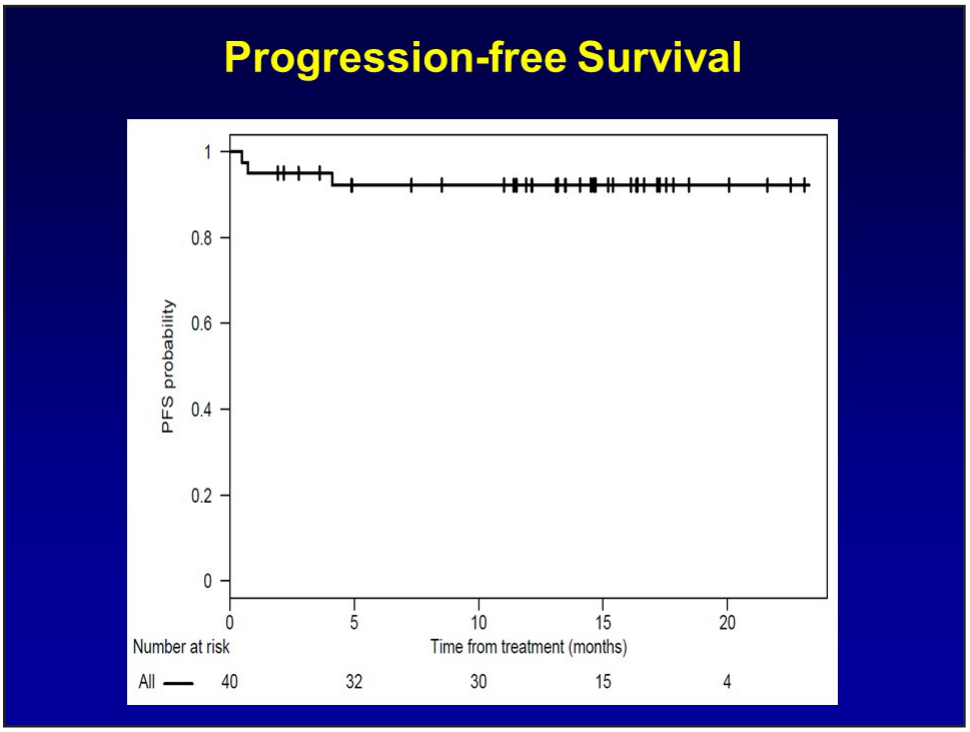
Slide 46. Grade ≥ 3 Adverse Events

And then the side effects are shown here. These are only the severe grade side effects. Generally, kind of what you would expect for – we do see low neutrophils with newly diagnosed myeloma patients getting triplet therapy, and we do see some low platelets. But the one thing that does seem to be something that warrants further study is the infection concern. So, there was some febrile neutropenia, shown at the top, which is low neutrophil count with fever. And there were some sepsis and also cardiac arrest and renal failure. So, again it's hard to know from a single arm study with 40 patients, were these sick patients to begin with or was this treatment-related? And the only way we really can tell those kinds of things apart is when there's a randomized study.



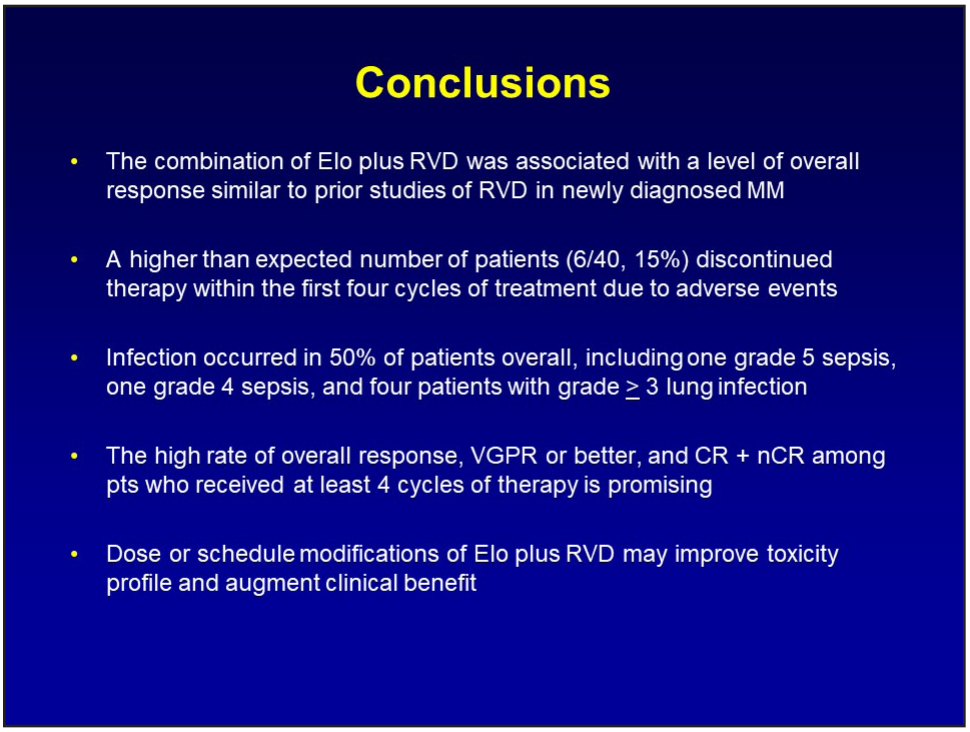
Slide 47. Response Data Among Pts who Completed at least 4 Cycles of Therapy

The best response here is shown here with 34 patients. Again, nearly everybody responded, 97%, including deep responses.



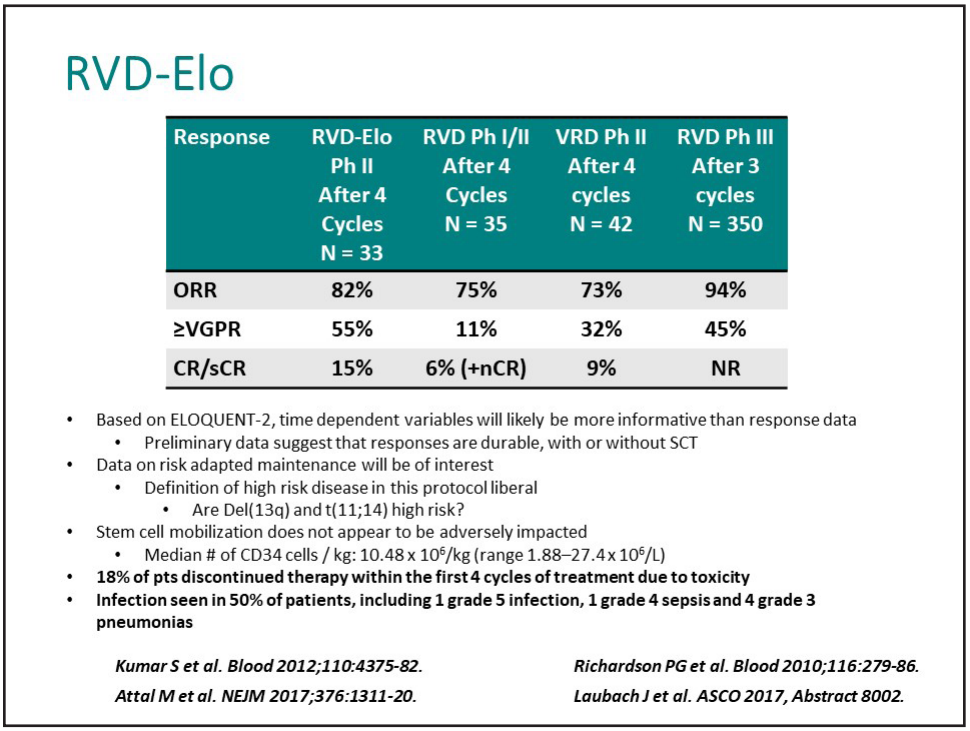
Slide 48. Progression-free Survival

And then the progression-free survival, which is how durable is the response, is excellent. Hardly anybody progressed. And the curve seems to be flat, so that's encouraging.



Slide 49. Conclusions

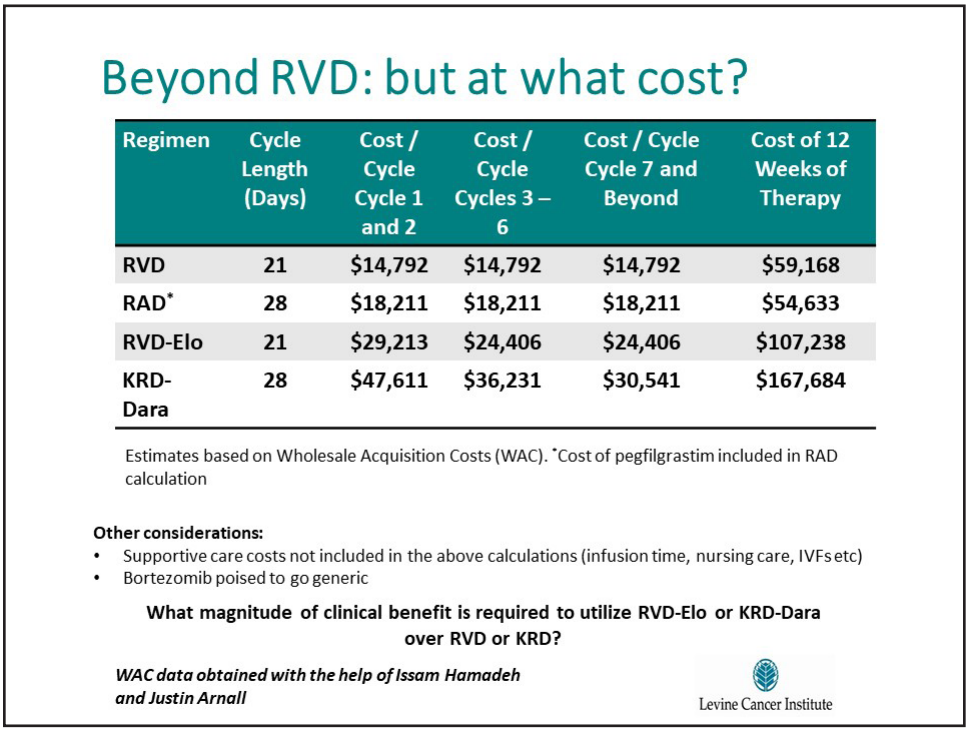
And so, the conclusions are that this seems to have a very good overall response rate. There is a slightly higher than expected discontinuation due to toxicity, including infectious issues as shown in that third bullet. The responses are good. And the question is how do we manage the risk-benefit balance to optimize treatment?



Slide 50. RVD-Elo

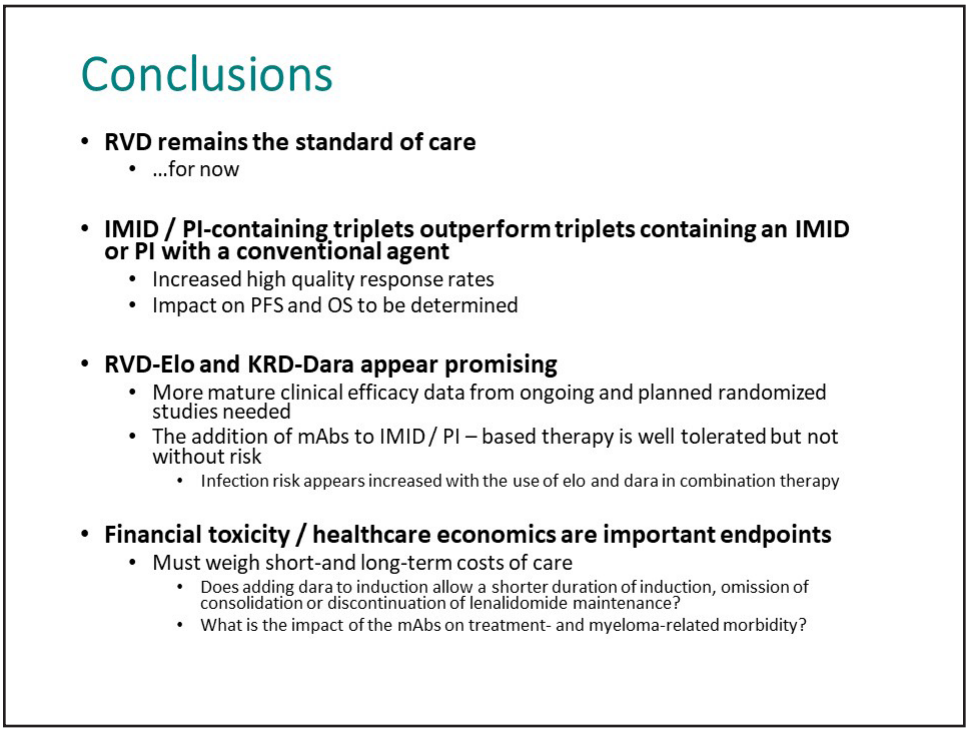
And to compare this particular study, RVD-elo vs the remaining 3, again, this is from Dr. Voorhees's table, in general we don't like doing these because it's not appropriate to compare across studies, but just to get a sense of whether we're

seeing an interesting signal that needs to be further studied, the response rate here is 82%, very good partial response, 55%, so that does look pretty good compared to the other studies, but I think again we need more time and there's that question about an infection concern.



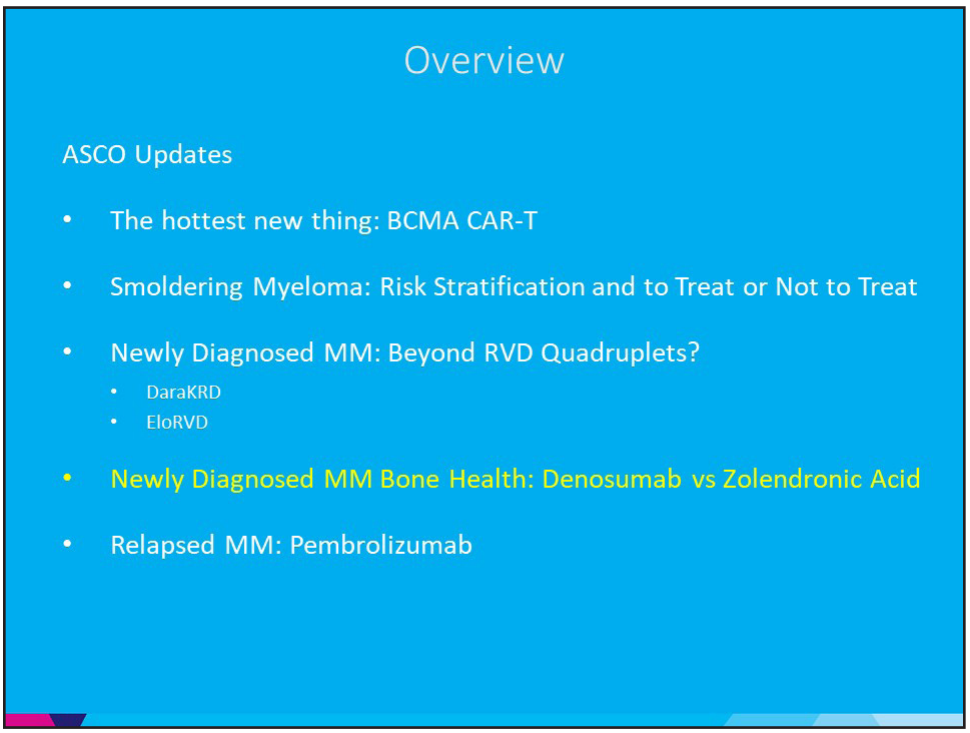
Slide 51. Beyond RVD: but at what cost?

And Dr. Voorhees also raises an important question for oncology, which is when we add a fourth drug, what is the impact on cost relative to the benefit? And so this just shows the cost of these different therapies. First is RVD, cost per cycle is shown there, $15,000, and then for 12 weeks, about $60,000. And then when you add elo or dara, the costs do go up significantly. Obviously clinical benefit is the most important, but going forward, a lot of oncology presentations are also keeping in mind cost to determine the risk-benefit cost ratio, if you will.



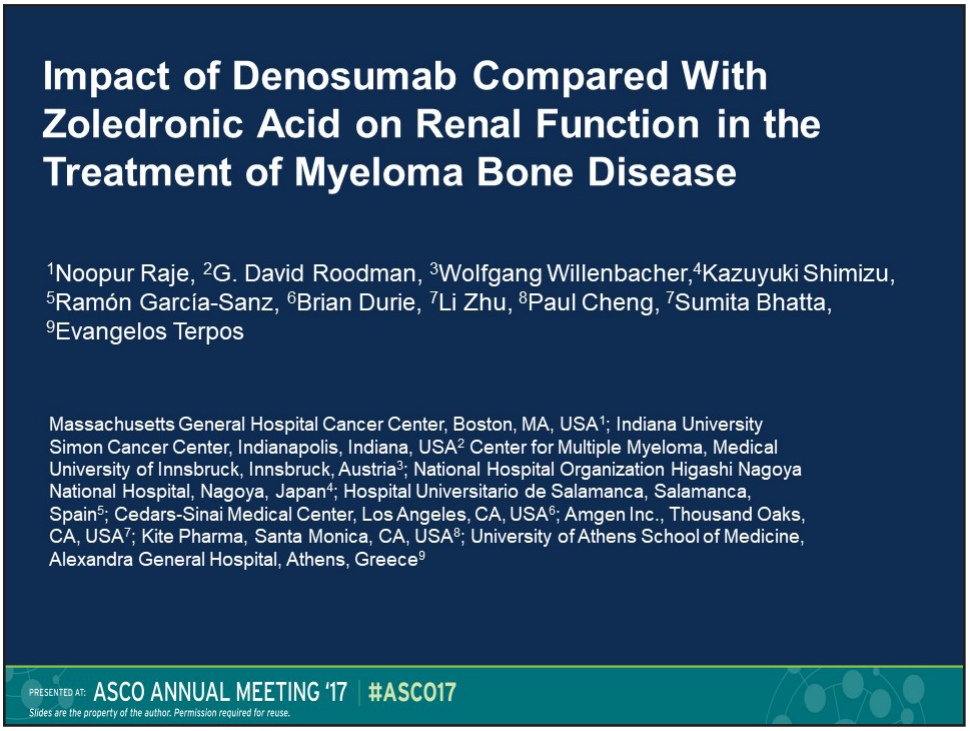
Slide 52. Conclusions

And to summarize, I think for the newly diagnosed studies, we see that RVD still seems to be an excellent standard of care. The vast majority of patients respond beautifully to that. And then the question is whether these novel antibodies like elo or dara add to that. I think the concern is we need more follow-up with these with respect to the duration of the remission, and also, we need to think about how transplant fits into this as well. If you're going to do the transplant and get a very deep response with that as well, what is the role of the monoclonal? So, a lot of interesting questions being raised and warrant further studies.



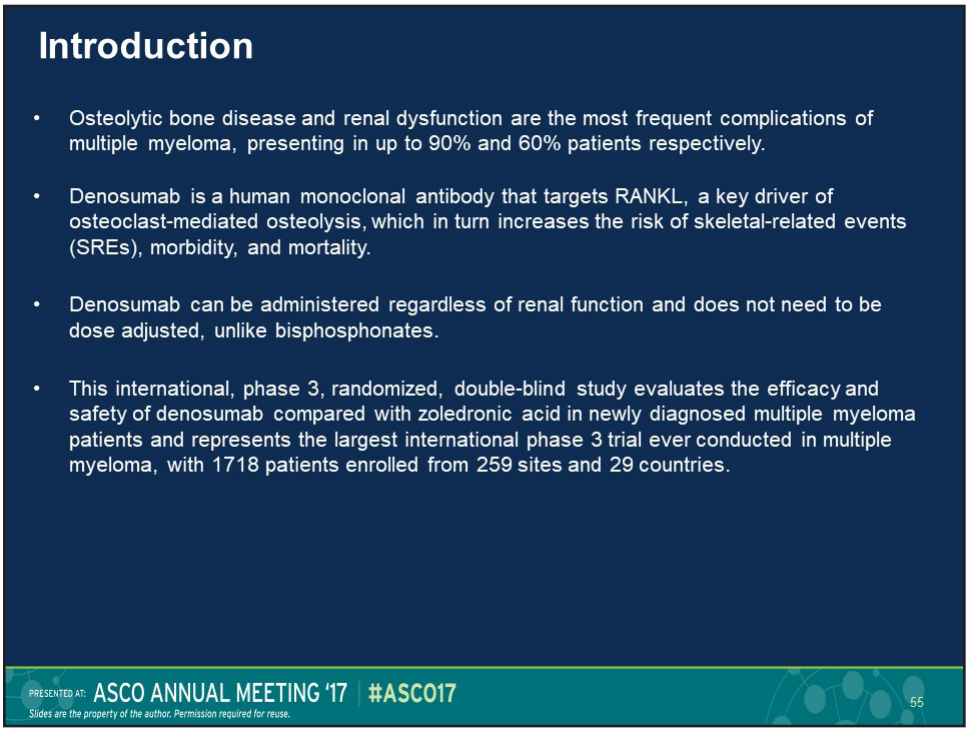
Slide 53. Overview

Moving now to something relating to bone health. You've probably all heard about zoledronic acid or Zometa®. And there's another drug that's actually already FDA approved for osteoporosis called denosumab or Xgeva®, and this is now being studied in cancer. It's already also approved for breast and prostate cancer, but hasn't been to date approved for myeloma.



Slide 54. Impact of Denosumab Compared With Zoledronic Acid on Renal Function in the Treatment of Myeloma Bone Disease

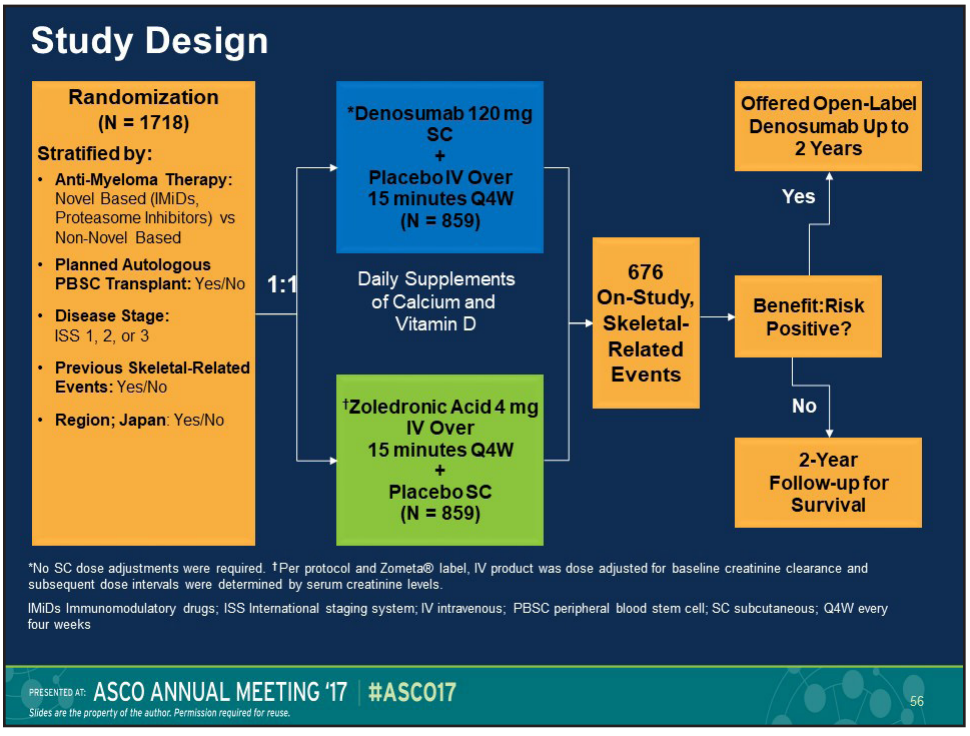
And this was presented by Dr. Raje from Mass General, and basically, it's the impact of denosumab versus zoledronic acid in patients with myeloma bone disease based on their renal function.



Slide 55. Introduction

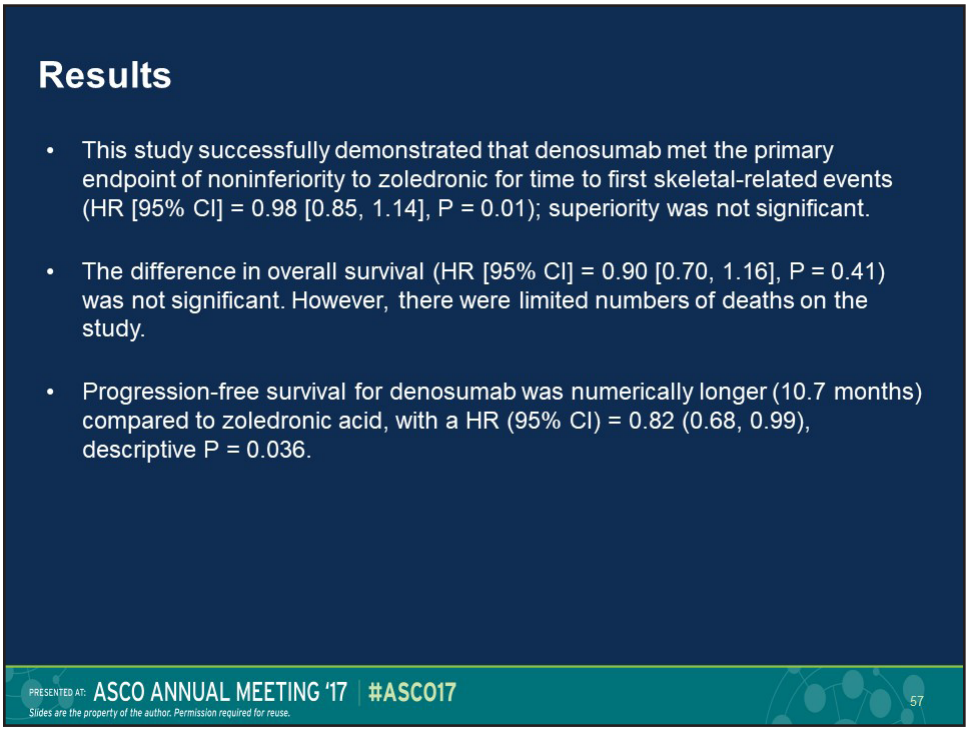
And we know that myeloma bone disease is an important complication of the cancer. The drug denosumab is an injection under the skin, so it's a subcutaneous injection that targets a protein called RANK ligand, which seems to be involved in destruction of bone, and perhaps blocking that can reverse or help prevent further bone damage.

And this is a randomized Phase III study and it's actually quite a sizable study, 1,700 patients.



Slide 56. Study Design

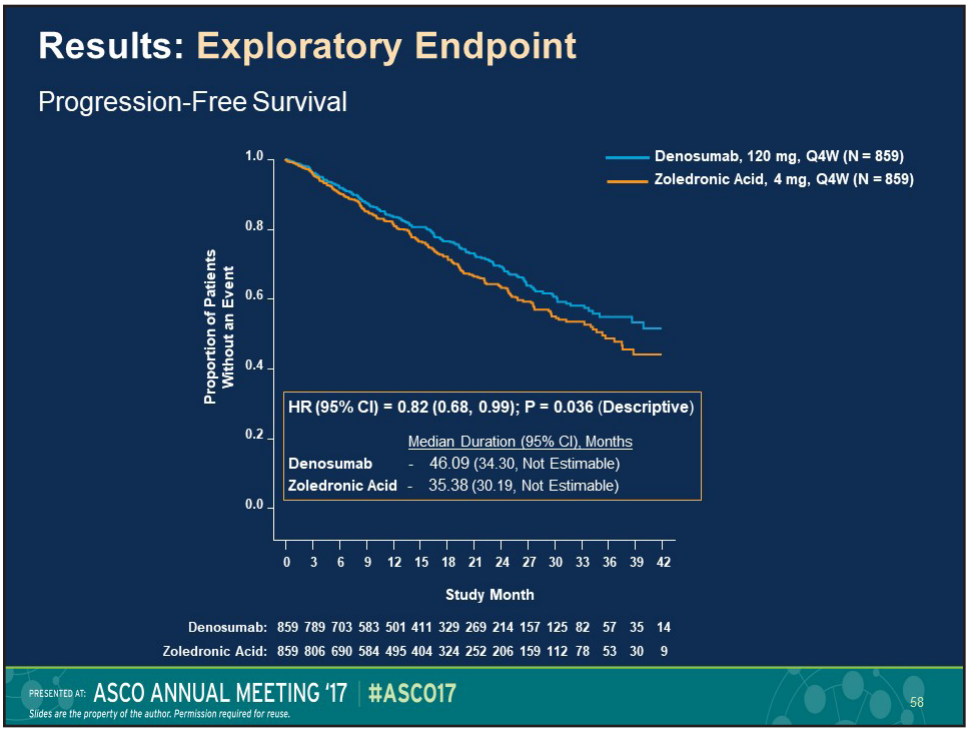
And on the next slide we see the design. And basically, these are newly diagnosed patients. They were being treated with whatever the treatments their local doctors wanted them to get. And then randomization was either to denosumab, the subcutaneous injection, versus a placebo. And then zoledronic acid or placebo in the skin. So, everybody was getting active drug with the placebo of the other arm. And the reason this needs to be done is because if you're giving a skin injection in the denosumab and an IV injection in the Zometa or zoledronic acid arm, to maintain everybody being blinded, there has to be that placebo control.



Slide 57. Results

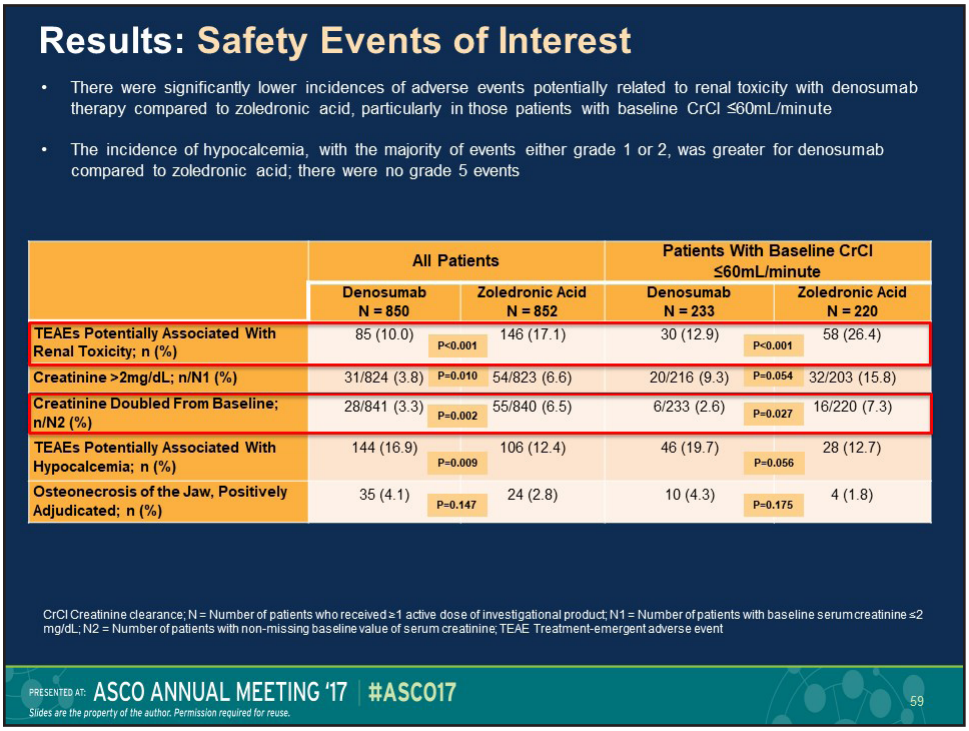
And then the primary endpoint was looking at the skeletal events or bone complications.

And what we see here is that the primary endpoint, which was that these two drugs were comparable in preventing bone damage, was in fact met, so there was no difference in the 2 groups. Patients, in terms of how long they lived, there was not significant difference there. But very interestingly, and maybe even unexpectedly to see this big a difference, the denosumab remissions lasted on average 10.7 months longer than zoledronic acid.



Slide 58. Results: Exploratory Endpoint

And that's shown in this curve here, where the blue line is the denosumab and the orange line is the zoledronic acid, and we see that there was a significant improvement in progression-free survival. So, suggesting that maybe targeting this RANK ligand might actually also help outcomes in terms of myeloma remission.

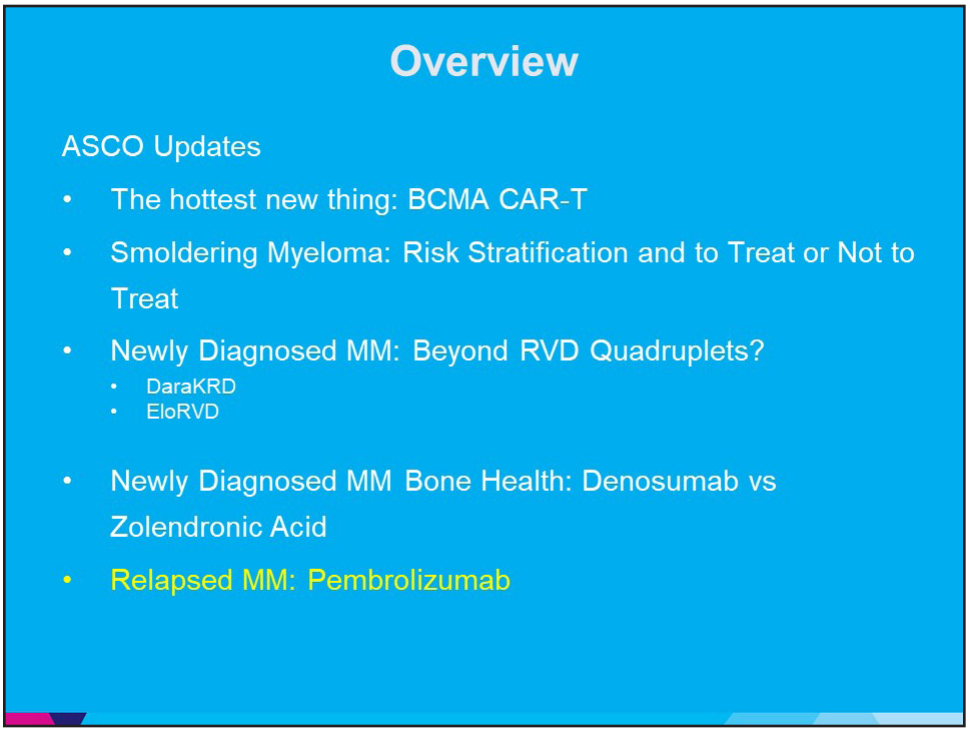


Slide 59. Results: Safety Events of Interest

The other interesting thing about this, which was the purpose of this abstract, was to look specifically at the kidney issues, because we know that up to a third of myeloma patients will have renal insufficiency or kidney issues, and zoledronic acid

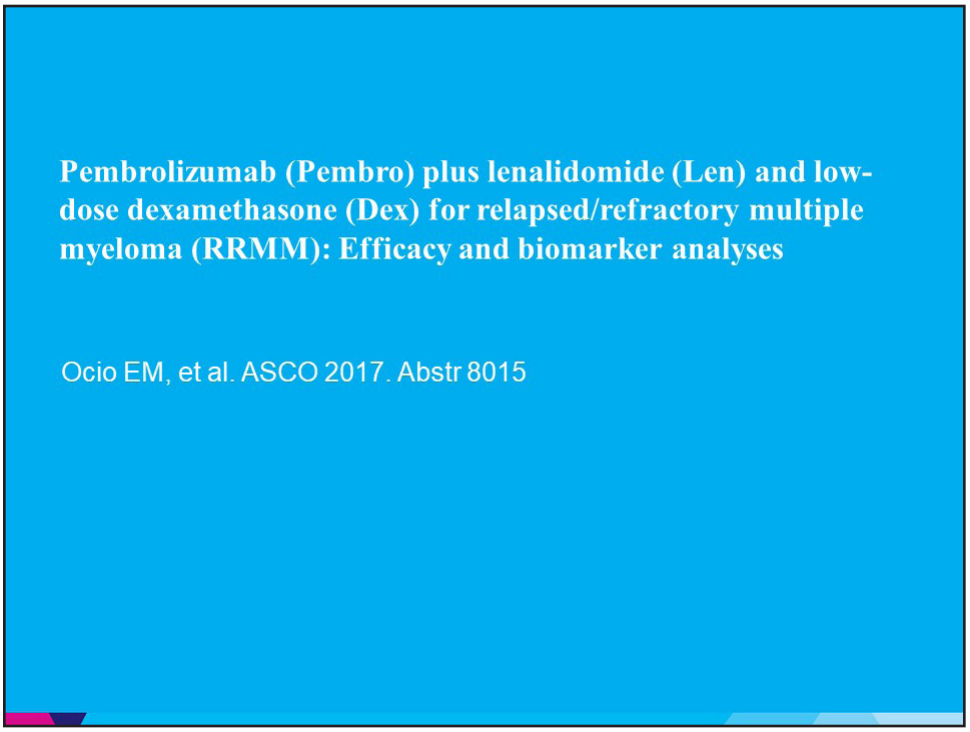
has been known to potentially exacerbate that. And what we see here is that when you compare the two arms, was there more renal toxicity in one or the other. We see it was 10% in denosumab versus 17% in zoledronic acid, so higher in the zoledronic acid. And on the right-hand side of this graph, it's for particularly patients who had renal insufficiency less than 60, and there it's 12.9% versus 26.4%. So, in people who had baseline kidney problems, denosumab seemed to have a lower side effect profile. And in terms of people whose kidney function doubled, that happened more commonly in both groups of patients, almost double with the zoledronic acid, so suggesting that maybe especially for people with renal insufficiency, this may be a better drug in terms of preventing the bone side effects, but also avoiding further renal issues.

The two things to keep an eye out for are calcium, because denosumab does lower the calcium more, so we did see 16.9% reduction in all patients versus 12.4% that had to come off for – or for significant calcium being lowered. And then again that did also seem to happen in people with renal dysfunction at baseline. And the other important thing, the osteonecrosis of the jaw (ONJ), which is a known complication for the entire drug class, was slightly more noticed in the denosumab arm, but was not found to be statistically significantly different. So, something that we always encourage all of our patients starting these drugs, to get dental clearance, because the biggest risk factor of ONJ is to have a tooth pulled after getting these drugs for a while.



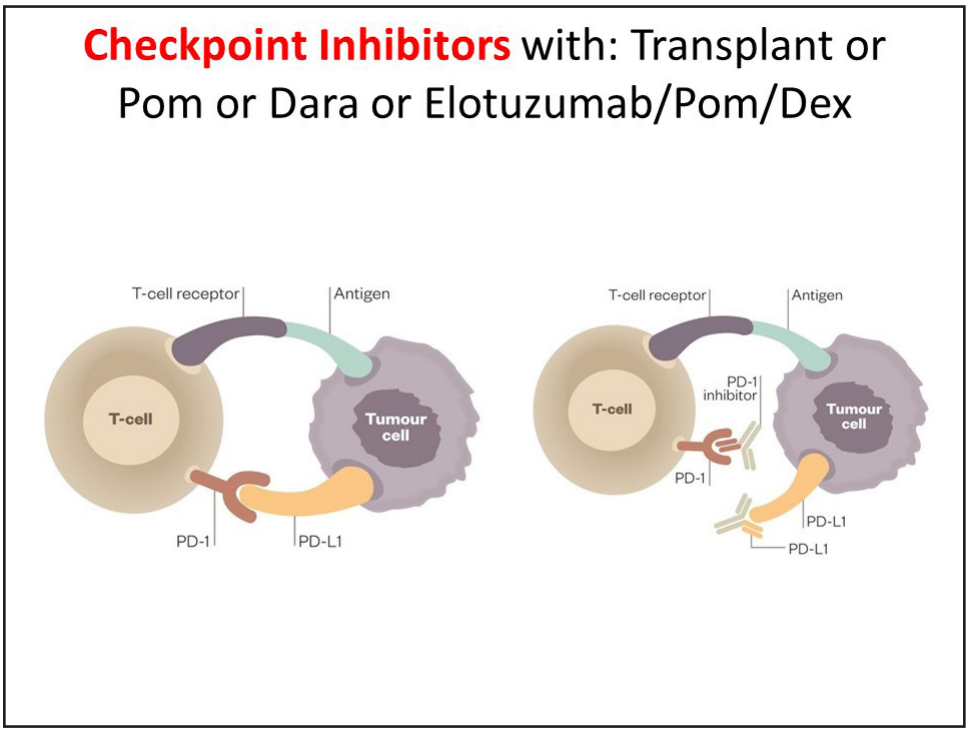
Slide 60. Overview

And then the last brief discussion from ASCO was pembrolizumab. This is for relapsed myeloma now.



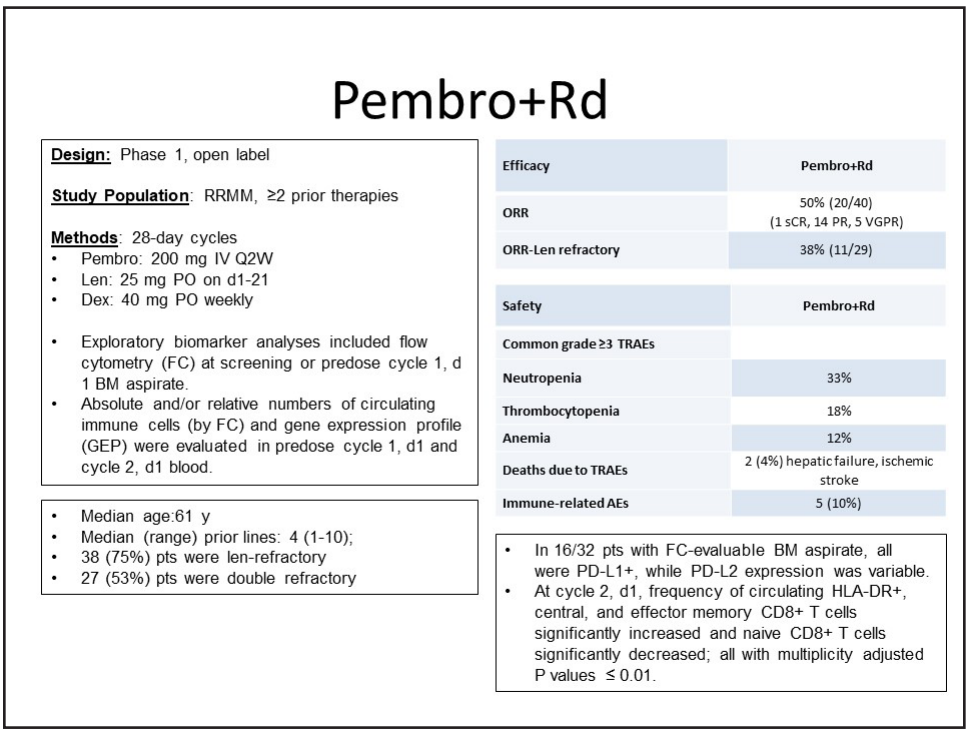
Slide 61. Pembrolizumab (Pembro) plus lenalidomide (Len) and low-dose dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): Efficacy and biomarker analyses

And this was a study from a Spanish group looking at this drug called pembrolizumab plus lenalidomide and low dose dex, for relapsed-refractory myeloma. And this is looking at efficacy and biomarker analysis.



Slide 62. Checkpoint Inhibitors with: Transplant or Pom or Dara or Elotuzumab/Pom/Dex

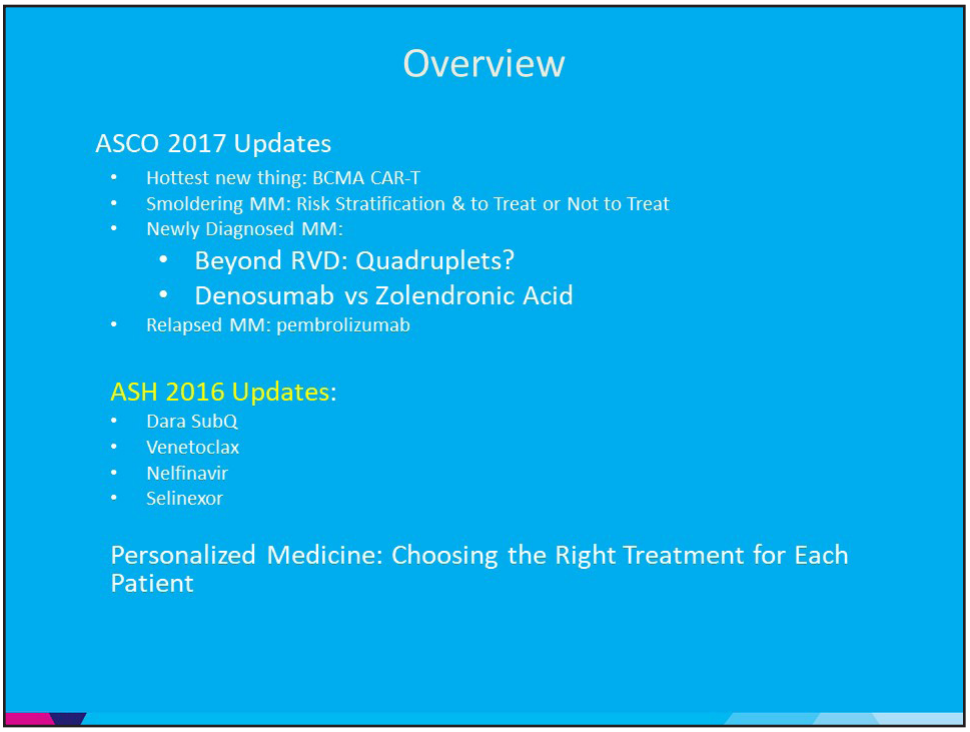
And basically, this group of drugs, which pembro falls into, is called the checkpoint inhibitor. And on this next slide you see the schematic between the T-cells and the tumor cells, and they're basically – if the tumor cell wasn't smart, the T-cell would recognize the tumor cell and kill it. But the tumor cells, and this isn't just myeloma, it's true of bladder, lung, many different cancers, cancer cells have basically cloaks to prevent them from being seen by the T-cell, and those cloaks are known as these PD-L1 or PD-1 related proteins. And when we give antibodies to block the cloak, the T-cell suddenly recognizes the cancer again and is able to help kill the myeloma.



Slide 63. Pembro+Rd

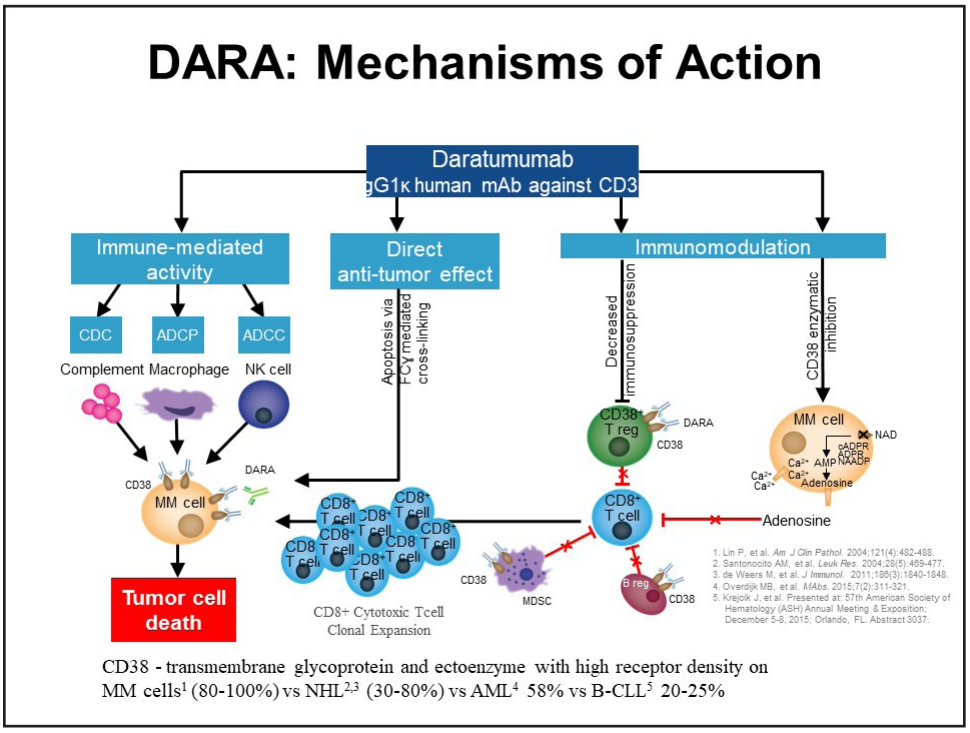
This isn't the first time this has been studied, but at ASCO this was the only related presentation. And it was basically patients who got len-dex with this third drug. It was a relatively small study and the patients – what was interesting is that even in people who were refractory to lenalidomide, so it was a 40-patient study overall, but about 30 of them were refractory to lenalidomide, even 38% of them had a response, suggesting that maybe we can use this drug to help re-sensitize myeloma to cancer therapies such as the pembrolizumab.

And this drug has also been studied with – and the class has been studied with pomalidomide. So, it just gives us another option of maybe extending some mileage out of our drugs that we currently have approved. They don't work by themselves and currently this would be considered an off-label use. But checkpoint inhibition is a hot area in all of oncology.



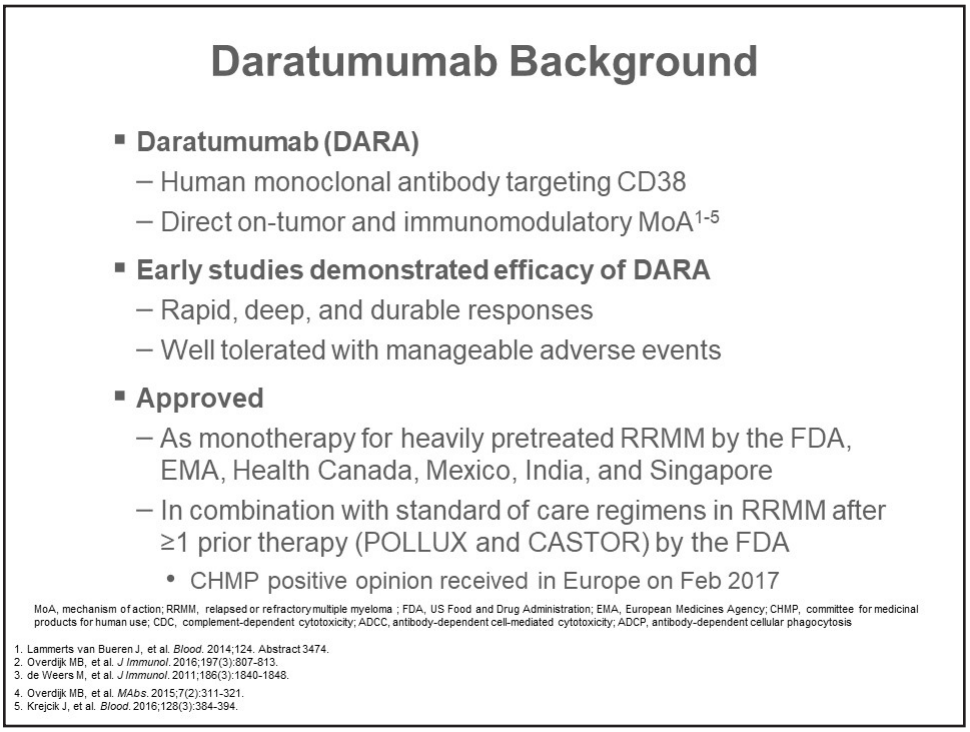
Slide 64. Overview

So, that was the bulk of our presentation today, was the ASCO. I'll briefly talk about the ASH updates that you probably – may have already heard about, because this was from December.



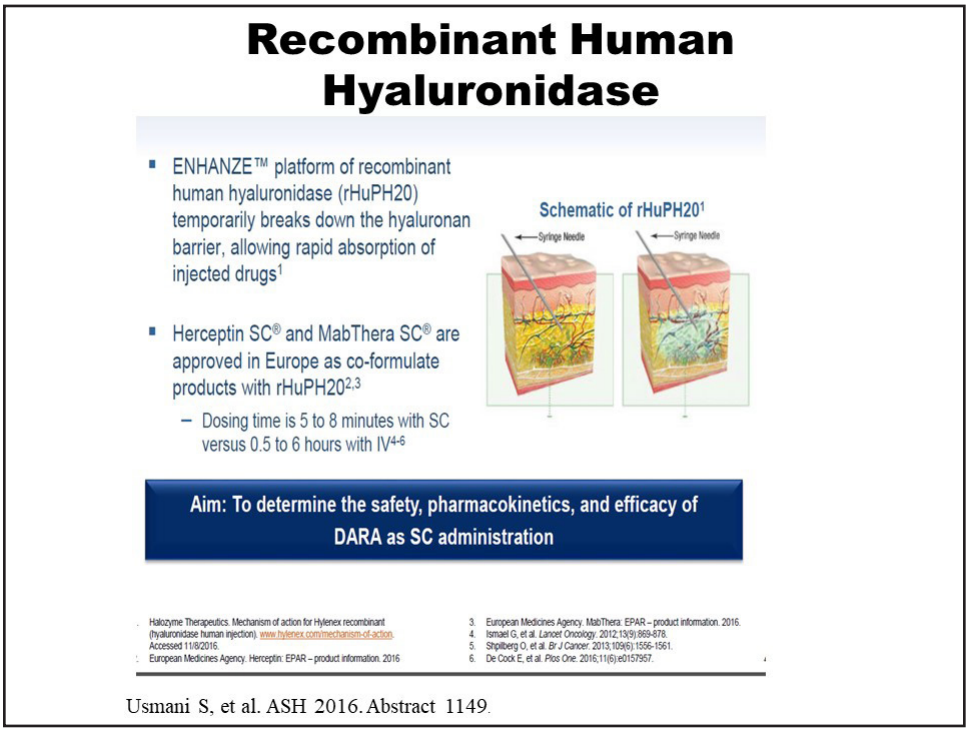
Slide 65. DARA: Mechanisms of Action

We've already talked about daratumumab and how it works.



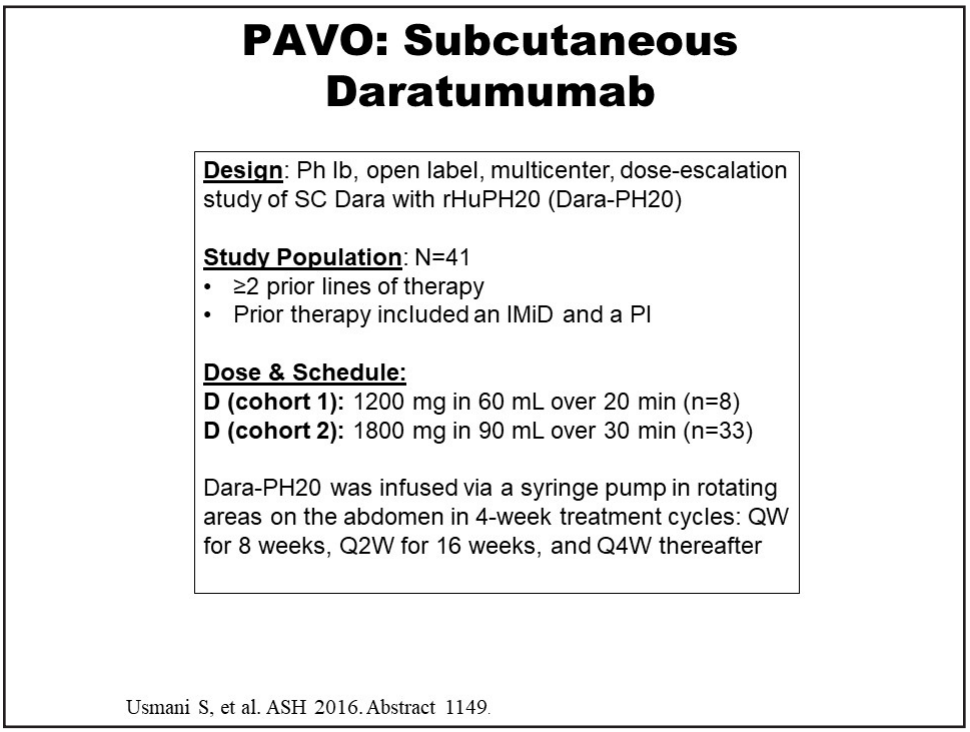
Slide 66. Daratumumab Background

But in the next slide – I'll skip this in the interest of time – what's interesting about this new presentation from ASH is daratumumab currently is being given intravenously and those of you who've received it or known somebody who's gotten it, know that the first infusion can be quite long, 7 to 8 or even 9 hours. And the reason for that is because a fair number of patients, almost 50%, will have these minor reactions, requiring the nurse to hold the drug, restart it, and then there's that stop and start issue.



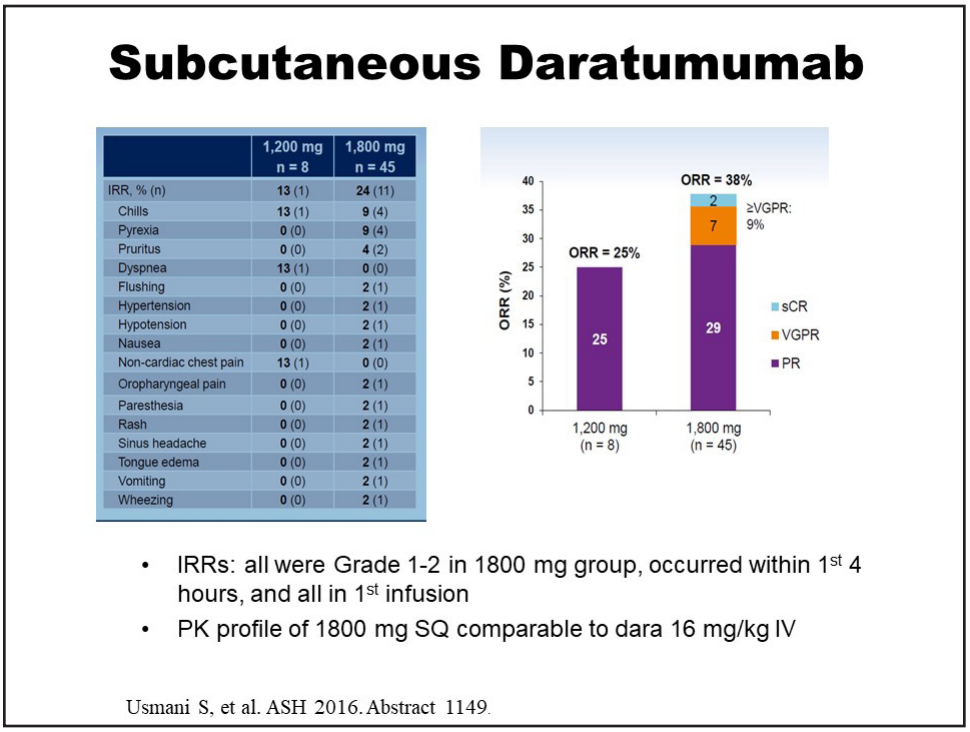
Slide 67. Recombinant Human Hyaluronidase

What if we could give this drug under the skin? Well, there's this – you can't just take a drug IV and squirt it under the skin. The volume of daratumumab given intravenously is a one liter bag, so that's obviously a large volume. So, in order to give a drug in the skin you need to change its chemical properties and the way this was done, is there's an enzyme called hyaluronidase, and what that does is it temporarily breaks down the barrier under the skin that prevents drugs from being absorbed systemically. And so what that allows you to do is give drugs that you have to give IV, but co-formulate it with this enzyme, and it allows the drug to be absorbed into the body. This has already been done for another monoclonal antibody called Rituxan® and it's been done in Europe for almost four years. The FDA just gave approval for this to be used with Rituxan this year in June, but DARA being forward-thinking, has also been looking at this formulation.



Slide 68. PAVO: Subcutaneous Daratumumab

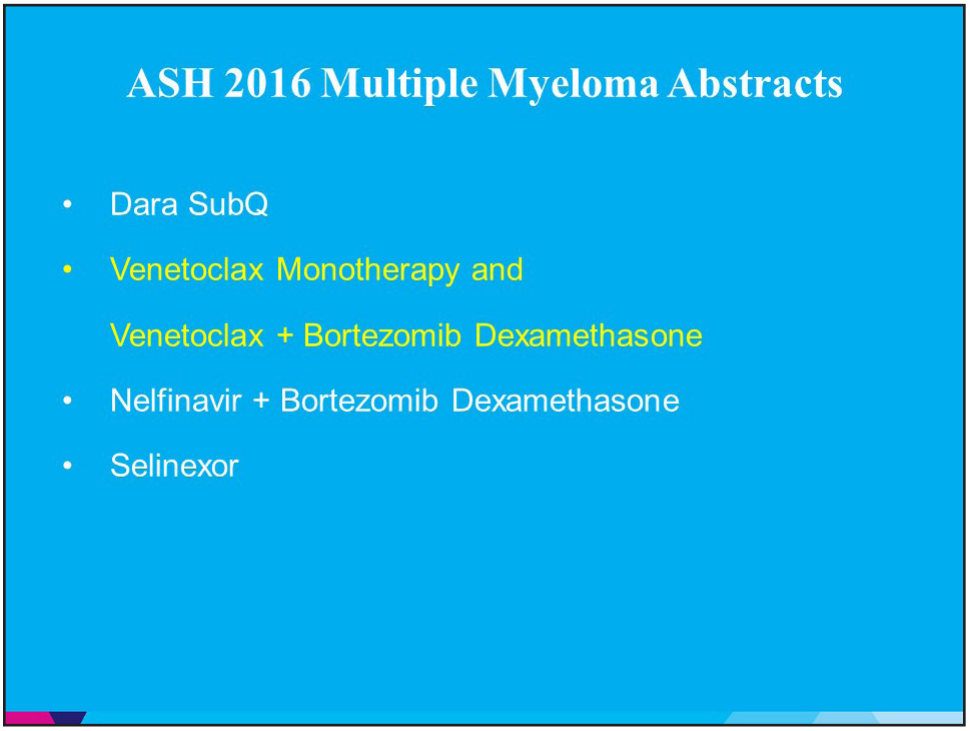
And in this next slide, again, this was a really exciting study for patients. We had 8 patients on this particular administration. And it's basically daratumumab being given in two different – one was low dose over 20 minutes and 60 mls, and then the other dose was 1,800 – 90 mls over 30 minutes. And the schedule is the same as DARA, weekly for a couple of months, and every other week, and eventually monthly.



Slide 69. Subcutaneous Daratumumab

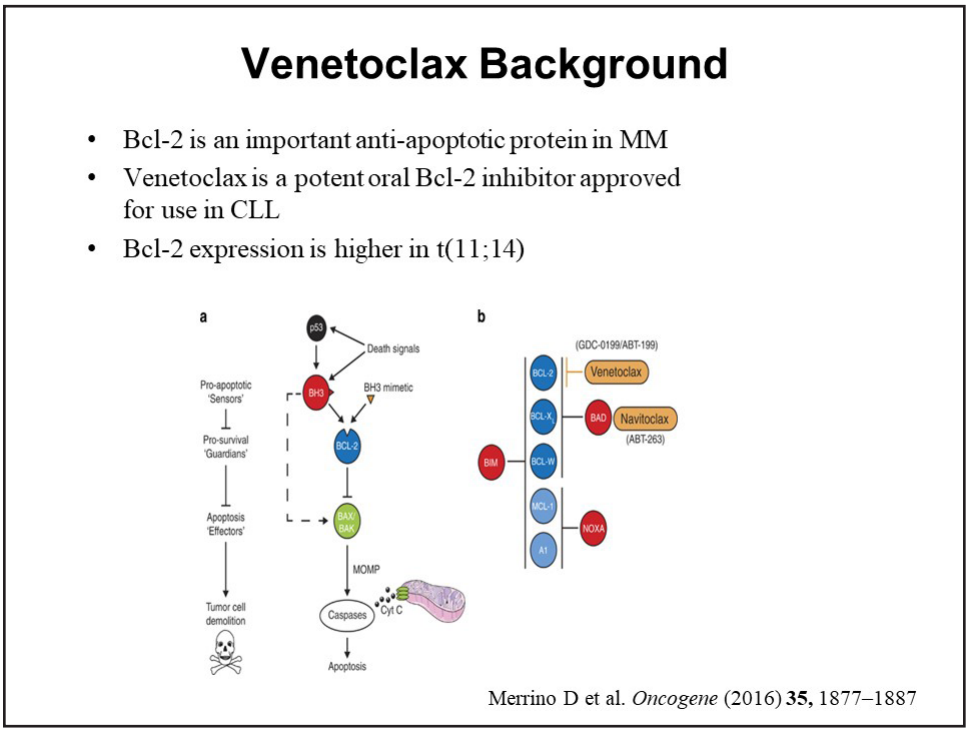
The response rate, the 1,800-milligram dose is what's going to be used, the response rate was 38%, and so that was comparable to what we would see. The infusion-related reactions, though, were actually lower. It was about 24%. So, lower than what we would have expected for IV DARA. And so that was really exciting. Basically, getting comparable efficacy with improved safety and much more convenience.

And the newest formulation of DARA is going to be even faster. It's going to be 3 to 5 minutes. We've dosed many patients with that at our center and will look forward to getting that data out soon.



Slide 70. ASH 2016 Multiple Myeloma Abstracts

The next drug, venetoclax, this is an important drug because it's already FDA approved. We're going to look at two presentations. One is as a single agent, the other one is in combination with bortezomib or Velcade.



Slide 71. Venetoclax Background

Basically, these drugs, the venetoclax targets a protein called Bcl-2. This is a basically – in cancer cells, prevents the cancer cells from dying. So, it's a resistance for the cancer cell to cell death. And this drug, by blocking that, can make cells more vulnerable to dying.

This Bcl-2 seems to be over-expressed in myeloma patients with this translocation 11;14.

Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

Design: Phase I, open label, study of venetoclax monotherapy

Study Population: RRMM (N=66)
- Median age: 63 yrs
- ISS stage II/III: 62%
- Median prior therapies: 5 (1-5)
- Prior BTZ: 94% (70% ref)
- Prior REV: 94% (77% ref)

Dosing & Schedule:
VEN: initial 2 week lead in period with weekly dose-escalation
- Final doses: daily at 300 mg, 600 mg, 900 mg, or 1200 mg
- Patients who progressed could receive VEN + dex and remain on study

- **Median time on VEN: 2.5 mo (0.2-23);**
- **26% received VEN + dex for a median of 1.4 mo (0.1-11)**

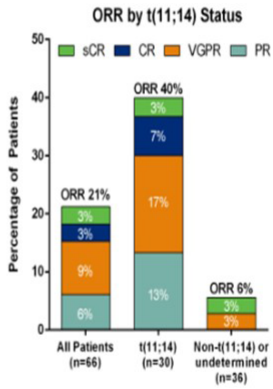
Kumar S, et al. ASH 2016. Abstract 488.

Slide 72. Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

On this next slide, we see the results of these 66 patients and they had a median of five lines of prior therapy and the venetoclax was given at a standard dose escalation. If anybody's been on it or read about it, there's a lot of fluid recommendations to drink lots of fluids because of cell death. That comes from the fact that this is actually approved for CLL or chronic lymphocytic leukemia, a sister cancer, if you will, where those cells can die very quickly. We haven't seen that much in myeloma, but the fluid guidelines are part of that, to keep people well hydrated.

Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

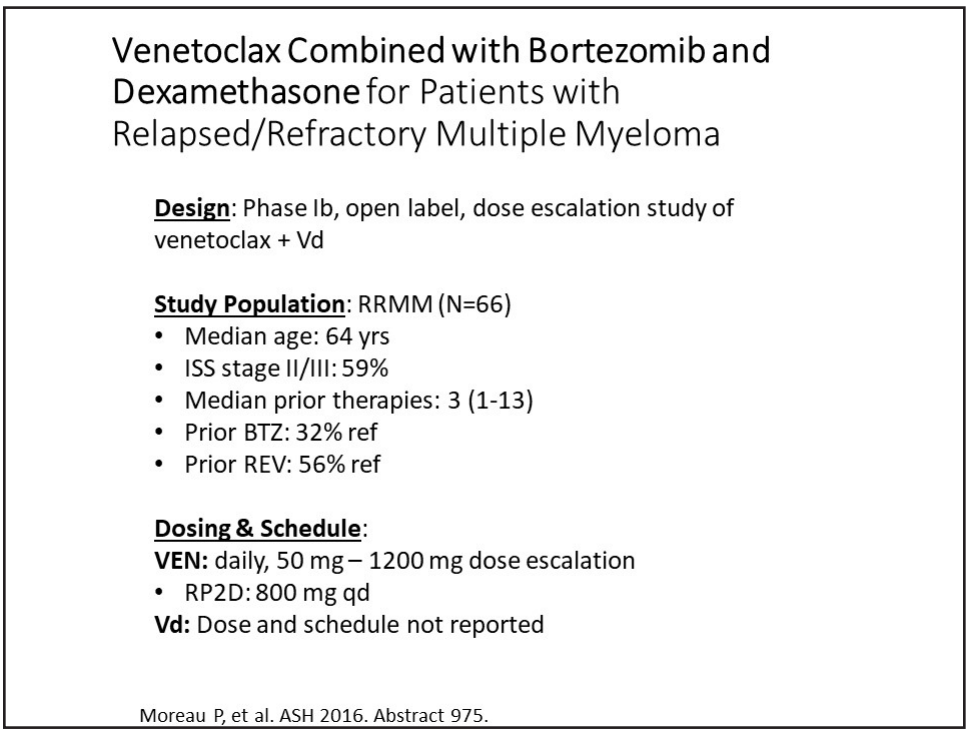
Safety, n (%)	Venetoclax
Gr 3/4 (≥10%)	Thrombocytopenia (26%), neutropenia (20%), lymphopenia (15%), anemia (14%), and decreased white blood cells (12%)
SAEs ≥2 pts	Pneumonia (n=5), sepsis (3), pain, pyrexia, cough, and hypotension (2 each)
Deaths	8 (all considered unrelated to VEN)



Kumar S, et al. ASH 2016. Abstract 488.

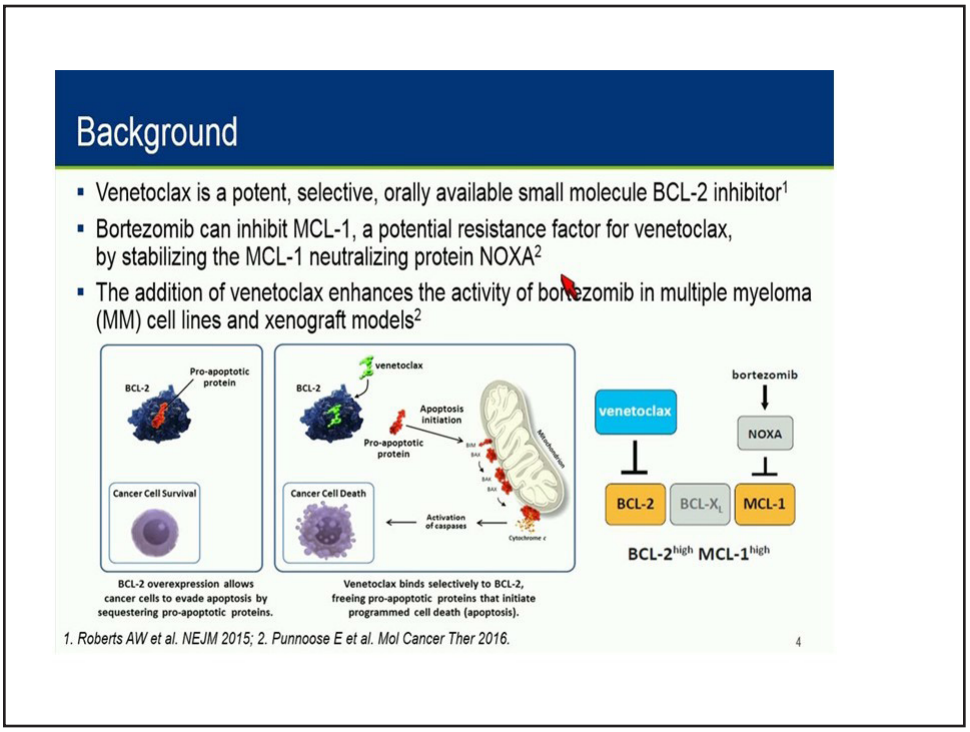
Slide 73. Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results from a Phase I Study

And in the next slide we see that the side effect profile was basically minor, count lowering, and then the usual complications with advanced myeloma like infections, etc. There were deaths, but these were not considered related to the drug. But the interesting thing is in this study, as a single agent, it worked in 21% of patients, so the overall response rates in that left bar is 21% for all patients, but it was even higher, almost double, in the patients who had 11;14, suggesting for the first time that we may have unique treatments that are sensitive to particular types of myeloma as opposed to, you know, one size fits all.



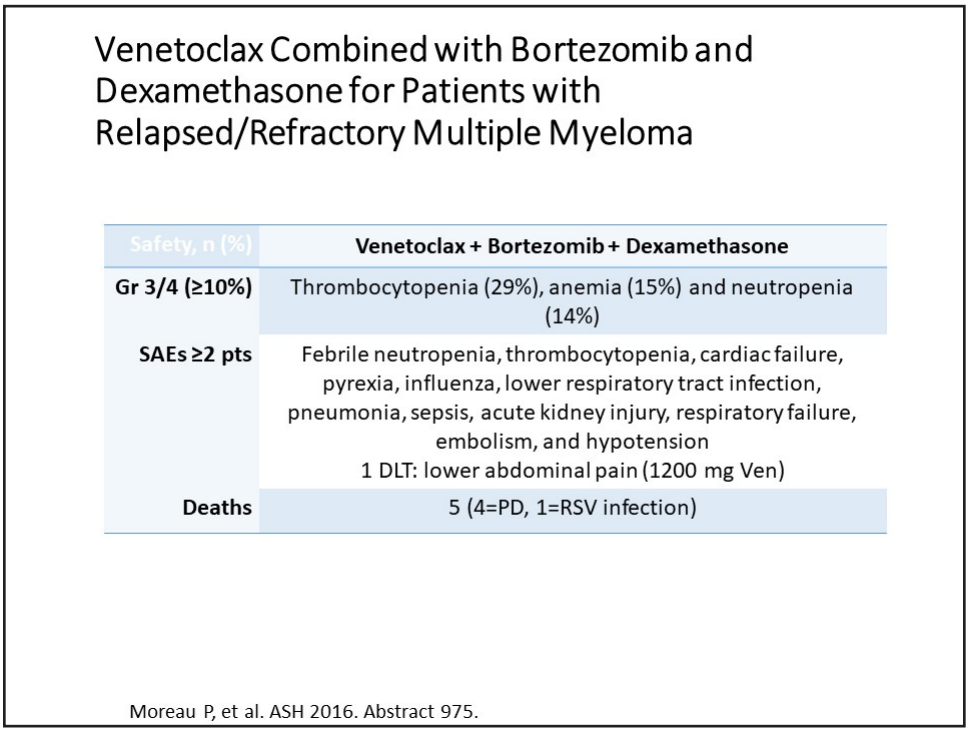
Slide 74. Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

The problem, though, is that not every patient is going to have that 11;14. And so can we do this in combination with other drugs? And the French group presented venetoclax in combination with bortezomib and dex. And this was a Phase I-B study, meaning again it's mainly looking at safety, but the dose – so the doses can range over a broad number of doses. And this is about 66 patients, median of three prior therapies.



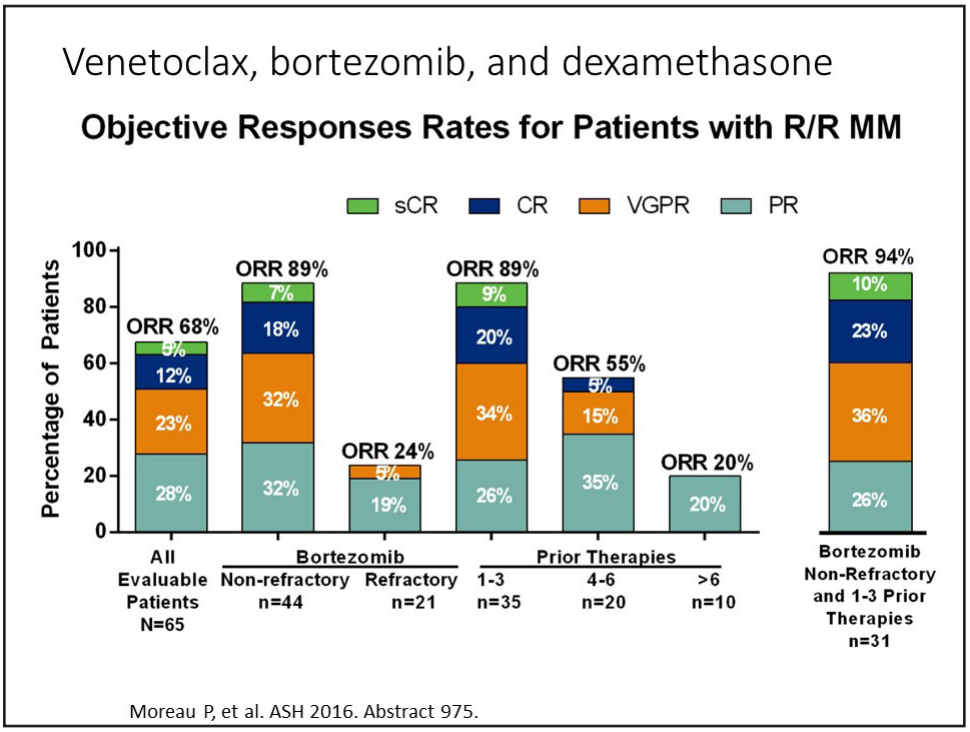
Slide 75. Background

And again, the rationale that this may be a double hit. You block one type of protein with the venetoclax and then you block another with the bortezomib, and both combined may be able to generate more toxicity to drive the cancer cell to die.



Slide 76. Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

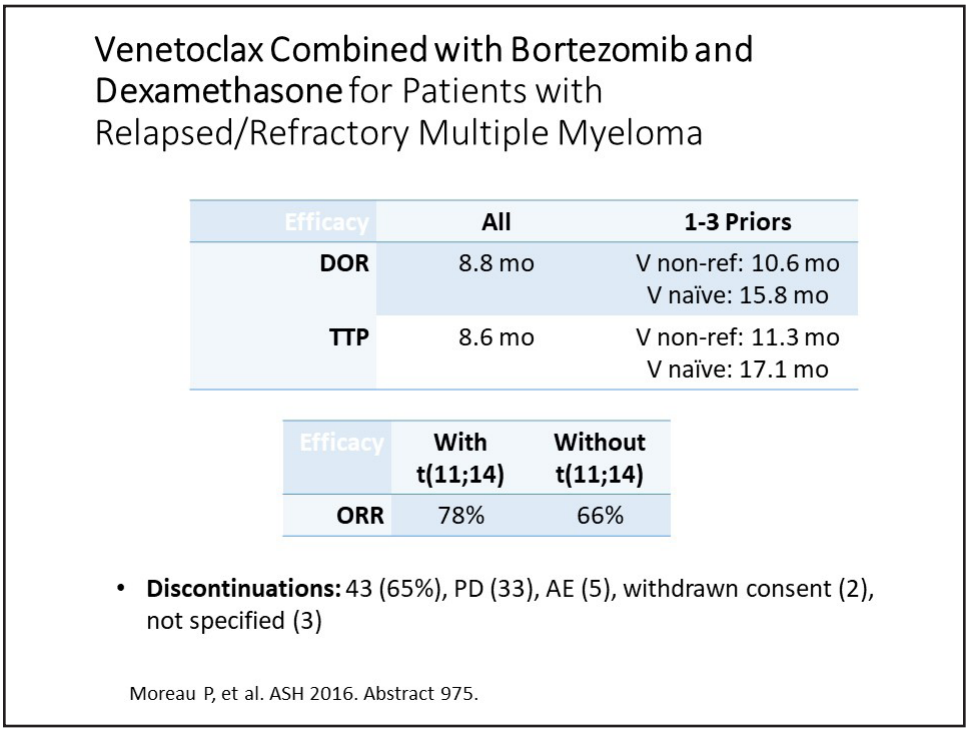
And the side effect profiles again, pretty similar to what you would expect with the individual drugs. A little bit of lowering of counts.



Slide 77. Venetoclax, bortezomib, and dexamethasone

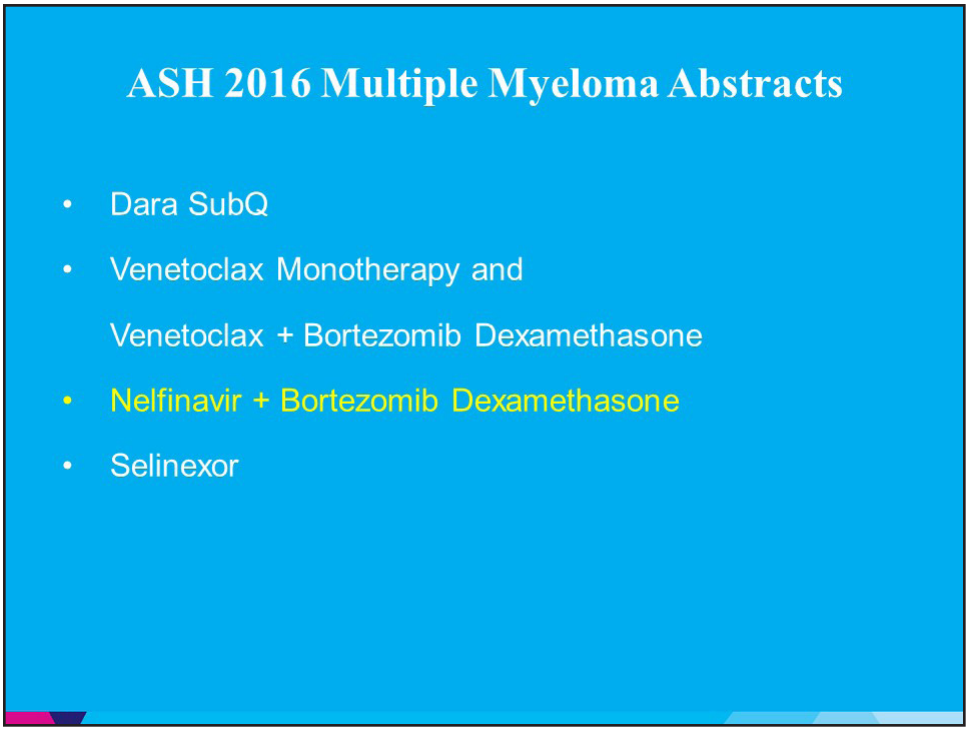
And then the response rates are shown here, so for all patients on the left, the overall response rate was 68%, which is pretty decent for several lines of prior therapy. And I always look to see what about the patients who were refractory to bortezomib. And you see in that third column, in the 21 patients who were bortezomib-refractory, the response rate was 24%. The reason this is important, again, in a single arm study where you don't know what the contribution of the new drug is, if you're seeing a response in people who were refractory to bortezomib and dex, it would be unlikely that patients would have a benefit unless the third drug was doing something. And the fact that we're seeing that here suggests that it may have an effect.

So, this is interesting and encouraging, although they're small, further studies need to be done, but it gives – both either as a single agent for 11;14 myeloma or in combination with bortezomib, this is a drug that's already sitting there, FDA approved, on the market. So, we've used this again off-label, but for patients who may not be eligible for other clinical trials and studies.



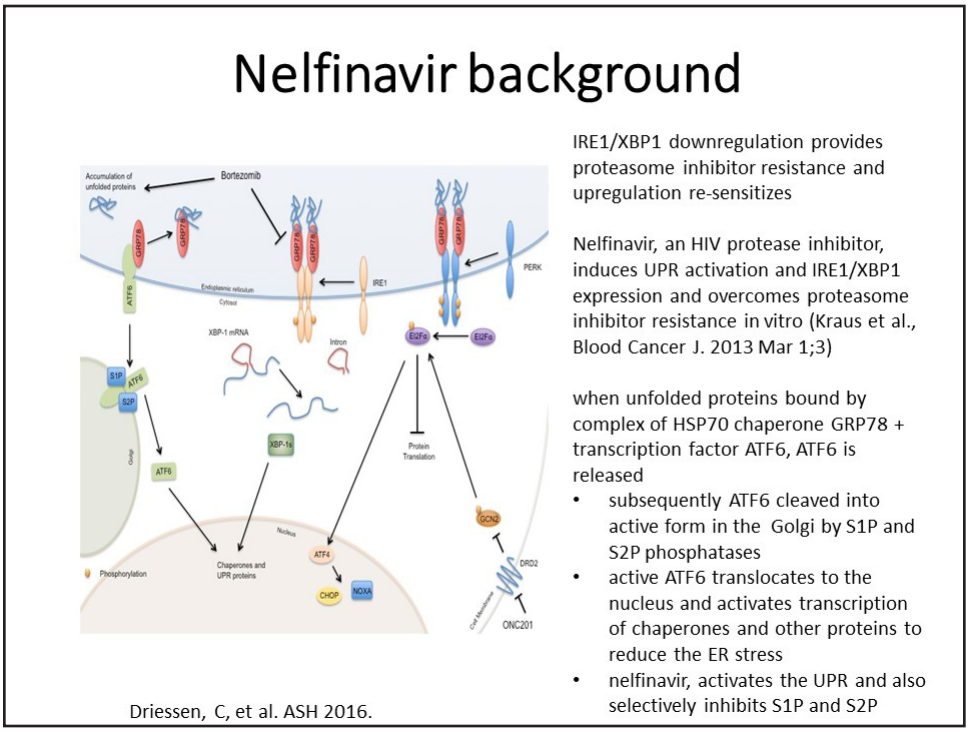
Slide 78. Venetoclax Combined with Bortezomib and Dexamethasone for Patients with Relapsed/Refractory Multiple Myeloma

The duration of response was 8.8 months and the overall response rate – here you see that whether you had 11;14 or not, 66 vs 78, doesn't seem to be as important because probably you're using the bortezomib backbone.



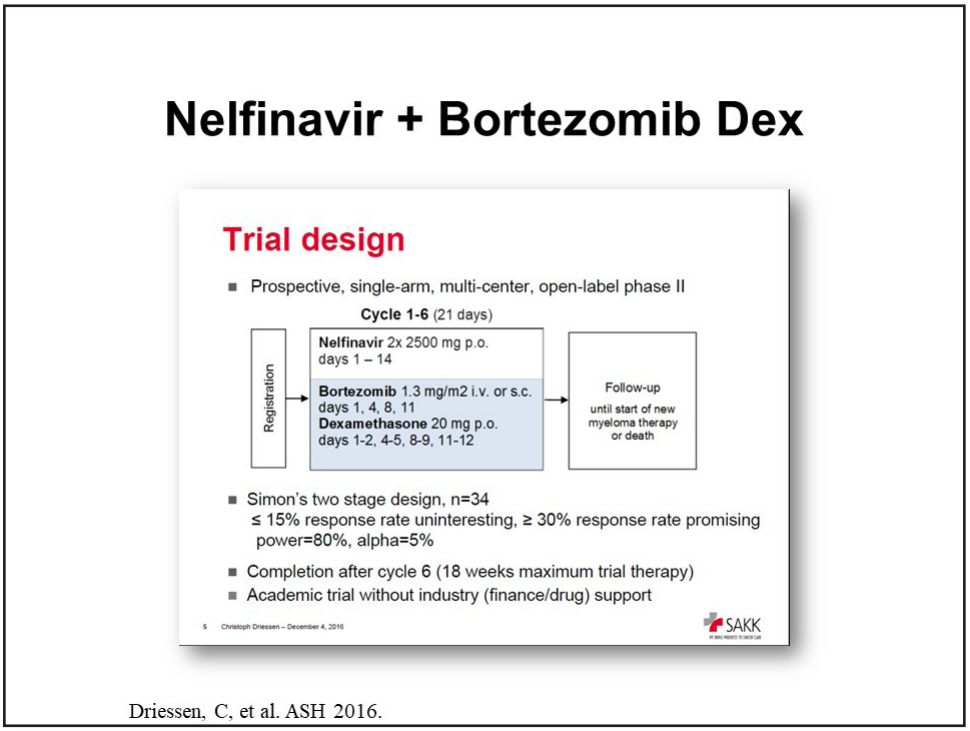
Slide 79. ASH 2016 Multiple Myeloma Abstracts

And then the two remaining studies are from ASH are nelfinavir and selinexor. And in the interest of time I'm going to go quickly on these as well.



Slide 80. Nelfinavir background

Nelfinavir is basically a protease inhibitor, and it's actually approved for HIV. But because when patients are treated with bortezomib, the cell can escape by different escape mechanisms, if you will, this blocks one of those escape mechanisms in the laboratory.



Slide 81. Nelfinavir + Bortezomib Dex

And this was a study presented from Sweden and it was 34 patients and they got bortezomib-dex with nelfinavir, so everybody got the drug.

Nelfinavir, bortezomib, dexamethasone

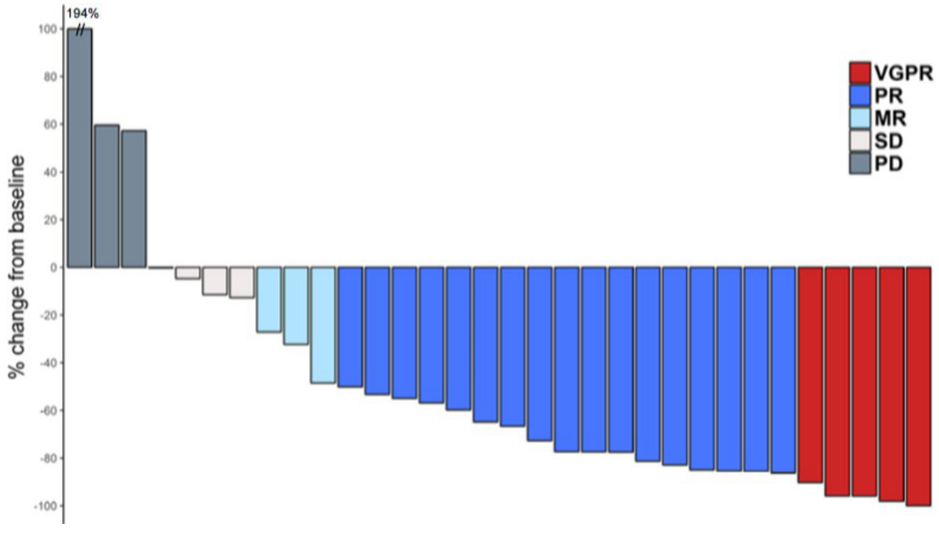
	Total - 34 patients n (%)	
	Exposed	**Refractory**
Bortezomib (BTZ) Number of lines, median (min-max)	34 (100%) 2 (1-5)	34 (100%)
Lenalidomide (LEN)	34 (100%)	27 (79%)
Pomalidomide (POM)	16 (47%)	15 (44%)
Carfilzomib (CFZ)	2 (6%)	2 (6%)
BTZ + LEN + POM + CFZ	1 (3%)	1 (3%)

Driessen, C, et al. ASH 2016.

Slide 82. Nelfinavir, bortezomib, dexamethasone

And these were significantly pretreated, in fact, everybody had to be refractory to bortezomib, so again going back to my previous point, how do you know what the third drug is doing. Here these patients would not typically be expected to respond to bortezomib and dexamethasone.

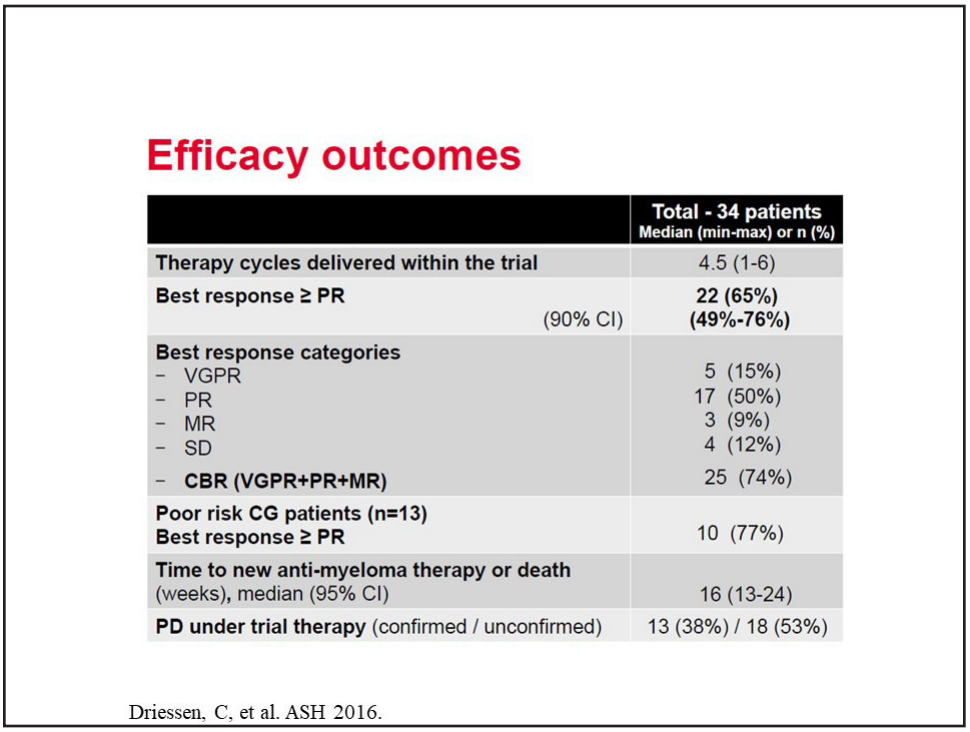
Nelfinavir, bortezomib, dexamethasone



Driessen, C, et al. ASH 2016.

Slide 83. Nelfinavir, bortezomib, dexamethasone

And in this study, you can see that almost everybody had a benefit because the proteins all came down below where they started, as shown by the decrease on the right side of the curve, including very good partial responses.



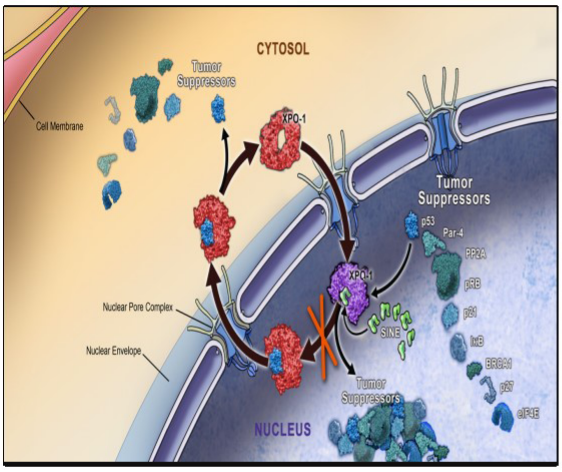
Slide 84. Efficacy Outcomes

And the overall response rate defined as PR or better was 65%, which is very impressive for just adding one drug that's already available commercially. So, again we've been using this for patients who may not be eligible for clinical trials and can tolerate bortezomib and dex.

Slide 85. ASH 2016 Multiple Myeloma Abstracts

And lastly, selinexor, probably the next medication that has shown activity and kind of an unmet medical need.

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression
- In a first-in-human Phase I study, selinexor in combination with dexamethasone showed a 27% ORR in heavily pretreated MM patients

86

Vogl DT, et al. ASH 2016. Abstract 491.

Slide 86. Selinexor Mechanism of Action

Basically, what this drug does is block protein movement from the nucleus or basically the brains of the cell and the body of the cell, if you will. And by blocking that, a lot of the proteins that are important for controlling cell growth, in particular cancer cell growth, are retained in the nucleus and help block the cancer cell from growing and can lead to cell death.

Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib and Anti-CD38 Ab Refractory Multiple Myeloma (MM): STORM Study

Design: Phase II study of Sd

Study Population: RRMM (N=79(
- 48 pts refractory to REV, POM, V, K (Quad)
- 33 pts refractory to above + anti-CD38 mAbs (Penta)

Dosing & Schedule:
S: 80 mg BIW for 6 or 8 doses of a 28 d cycle
D: 20 mg BIW

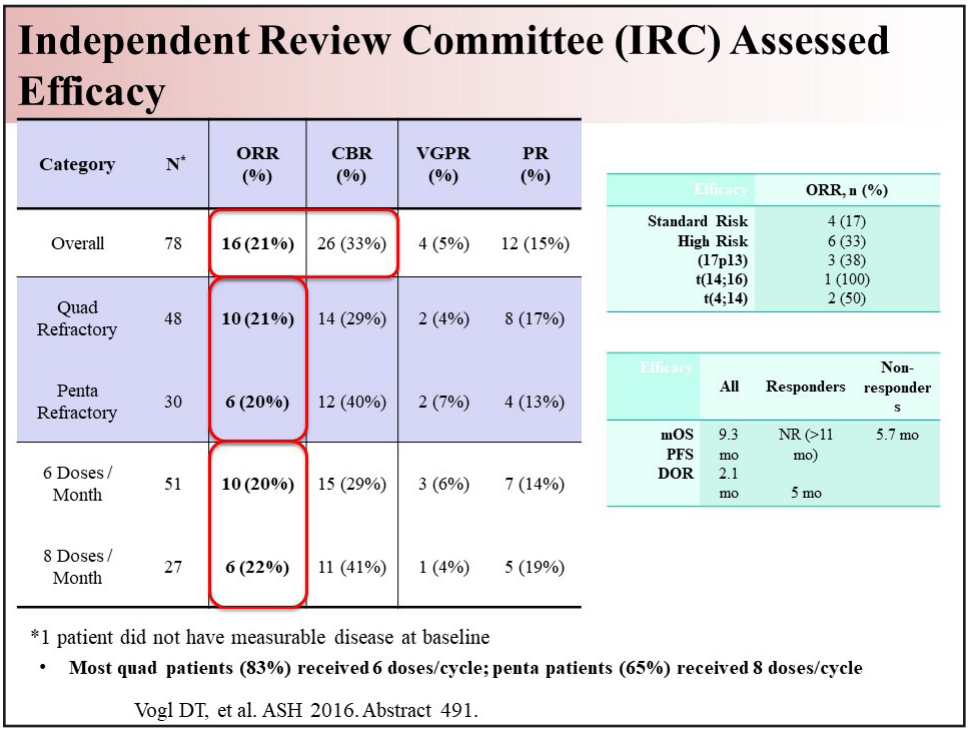
Median age: 68 yrs

Safety, n (%) Gr 3/4 (≥10%)	All patients
Thrombocytopenia	58
Neutropenia	21
Anemia	25
Fatigue	14
Hyponatremia	20

Vogl DT, et al. ASH 2016. Abstract 491.

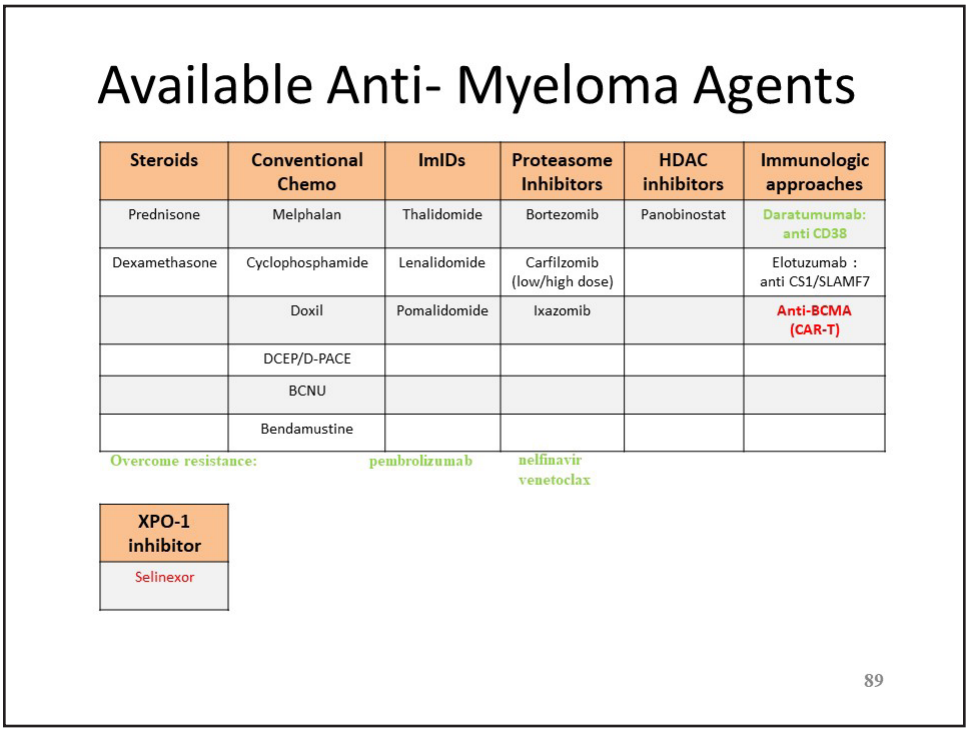
Slide 87. Selinexor and Low Dose Dexamethasone (Sd) in Patients with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib and Anti-CD38 Ab Refractory Multiple Myeloma (MM): STORM Study

And this was about 80 patients with heavily pretreated myeloma. And the drug is given orally twice weekly.



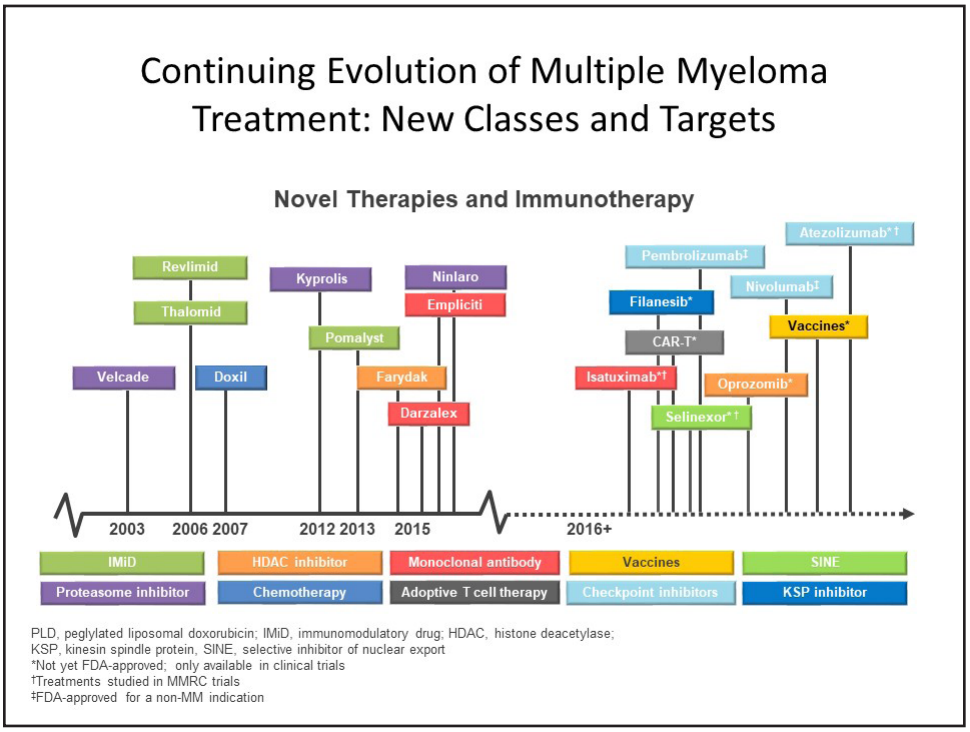
Slide 88. Independent Review Committee (IRC) Assessed Efficacy

On the next slide, we see that the response rate overall was 21%. And then we have Quad and Penta refractory. What does that mean? Quad refractory is basically double IMID, double PI refractory, so we're talking lenalidomide, pomalidomide, bortezomib and carfilzomib. And Penta refractory is with dara thrown in. So, while these numbers may not be as high as we would obviously love to see, but the fact that we're seeing 20% response rate with just this drug and dexamethasone tells us that this is a novel mechanism of action and it's an unmet medical need for patients who've already exhausted a lot of our usual drugs for myeloma. And importantly, there were a lot of high risk patients here as well, so this is an important drug that is being expanded in study and its main side effects are lowering of blood counts and GI.



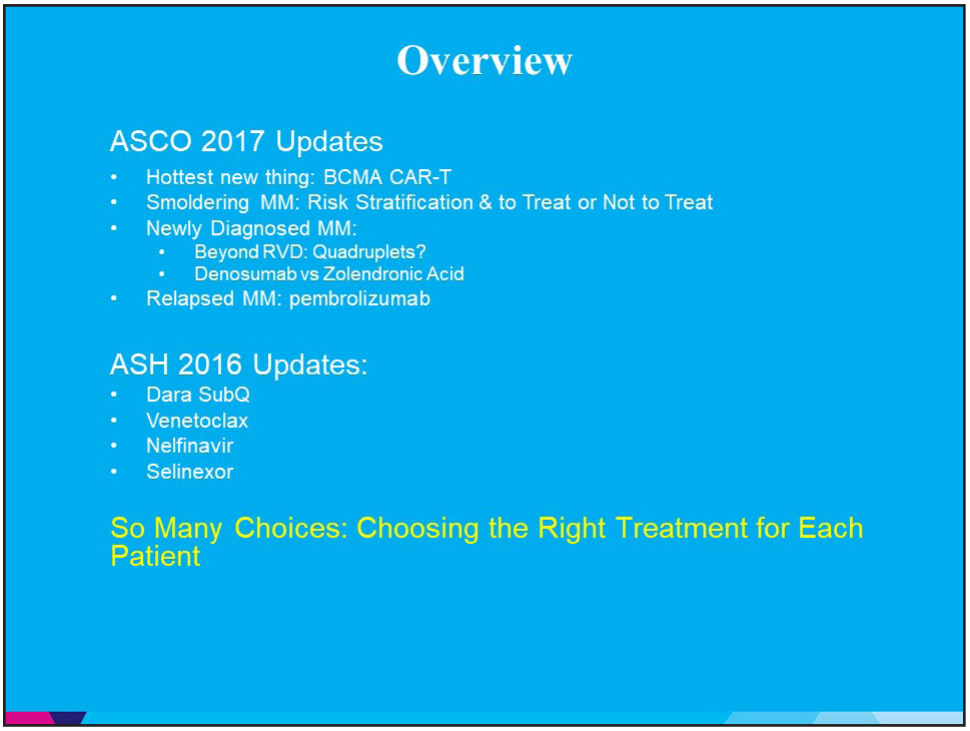
Slide 89. Available Anti- Myeloma Agents

So, to summarize I think what we've talked about today, we have those six classes of drugs, in green, are developments in overcoming resistance or novel formulations. So, we talked about checkpoint inhibition of overcoming IMIDs. We talked about two ways of overcoming proteasome inhibitor resistance, nelfinavir and venetoclax. DARA being moving to subcu. Very exciting CAR-T. And then selinexor, which is a brand new class of drug, which would be now the seventh class of drug for potential myeloma treatment.



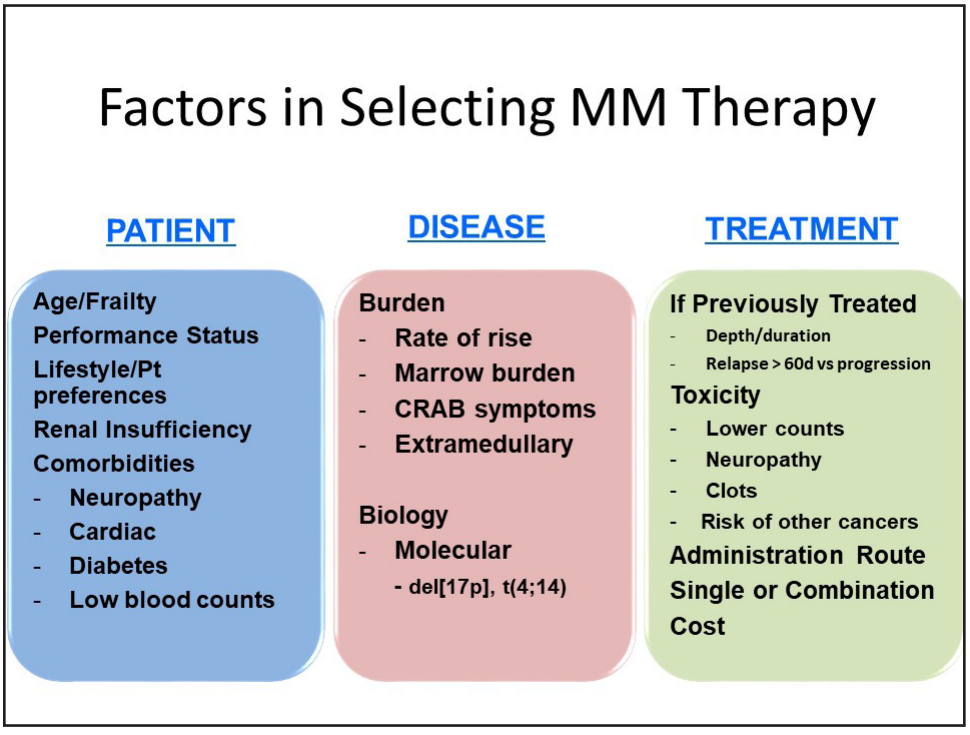
Slide 90. Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets

And in this next slide you see all the development and research that's going on. And on the left are drugs that are already approved. On the right are all the different mechanisms of action that we've talked about – checkpoint, CAR-T, a novel CD38 antibody called isatuximab, we talked about selinexor, an oral proteasome inhibitor. So, a lot of work being done. Vaccines. And I think it's an exciting future.



Slide 91. Overview

And then to close out just briefly, I think turning to kind of what patients are dealing with every day, and what are we doing now in 2017.

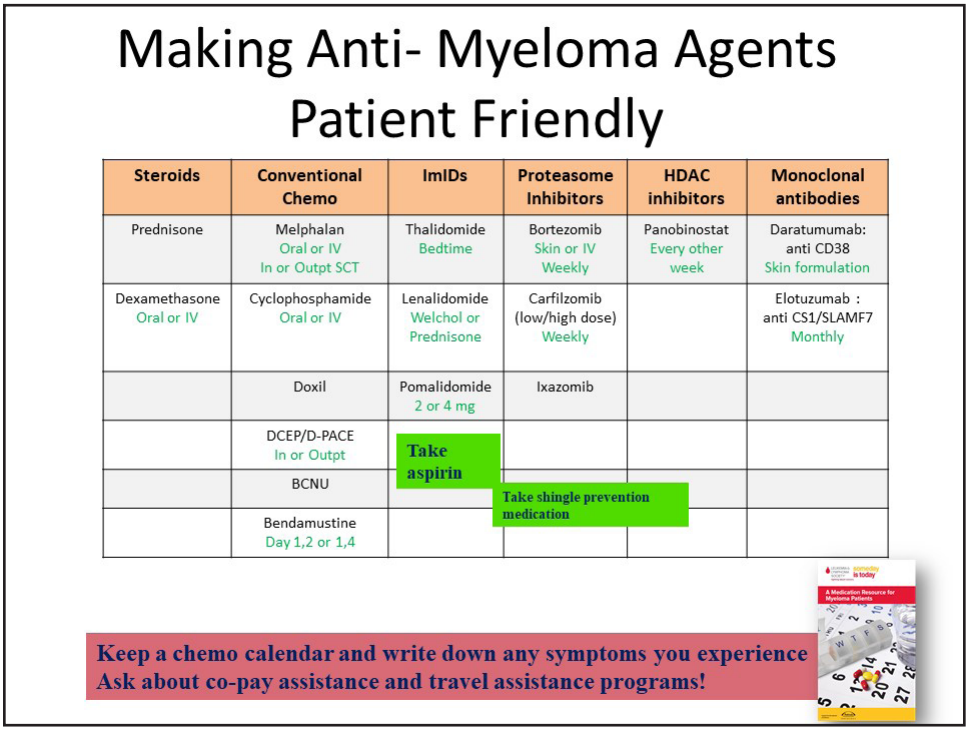


Slide 92. Factors in Selecting MM Therapy

When you have so many choices, how do you pick the right drugs and right combinations of drugs? And I think it's important to always consider three different things: patient, disease, and treatment. When we talk about the patient, how old is the patient, importantly not just the age, but is this a young 70 or an old 50, because you could be very fragile and be young, or be very fit and older. How healthy is the patient or performance status? Is the patient working, are they able to come for IV treatments, or do they need an oral regimen? What's the kidney function, what are their side effects like neuropathy, heart issues, diabetes, their blood counts, because some of these treatments that are going to lower counts can be challenging if you're starting off with low counts.

Secondly, burden of the disease, is this just a little bit of protein going up or is it rapid increase? How much disease is there in the marrow? Are there any symptoms that need to be reversed immediately, or is this what we would call a biochemical relapse, where the numbers are slowly increasing? Is there any myeloma outside of the marrow? Which we call extramedullary disease, which is considered high risk, as are the so-called molecular genetic defects that can be consistent with high risk disease.

And lastly we have to look at treatment. What are the prior treatments that patients have gotten, were they sensitive or refractory, well, how did they tolerate them, how are the drugs being given, is it single agent or combination? Particularly for oral drugs, what's the cost? Where LLS can be very helpful, and other nonprofits.



Slide 93. Making Anti- Myeloma Agents Patient Friendly

And then this last slide is basically what are the things that you as a patient can advocate for or ask about or prevent side effects from developing? In green I've just given some examples; dex can be given orally or IV. Some people who have a lot of reflux may be better to get it IV. If you're going to take it by mouth, best in the morning with food.

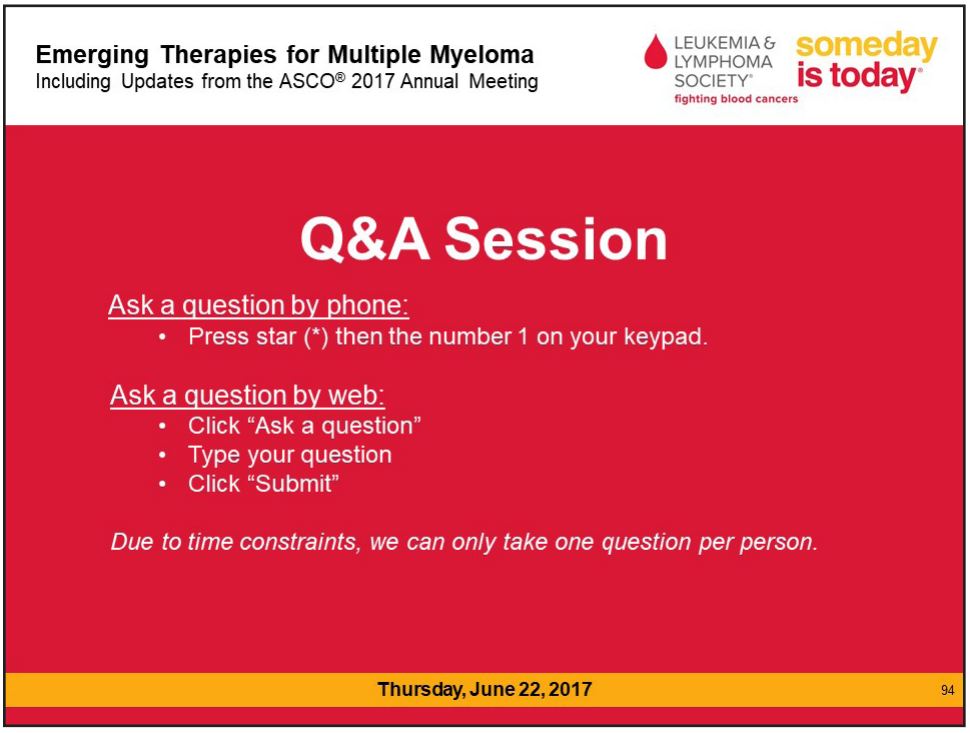
When we look at conventional chemotherapies, melphalan can be low dose oral or IV. Some centers are doing outpatient transplants because we're getting so good at monitoring patients. Cyclophosphamide can be given oral or IV. DCEP or D-PACE, which is a 96 hour infusional chemo, can be given as an outpatient if somebody has a port. Bendamustine can be given either two days back to back or three days apart. So examples there. Thalidomide should be taken at bedtime because it usually causes sleepiness. Lenalidomide, some patients have diarrhea. WelChol, it's a bio sequestering drug, that can be very helpful for mitigating diarrhea. And we also published a paper that people who have rash can be managed effectively with steroids being split over several days instead of getting one large dose once a week, low doses over the week. Pomalidomide can be taken at 2 or 4 milligrams if somebody doesn't tolerate it well. Importantly, for that entire drug

class, aspirin needs to be taken to prevent blood clots. For the proteasome inhibitors, bortezomib can be given in the skin preferentially, but if somebody has a really bad skin issue, they could also get it IV, although we think generally there's more risk of neuropathy with that. Carfilzomib, generally initially approved for twice weekly, but there's emerging data for giving it once a week. All of the drugs in the PI class should have a shingle prevention agent because of the risk of reactivating shingles. Panobinostat, not used very much, but could be used perhaps better by giving it every other week to minimize some of the side effects like diarrhea. We talked about dara being given under the skin. Elotuzumab generally is given twice monthly during the maintenance phase. This is an anti-CS1. It's another monoclonal antibody, but there's emerging data to maybe give it once a month.

And I always encourage people, one of the things with myeloma, is because the schedule of myeloma drugs is often several drugs on, one week off, or some drugs are weekly, some are daily, to keep a chemo calendar. And if there's anything weird or new that you're thinking about, that you're not sure what's relating to what, it helps us as your clinical team to figure out when you're having that in relation to chemo. Ask about copay assistance programs, ask about travel assistance programs. A lot of the drugs that are IV, the companies understand that it may not be easy to get to the cancer center, so, you know, use the social workers, use all the resources you have available.

So, with that I thank everybody for their time and attention and happy to take questions. And also thanks again to the LLS for bringing this group together.

Lizette Figueroa-Rivera:
Thank you so much, Dr. Chari. Your presentation was very clear and gave us a lot of good information, and thank you for updating us from both ASCO and ASH.



Slide 94. Q&A Session

It's now time for our question and answer portion of our program.

Lizette Figueroa-Rivera:
We'll take the first question from our web audience. Doctor, Anthony is wondering if you have any tips on how to deal with peripheral neuropathy.

Dr. Ajai Chari:
Sure. Peripheral neuropathy's significance wasn't really appreciated until the first few drugs that were approved for myeloma, like thalidomide and bortezomib, came into play, because clearly those drugs can be associated with neuropathy, but when those were initially approved and investigated, it turns out a substantial number, maybe 20-30% of myeloma patients will present at baseline with neuropathy, even before they're treated, and it could have something to do with the proteins that the plasma cells make somehow also targeting the nerves. In fact, there's even reports of patients with MGUS who have neuropathy from their protein.

I bring that up because it's always important to figure out when you're talking about a side effect, what is the mechanism, is it disease or is it drug? And if it's somebody who didn't have much at baseline, then probably it's less likely to be disease, but if there's a fair amount, it's important to treat the disease.

Now when picking then, if it's a treatment-related neuropathy, it's important to try to minimize the side effects as much as possible. Probably the drugs that are most likely to be associated with neuropathy would be the bortezomib and thalidomide. And the ways you can try to minimize those are giving the thalidomide at a lower dose. Again, thalidomide tends not to be used as much. With bortezomib or Velcade, giving it in the skin, giving it once weekly, lowering the dose, giving a break, all of those can be helpful.

Last thing that can be done, which we do in our population as well, is looking for the supportive care intervention. So, we can do tests, for example, to check Vitamin B12, whole blood thiamine, which is Vitamin B6, and carnitine. Those are all vitamins that could be easily replaced and some patients have found very significant benefit by taking those.

And lastly, there's also things like complementary medicine. You know, some people like acupuncture, massage, peppermint oil. So, a lot of interventions that really people can try and find what works best for them.

But important to always mention to the doctor and nurse so that we can adjust the chemo dose and schedule if at all possible.

Lizette Figueroa-Rivera:
Thank you, Doctor. And we'll take the next question from the telephone audience, please.

Operator:
Thank you. And our first question comes from Elizabeth from Michigan. Please state your question.

Elizabeth:
Hi, thank you. I recently went to 5 milligrams of Revlimid every other day and I've been on this regimen now for almost 2 years. I don't know why I said recent. But I've been thinking of going down to 2.5 milligrams of Revlimid every other day. I haven't talked to my doctor about it yet. I'm going to bring it up next month with my appointment. But I'm kind of worried, well, will this work or not. I know you can't really give me a yes or no, but I was just wondering your opinion on that. I stopped taking my dexamethasone about a year and a half ago and I've been treated for multiple myeloma since 2010 and 2011 I had a stem cell transplant. But that's my question.

Dr. Ajai Chari:
Sure. I think the broader question I would make it is how do you continue – you're asking dose and duration of therapy. And as a general rule, you have to keep in mind risk and benefit. Going back to the table of our drugs, so we're talking specifically about lenalidomide or Revlimid, and the approved dose, just to remind everybody, is 25 milligrams for treatment and then if somebody has renal issues, it can be lowered to 15 or even down to 10. Maintenance therapy for most clinical trials with lenalidomide is 10 milligrams. And usually it's 10 milligrams until progression.

So, below 10 is not usually well studied for myeloma and you might ask why are these drugs even then made. And it's important to remember that Revlimid is also used for other conditions like myelodysplastic syndrome, for example, and CLL. And so those conditions may use the lower dosing.

So, when you're going below the standard myeloma dosing, the question is what benefit is there. And then the flip side of things, what is the risk, right? I always say maintenance should be mindless, and meaning people should have a reasonable quality of life and it shouldn't be debilitating to be taking a drug forever. The reason we're doing longer and longer durations of therapy is because studies are showing that treating to progression seems to result in better outcomes than fixed duration of therapy. And there was a study that looked at that, where they stopped Revlimid for older patients, they stopped it after 18 months, or continued until progression. And it looks like the ones who continued to progression did better. However, that needs to be counter-balanced by patient-specific issues. Now if somebody has miserable fatigue, diarrhea, lowering of blood counts, maybe that's not the right approach, maybe it's not the right drug, maybe it's not the right dose. But if somebody's really having that many side effects, I would think more about a chemo break, switching drug classes, rather than going down to very, very low doses. Because what we don't know when you go to very, very low doses is might you then be creating more resistance in the myeloma and then making it harder to treat down the road with that drug should you want to use it in the future at full dose.

So, important things to think about and discuss with your doctor, but I think the other important thing from our caller's question is really communicating your concerns with your doctor so you can adjust your treatment. You see that there's a lot of chocolates in this box, if you will, right? And so, if one is not right, find another one.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question comes from our web audience. Patrick is asking, I've heard that the shingles vaccine is a live virus and should not be taken as a multiple myeloma patient due to the lowered immune system, is that true?

Dr. Ajai Chari:
Currently the shingles vaccine is not yet approved for patients who have blood cancers for that reason. The pill that we mentioned, like acyclovir or valacyclovir, have been shown to be effective in preventing shingles. The studies are ongoing for those and on the topic of vaccines, I do think it's important for myeloma patients to get an annual flu vaccine as well as pneumonia 13 and 23 every 5 years. Those are all safe and have been shown to be effective and can help decrease the risk of infection, which is a complication as you heard in many clinical trials, particularly in advanced myeloma.

Lizette Figueroa-Rivera:
Thank you. And the next question also comes from the web. Katrinka is asking, can multiple myeloma be cured with allogeneic stem cell transplant?

Dr. Ajai Chari:
That's a good question. Allogeneic transplant differs from autologous transplant in the sense that the cells are being taken from a donor, not the patient them self. And so, one of the risks of doing that is what's called graft-versus-host disease because even though the patient and donor are matched genetically, there's still, unless it's an identical twin, even siblings will have slightly different proteins and genes that make them react to somebody else's immune system. So, when a new immune system creates that graft-versus-host disease, that can be mild, moderate, or severe, and if severe, it can be quite debilitating, can affect the skin, liver, gut, and increased risk of infection.

The flip side of that is also graft-vs-myeloma. So, if you have more mismatch from the donor and the patient, there may also be more of an attack on the myeloma. And while theoretically that might be encouraging, it needs to be counter-balanced by the risk of the graft-vs-host disease. So, again, it goes back to that risk-benefit question.

And so, to date most of the myeloma studies that have been done, where everybody gets – and the way the myeloma studies are done for auto and for allotransplant, is typically everybody gets an autotransplant and then there's a randomization, if somebody has a match of a sibling or donor, they go to allo, and then the other half doesn't. And to date most studies have not shown a benefit for allo and it's because the typical patient, we don't know whether that GVH and myeloma balance is going to offset towards the favor of controlling the disease.

To the point specifically about a cure, you know, the problem with that is if patients are getting sick or potentially dying from complications of the allo, it's hard to even talk about the cure because you're losing a fair number of people early. That said,

there are some patients who may not relapse and what we call a tail on the progression curve and overall survival curve, meaning they don't seem to relapse, and that's a potential sign for a cure. But I think right now I would say if you had to ask the field, I think people are a lot more interested in CAR-T than allo because even though there's that cytokine release, which we talked about, it's a one-time thing and it's not something that you're going to live with for a long time, whereas graft-vs-host disease is both acute and it can be chronic. And the risk is, to date – in fact, insurance companies don't even pay for allos for myeloma if it's not done in the setting of a clinical trial because the data have not been compelling enough.

So, I would encourage those who are young and fit enough to tolerate an allo to think about getting a CAR-T consultation.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question comes from our telephone audience.

Operator:
Thank you. Our next question is from Phil from Texas. Please state your question.

Phil:
Hey, thank you for your time. General question, I was diagnosed and treated and I've been in complete remission for about 6 years. So, my question is, when is it indicated that an individual gets MRD testing for peace of mind, if nothing else. I'm in my seventies and I'd just as soon dismiss this idea of recurrence.

Dr. Ajai Chari:
Yeah, that's a good question. So, whenever we teach medical students, we always say don't do a test unless it's going to change your management, right, because there's a lot of testing that's done unnecessarily in medicine and we don't do anything with the results anyway.

There are a lot of issues with MRD. First is the standardization of the technology. For example, we all know that a normal hemoglobin or red cell should be, say, around 14, in somebody who has no problems at all. We know that 8 or 7 is quite low. And if that same patient went from hospital to hospital, lab to lab, everybody would get a number around 7, warranting potential consideration of a transfusion.

The problem with MRD is it's not like that and there's a lack of standardization. There's different techniques, first of all, and you could be negative by one and positive by the other. Some techniques are more sensitive than others. Some are easier to do than others. The two big techniques are flow and PCR. And so, flow may be less sensitive, but PCR may not be successful on everybody either. And so, while it sounds like a boring topic, but it's an important topic, because if you're not standardizing the technique, it's like talking apples and oranges. So that's number one.

The second thing is what do you do with that result? Right now, I think MRD's best use is in probablypeople who have earlier disease myeloma, like newly diagnosed or maintenance, because then that's where our responses are getting so good, and you heard about the quadruplet therapies, okay, so quadruplets at a high level look better, but are we getting deeper responses by MRD? That would be a question that's worth investigating. Or if we're trying to think about maintenance therapy duration, like the last caller asked, if somebody's an MRD negativity, is it worth considering discontinuation? So, these are the areas I think we need to look at MRD in clinical trials, but if you were to say today in prime time real life, are we ready to use MRD to make treatment decisions, I would say no, because the technology's not standardized and to date we have no prospective studies that say okay, if you have 1,000 patients and, specifically in this setting post-transplant, half are in maintenance, half are not, and we stopped the maintenance therapy in those who were MRD negative compared to those who didn't stop, that's how you would be able to get that question of what is the significance. But we really have no data to guide us on treatment decision-making with MRD right now.

Lizette Figueroa-Rivera:
Thank you, Doctor. And our next question is from the web. Rhonda asks, is there a genetic link? My sister and I both have multiple myeloma.

Dr. Ajai Chari:
So, the studies seem to suggest that for the vast majority of patients, there is no family member or other person – there's no genetic predisposition to getting myeloma and most patients don't have to worry about passing it on to children, etc. That said, when you do large population studies and you look at people with myeloma, there's a slightly higher risk of having somebody else in the family with a related cancer. It's 2.4 fold higher than somebody who didn't have myeloma. And there are rare, very, very rare family pedigrees where there's a significant familial predisposition.

I would encourage people who have family members with related cancers like leukemias and lymphomas, to visit academic medical centers where there's a lot of interest, for example, at our site and other sites, of looking at familial B-cell related cancers. Because the thought is that if we can find the genetic link in these few families that may have them, maybe that'll give us some insights into either pathogenesis, meaning what causes myeloma, and obviously on the other hand, what novel treatment mechanisms.

But for now, we're not recommending any specific testing or monitoring for family members of myeloma.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question also comes from the web. Rosalee asks, why are clinical trials for myeloma not available to local oncologists or local hospitals, to make it easier for patients to get to, especially if patients are not that well?

Dr. Ajai Chari:
So, clinical trials have to be divided into different categories, so we can have observational studies, where you're just collecting data on what drugs and side effects people are having, those could be done remotely, even through the web, phone, etc. Then we have Phase I studies, which is first in human. So, for example, the daratumumab subcutaneous studies that we talked about today, the CAR-Ts, these are very early phase. And we don't know the complete side effect profile yet of these drugs, and that is not a good drug to be tested locally because it takes a lot of resources to do these studies. You need to have trained pharmacy to mix these novel agents, you need to have trained nursing, trained physicians, trained hospital administrators to get the beds arranged. And so, it's a lot of training that is difficult to recapture.

Then when you go to Phase II, if it's a relatively easy to give drug, sometimes those can be done locally. Phase IIIs are great for local oncologists because it's basically new treatment versus old treatment, and to see if the new one has anything to add, and that could be done locally.

But the thing is that it's also a lot of work to do a clinical trial. It takes a lot of time and effort and busy community practices may not have the resources and time to be able to do these studies. So, there's a lot of factors that go into why that's not feasible.

But there's often, you know, there may be other academic sites that are closer to home. And there's always a partnership. And sometimes what we also try to do, keeping in mind that it's difficult for patients to always come, is maybe they get their treatments with us, but then they can get some in between monitoring from the local doctor. So, there's ways to create partnerships to make it easier, but those are the reasons why currently many early phase clinical trials are restricted to larger academic sites.

Lizette Figueroa-Rivera:
Thank you, Doctor. And we'll take the next question from the telephone audience, please.

Operator:
Thank you. Our next question comes from Richard from New Jersey. Please state your question.

I've been a multiple myeloma patient now for like eight years and gone through everything from stem cell transplant to clinical trials. Seems like every time I go back to the doctors, I tell them I feel weak, tired, woozy, and finally one nurse said to me maybe I should go see a psychiatrist because maybe I have depression. And I said to myself, gee, these are like physical problems, not mental problems. So, it kind of hurt me when I heard that. But what does the doctor think about when you have those type of symptoms, can depression play any role in that?

Dr. Ajai Chari:
So, that's a great question. I think the way mental health diagnoses usually work is first, to your point, you have to rule out an underlying medical issue, a physical and, you know, biological issue that's not just a brain chemistry issue. A great example of that would be, you know, for example, blood pressure. Blood pressure can be due to obviously increased – the deposition in the arteries over time in aging – panic attacks can cause high blood pressure, too. And so, you don't want to assume somebody is having a panic attack if really, it's the garden variety blood pressure.

So, the symptoms you're referring to, for example, one of the things I would also encourage your healthcare providers to evaluate, we published a study, and it's not well understood and well recognized I believe yet in myeloma, but there's a condition called adrenal insufficiency, where what happens is that because, as you know, a lot of myeloma treatments use steroids, when people are getting steroids they feel okay, but then once the steroids leave the system, not only are they not getting steroids, but the adrenal glands in the body also have been suppressed over many years of getting steroids, and can manifest in symptoms like nausea, vomiting, profound fatigue, lightheadedness when you stand up. And so that needs to be tested for adrenal insufficiency.

Other causes of fatigue and kind of lethargy would be anemia, B12 deficiency, thyroid, so some of those may be even better dealt with a primary, right, somebody who's known you well. So, it doesn't have to be an oncologist. But I think if they've done this exhaustive work-up and everything is negative, it doesn't hurt to see a mental health professional, could be a therapist or social worker, a psychiatrist, to see if you do have any symptoms of depression. Certainly, doesn't hurt to get diagnosed and treated for it if that's what it is.

Richard:
I kind of blamed it on all the drugs that I'm taking, everything from the steroids, which they've been switching me back and forth between dex and prednisone, and then also the acyclovir and you name the drug. Right now, I'm on that immunotherapy and that's going real well. I'm on once a month now instead of going every week. So, everything's going well, but I have a feeling that it's a combination of all the drugs. Because when you read the side effects, they all list drowsiness, this, that, be careful with driving. You know, so the combination of drugs I think is the problem, you know?

Dr. Ajai Chari:
Yeah, I think you bring up an important point. You know, this is where I talked about the chemo calendar. Almost every drug is listed with every side effect and it can be overwhelming to try to kind of figure out what's going on. But again, I would encourage – the disease, also it's important to remember if the disease is uncontrolled it can cause that, so between drugs, those other things I mentioned, can cause fatigue and mental health issues as well. I think this is why we have oncology as a subspecialty and not just internal medicine doctors, because you do need to know all the drugs. But again, I would suggest going to – you can always consider a second opinion, going to an academic medical center, these are things to help further elucidate what might be going on. But it sounds like you're doing well at least from the myeloma control with the immunotherapy, which tends to have the least amount of side effects. But hope you feel better.

Lizette Figueroa-Rivera:
Thank you, Doctor. And the next question comes from our web audience. Dixie asks, how often is it necessary to have bone marrow biopsies when following multiple myeloma? If lab work indicates things are smoldering, does a biopsy have to be repeated and why?

Dr. Ajai Chari:
So, it sounds like this question is coming specifically from a smoldering perspective. And the number – an initial diagnosis of marrow is always required because we need to know is it less than 10% plasma cells, which would put it into the MGUS category, or in that 10 to 60% category. As you heard, there's some thought that maybe over 60% is very high risk and therefore should be treated. So, that's important to one's baseline diagnosis correct. Thereafter with monitoring, often you can use the proteins and imaging to guide whether or not a marrow needs to be repeated. And again, I would always ask how would the bone marrow change your management. Because if you think about it, it's just another test. How would a bone marrow change your management? So, it might change your management if you're more than 60% plasma cells, it might change your management if the blood counts are dropping. So, if somebody's white count is dropping, they're becoming more anemic, their platelets are dropping, I would want to know why. Is it because there's more plasma cells

coming from the myeloma and that's why that's happening and we need to treat it, or could it be because it's an unrelated bone marrow issue, could there be B12 and folate deficiencies, etc.?

I would say the number one reason to do the marrow is initial diagnosis, followed by evaluation for low counts, and third is to understand the genetics of the disease.

For people particularly with advanced myeloma, a great reason to do repeat marrow is we now have different protocols, for example, MMRC has a profiling protocol, a molecular profiling protocol where a patient's marrow aspirate can be sent and analyzed for mutations in genes that could be targeted by drugs that are maybe not used for myeloma, but are used – available and approved for other cancers. And certain protein changes or aberrances. So, by doing a marrow, we get to potentially expand that toolbox of drugs which we already have and use drugs – and insurance companies will often look for that genetic information to support paying for a new drug off-label.

Lizette Figueroa-Rivera:
Thank you. And the last question today is also from the web. Peter asks, I'm very fortunate to have been in remission since an autologous stem cell transplant in 2004. Is there any likelihood that the longer I remain in remission, the longer I am liable to stay in remission?

Dr. Ajai Chari:
Yeah, that's a great and unique perspective to be in. Generally, we think of a functional cure as the absence of relapse and depending on the disease, 5-10 years. And there was a publication in Blood that showed that about 10% of patients with myeloma don't relapse within ten years. And in some ways, we could say that might be a functional cure. And that would be consistent with a cure because if you're not doing any maintenance therapy and the disease hasn't come back for more than 10 years, that would be how we would usually say cure for any other cancer. And so, I think the way to no one is going to be able to guarantee that, but I would really enjoy life and the remission. Leave this on the back burner. I think sometimes when we have these chronic conditions like MGUS, smoldering, myeloma in remission, it feels like there's always something looming over the head and we're always waiting for the other foot to drop, but I would encourage people to flip it around and say I'm doing great, this could go on indefinitely, enjoy and live each day to the fullest.

And I think as the other caller also brought up, we have all these advances in myeloma, we're trying to help people live longer, but it should also be helping people live better and maintaining that great quality of life.

So, hopefully today's session has given people a lot of tools to go back to their doctors and healthcare providers with, to do that.

Lizette Figueroa-Rivera:
Thank you so much, Doctor, and thank you, Peter, for your question and we are happy to hear that you are still in remission.

Thank you, Dr. Chari, for your continued dedication to patients.

Slide 95. Support Resources

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps. And if we weren't able to get to your question today, you can call an Information Specialist at The Leukemia & Lymphoma Society toll-free at 1-800-955-4572. And we're here from 9 AM to 9 PM Eastern Time. Or you can reach us by email at infocenter@lls.org. Information Specialists are available to answer your questions about treatment, clinical trials, support, and financial assistance, including information on our copay assistance program for myeloma patients.

Again, we want to thank our supporters, Amgen, Bristol-Myers Squibb, Celgene Corporation, Sanofi Foundation for North America, and Takeda Oncology.

And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us today. Goodbye and we wish you well.