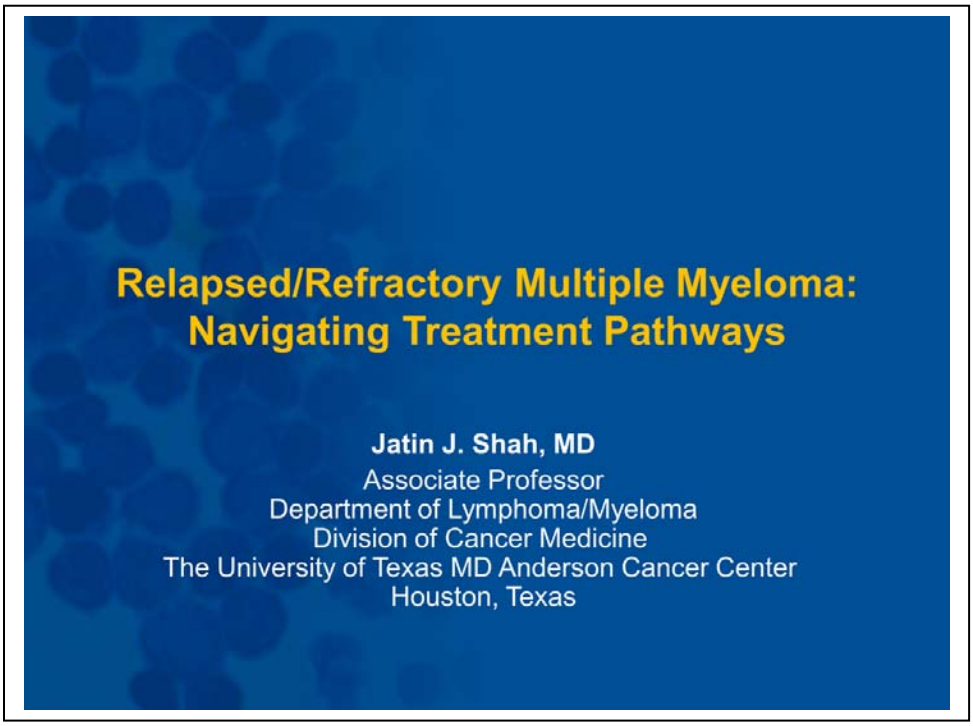
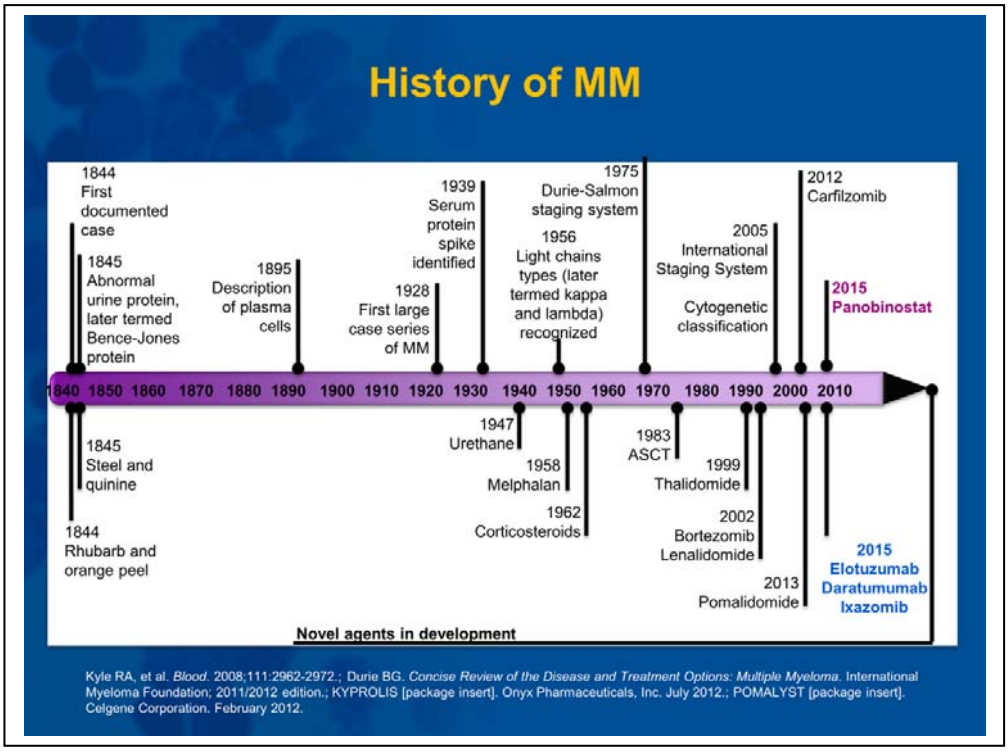
[Editor's note: Dr. Shah's video transcript has been edited to improve readability]

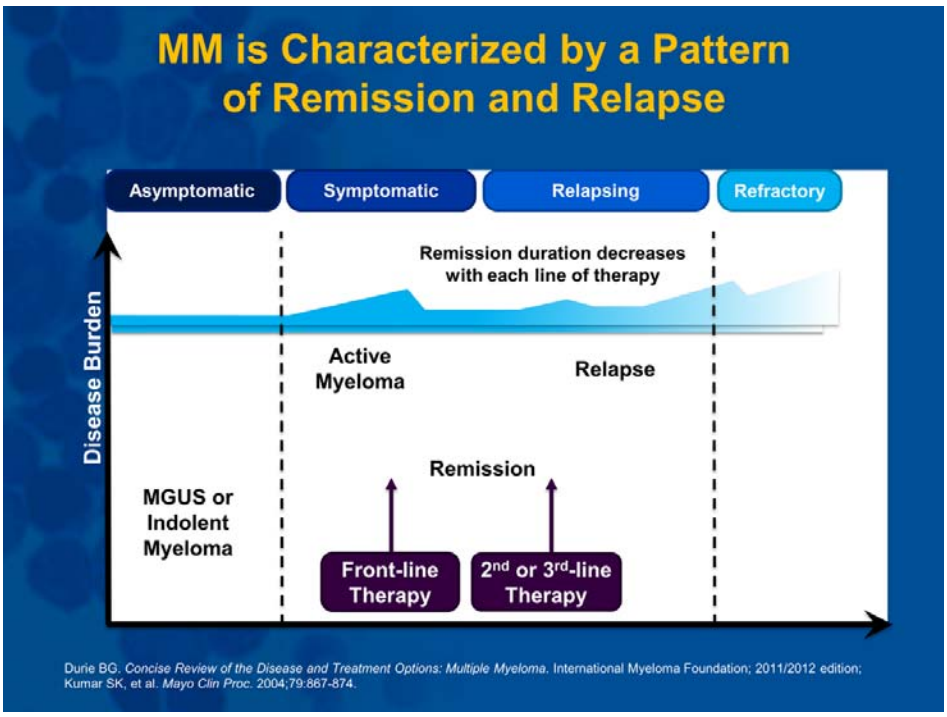


Hi, my name is Jatin Shah, and I am an Associate Professor in the Department of Lymphoma and Myeloma at the MD Anderson Cancer Center in Houston, Texas. It's a pleasure to be with you. Today, I am going to focus on relapsed/refractory myeloma – specifically, navigating the treatment pathways and the multiple treatment options we have in relapsed/refractory myeloma.

As you know, the history of myeloma has had a rapid evolution over the last 10 to 15 years. This slide highlights the rapid advances that we've seen with the approval of multiple new drugs over the last 15 years, beginning with bortezomib and lenalidomide in 2002, continuing with carfilzomib in 2012, pomalidomide in 2013, and, more recently, in 2015, four new approvals with panobinostat, ixazomib, daratumumab, and elotuzumab – all for relapsed/refractory myeloma. Today, we will review much of the data that was reported over the

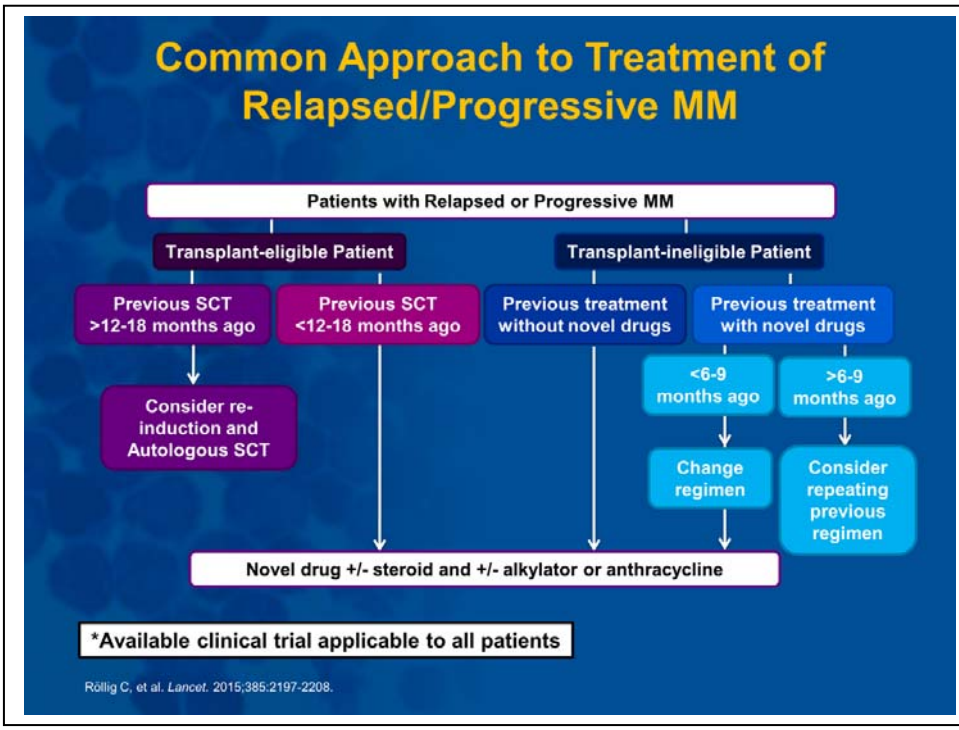


last year in the phase 3 setting, focusing on how we can use this information to manage relapsed/refractory myeloma.

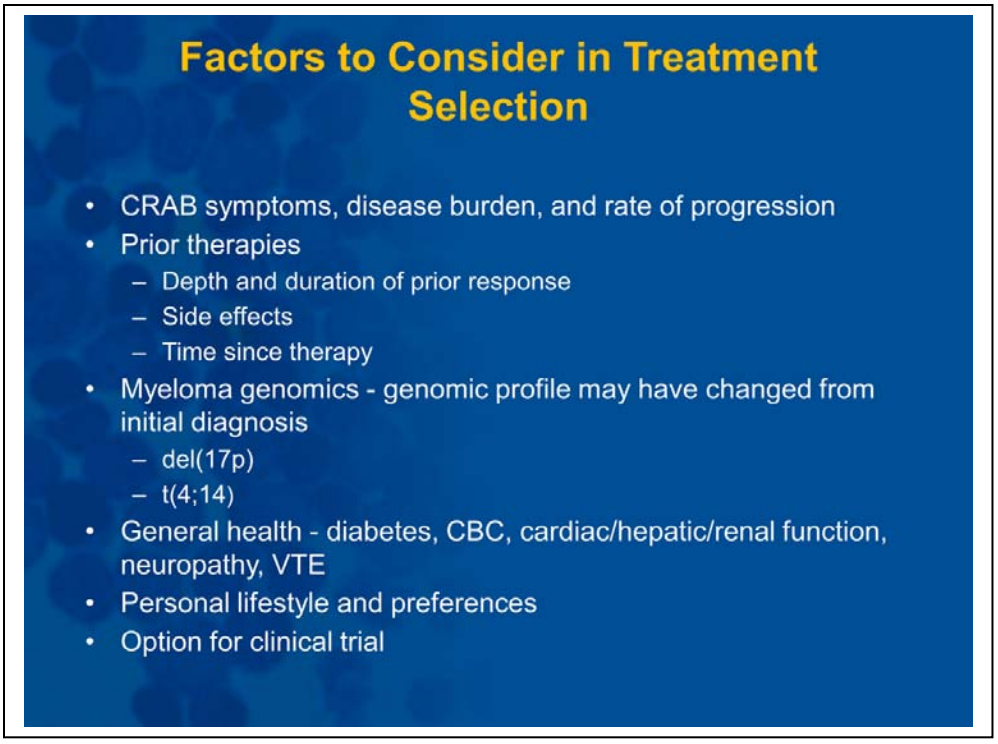


As you know, multiple myeloma patients with newly diagnosed disease who get front-line therapy often have prolonged disease control; however, ultimately, most of these patients will relapse, and, with second and third relapses, will see shorter and shorter durations of progression-free survival and disease control.

This slide summarizes a common approach to the treatment of relapsed/refractory myeloma. We still think of patients as transplant-eligible or ineligible. At the time of relapse, if they have had a prolonged period of disease control after the initial transplant, we will always attempt a second, or salvage, autologous stem cell transplant. For patients who had prolonged disease control of greater than 18 to 24 months of PFS, we will consider the potential benefit of a second transplant. Otherwise, other novel treatment options are also an important option for these patients.



We can consider multiple options for those patients who are transplant-ineligible at the time of relapse, as well. As you can see on this slide, historically, retreatment has been an important therapeutic option for these patients. So, for patient who had disease control with their initial treatment, we will often consider retreatment as an option, or will consider using other novel therapies, as well. However, I think it is important to realize that these treatment paradigms are now changing. Historically, when we had limited therapeutic options, when we still only had bortezomib and lenalidomide then clearly, we had to consider retreatment with these agents. Retreatment is an important therapeutic option for patients. However, in today's clinical practice, with multiple new therapeutic agents and with improved treatments, I think retreatment is less and less often an option for these patients, based on the availability of improved therapeutics.

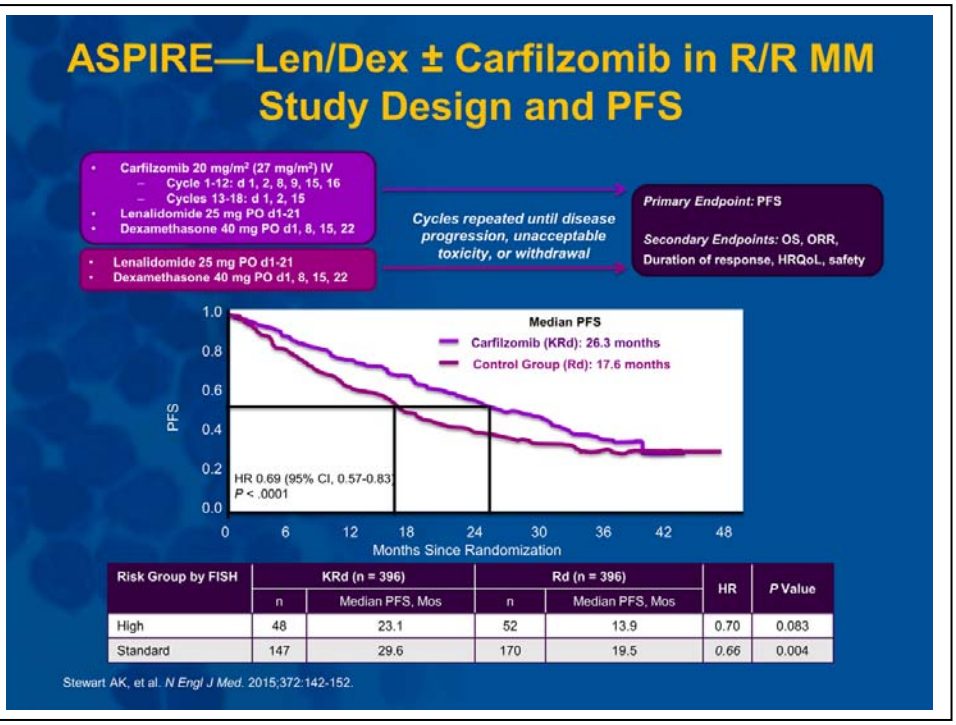


These are the factors to consider in retreatment. Multiple options are considered here, including (1) What is the rate of progression? Are patients having CRAB criteria or end-organ damage, or they experiencing a rapid proliferation with hypercalcemia, progressive renal dysfunction and cord compression, and what is the rate of progression that we see? (2) What are the prior therapies that the patient has previously had? What was the depth and duration of the prior response? What are the side effects they had with the prior therapy and how long has it been since their last therapy prior to the beginning of the treatment-free interval, to consider treatment options? (3) It is also important to consider the biology of the disease: what mutations have they acquired in terms of high-risk features that may have been acquired as the disease progresses, and which may have changed from the time of initial diagnosis? (4) And finally, what other patient-related factors are present, such as comorbidities associated with diabetes, hypertension, renal dysfunction, or cardiac dysfunction, all of which are important factors in weighing treatment decision options.

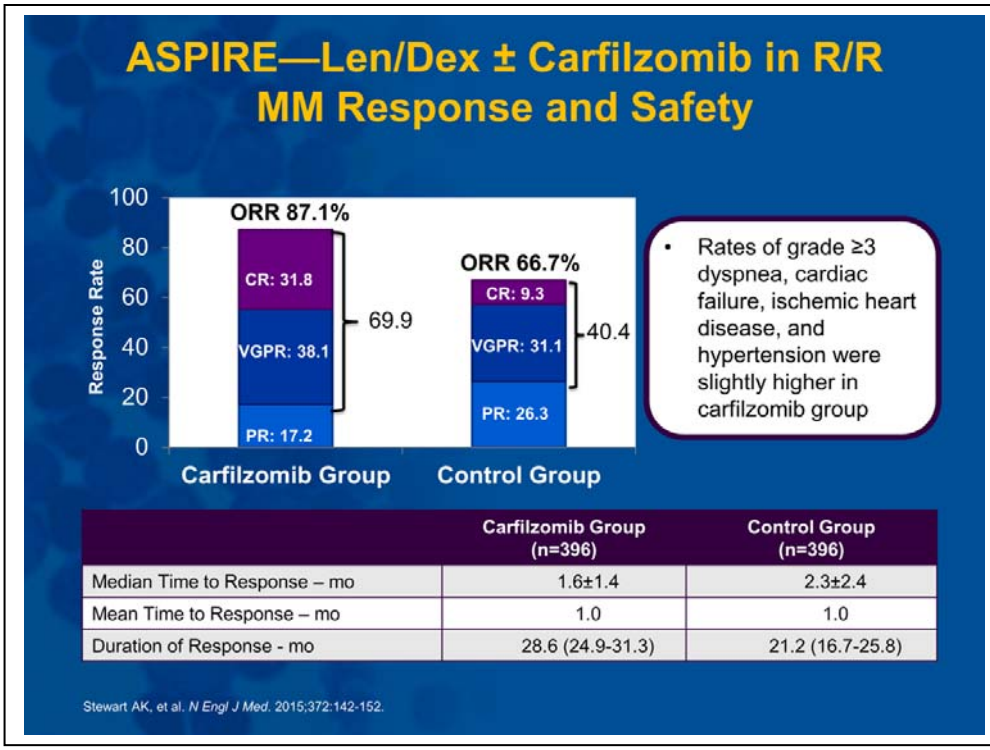
I will now review several phase 3 clinical trials which will help guide analysis of symptoms, and will demonstrate how we optimally manage relapsed/refractory myeloma, and how we incorporate these novel therapies into our treatment paradigm.

The first study I want to review with you is the ASPIRE study, and in this phase 3 study, patients were treated within the experimental arm with lenalidomide, dexamethasone, and carfilzomib versus

lenalidomide and dexamethasone. This is a phase 3 study in relapsed/refractory myeloma in patients with 1 to 3 lines of prior therapy. What we see here is the data from patients who have received either lenalidomide and dexamethasone, or the combination of lenalidomide, dexamethasone and carfilzomib. Importantly, you will note several points as you look at this data; the first is that carfilzomib was stopped in all patients after 18 months of treatment. This is in contrast to continuing on treatment indefinitely until time of progression – which is how all the other phase 3 studies are conducted, and how we practice myeloma now. And here, we see carfilzomib was stopped after 18 months. The second point is that, as we look at some of these data over the next several slides, we're going to focus predominantly on overall response rates and progression-free survival. Importantly, this has been really the mainstay of how we judge therapeutics; in terms of their efficacy, we look at the overall response rate and their PFS as a way of assessing efficacy. However, in this novel agent, we need to start looking at various immunotherapeutic regimens. It is important to look at other options, as well, beyond the bottom line of ORR and PFS. So, now it is important to start thinking about things like minimal residual disease (MRD) and depth of response. It is important to think about the durability of these responses and what will our long-term disease control be with 3- and 4-year PFS? It is also very important to look at the Kaplan-Meier curves and the shape of these curves. When do you see the separation of the Kaplan-Meier progression-free survival curves? Do they come back together? I think this gives you a global perspective on the efficacy and activity of each one of these combinations. So, keep in mind that, looking beyond, ORR and PFS are really just two of the key points to consider here.



We'll start with the ASPIRE study, and what you will notice here is that there is a significant improvement in progression-free survival. In fact, the progression-free survival benefit increased 8 months, from 17.6 to 26 months, and this is the highest progression-free survival we have ever seen in any relapsed/refractory trial; it is very comparable to what we see for newly diagnosed myeloma, highlighting the activity of carfilzomib, lenalidomide, and dexamethasone in combination. Importantly, this is despite stopping carfilzomib after 18 months, and you will still see a durable response and benefit, with patients having progression-free survival of 26 months. On the bottom, you'll see that patients with high-risk, as well as standard-risk, disease benefit, with equivalent or similar improvement in progression-free survival by about 10 months.

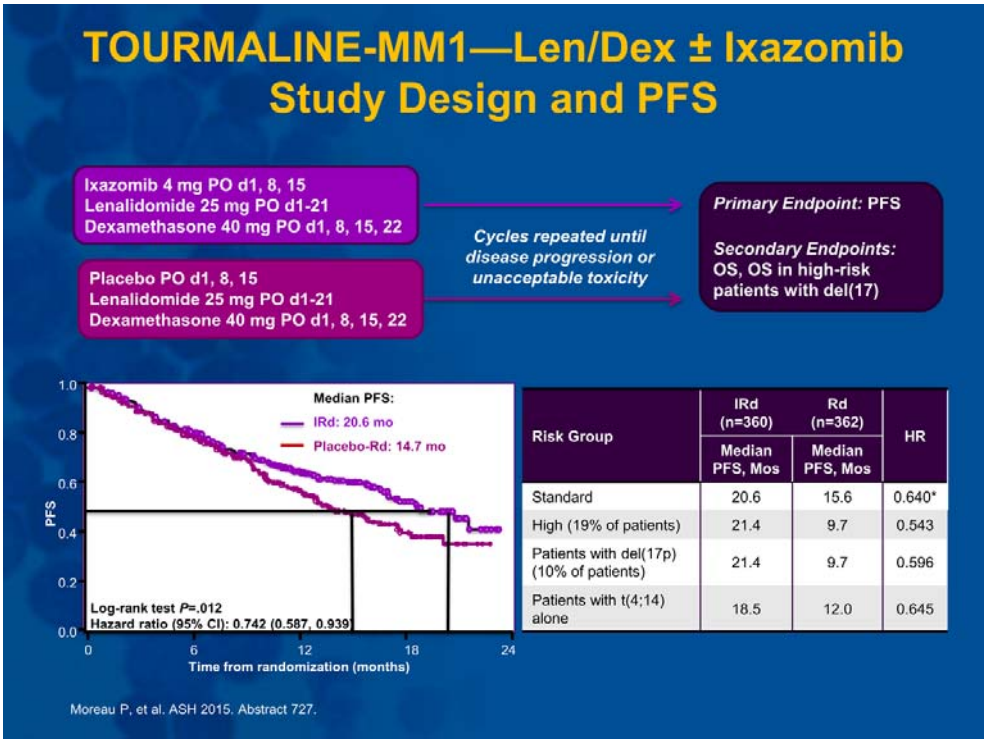


Here, you see the overall response rate. You see an improvement in the overall response rate from 66% to 87%, so an absolute increase of 20% with addition of carfilzomib; importantly, what you'll also notice here is a tripling in the complete response rate. You see a significant improvement in the depth of response from 9% to 31% with addition of carfilzomib. This situation is very similar to what we see with carfilzomib in multiple trials, where you see significant improvement in the depth of response, especially in the newly diagnosed setting, where you also see that addition of carfilzomib leads to improvement in the complete response rate, as well as in minimal residual disease.

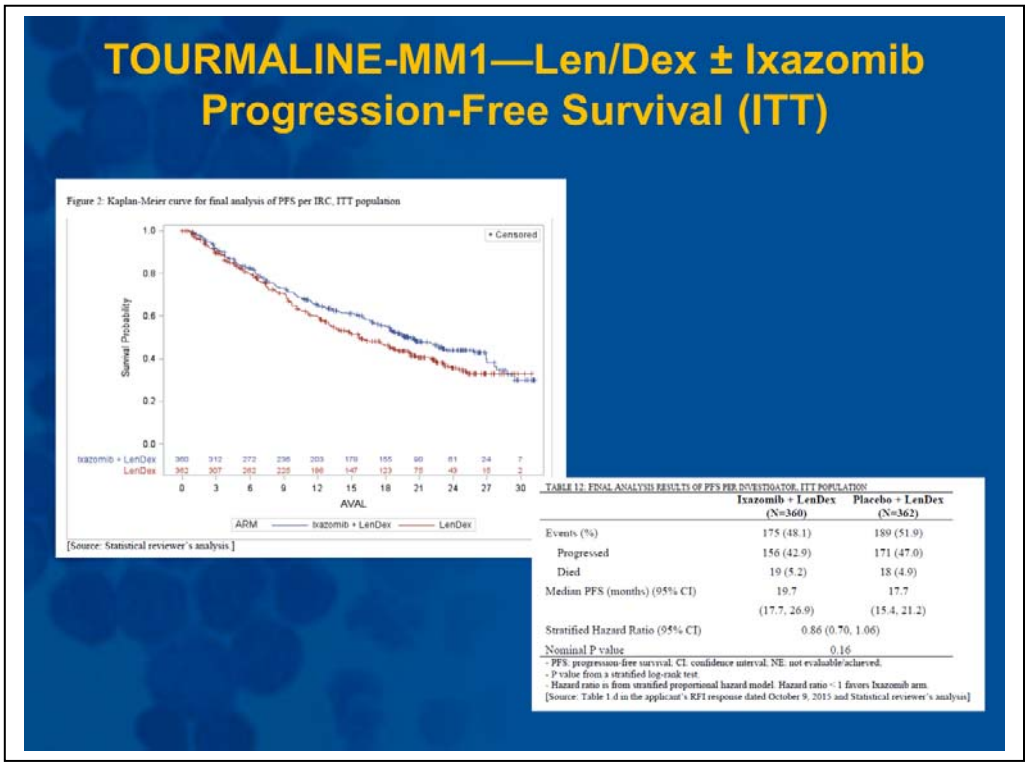
Importantly, there are some side effects to be aware of with carfilzomib. Often, we'll focus on cardiac issues that we see with carfilzomib, though we'll only see a small number, approximately 4% of patients, with cardiac dysfunction. However, it is important to realize that most of these patients will develop a decrease in their ejection fraction, often after several months, will have complete resolution of their symptoms and recovery of their ejection fraction, without any detriment in their quality of life.

The other important side effect that we see in patients treated with carfilzomib is hypertension: 25-30% of patients will have hypertension, as well as a transient shortness of breath. This is important for physicians, as well as nurses, healthcare providers and patients to recognize. Importantly, patients will acclimate to both hypertension and shortness of breath, and both will continue to improve over time. This can be managed both through supportive care, as well as with diuresis.

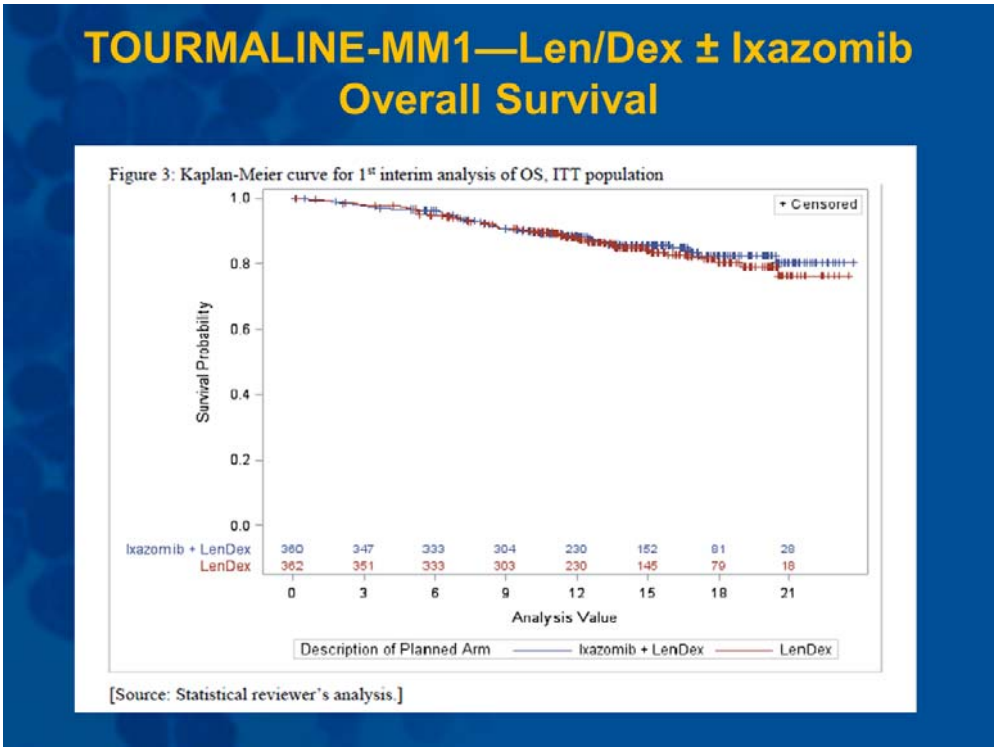
The second phase 3 trial I want to review with you is the TOURMALINE study. This trial is a phase 3 study in relapsed/refractory myeloma, again with patients with 1 to 3 lines of prior therapy; here, they compared lenalidomide and dexamethasone versus the experimental arm of lenalidomide, dexamethasone, and ixazomib. What you see in the interim analysis is a 6-month improvement in progression-free survival from 14 months to 20 months.



Risk Group	IRd (n=360) Median PFS, Mos	Rd (n=362) Median PFS, Mos	HR
Standard	20.6	15.6	0.640*
High (19% of patients)	21.4	9.7	0.543
Patients with del(17p) (10% of patients)	21.4	9.7	0.596
Patients with t(4;14) alone	18.5	12.0	0.645

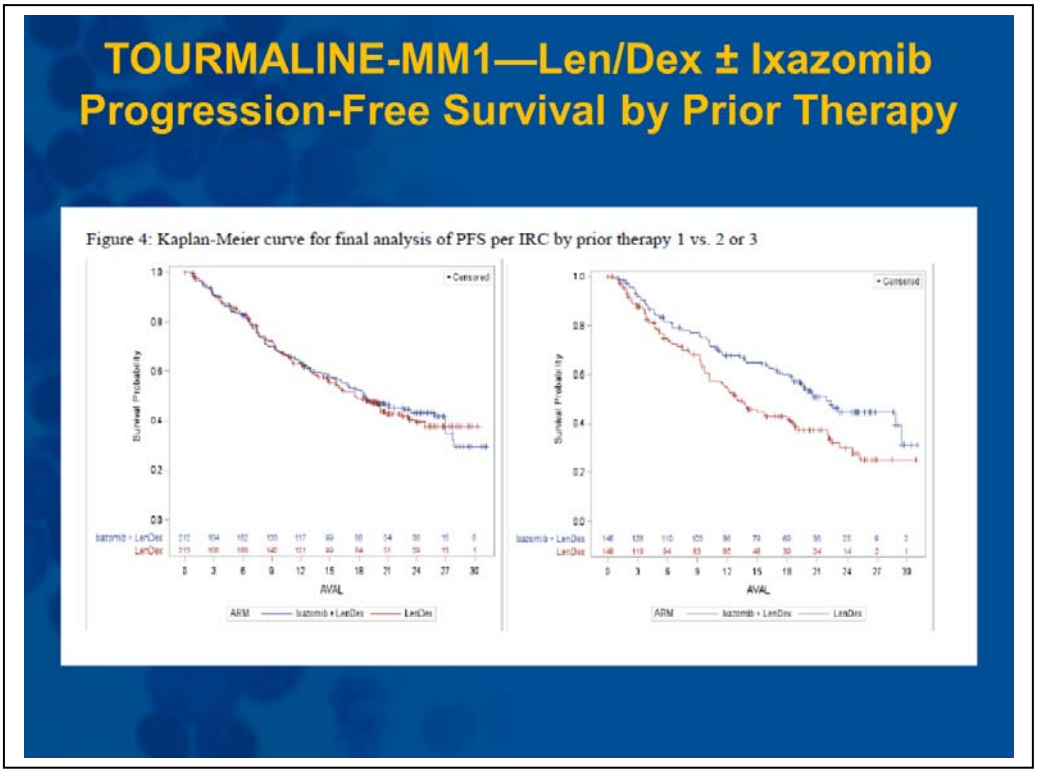


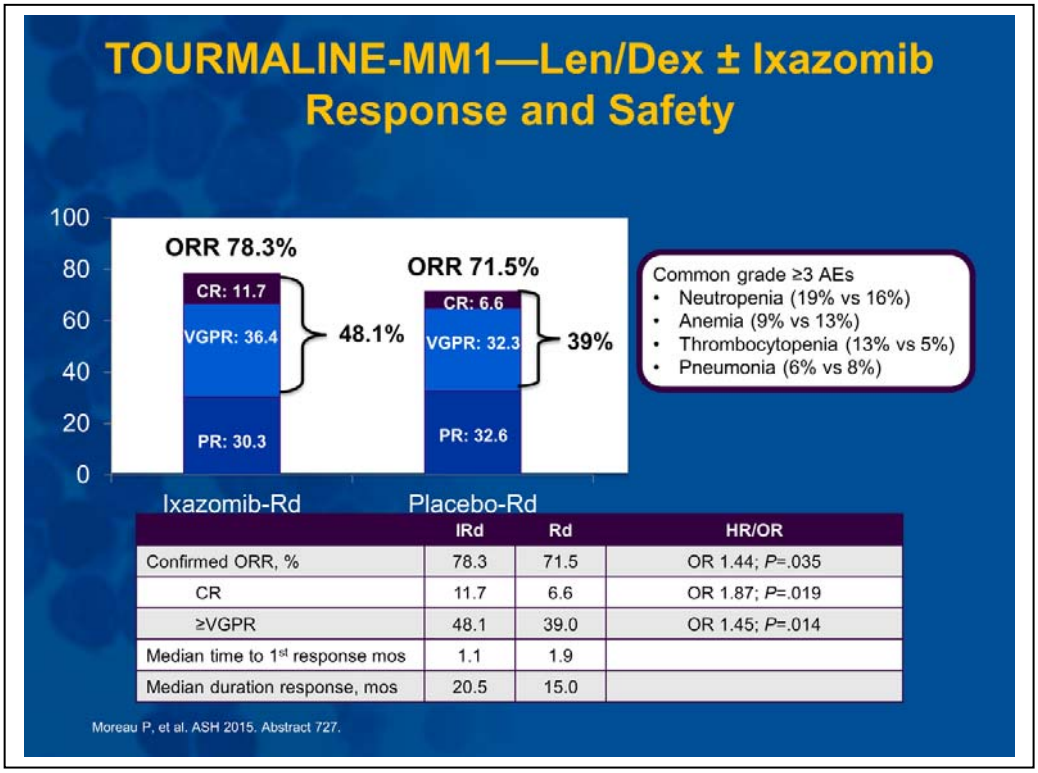
However, when you look at the final progression-free survival by investigator, on an intention-to-treat basis, the progression-free survival was 2 months. Importantly, also, when you look at PFS, at the Kaplan-Meier curves, in fact, you will see that the progression-free survival starts to separate at a later time point, at 9 months, as opposed to the early separation that we typically see in most phase 3 studies with a three-drug versus a two-drug combination.



When we look at overall survival, although this is an early first interim analysis, there was no difference in overall survival with the three-drug versus the two-drug combination.

And finally, when you look at the FDA statistical review, at progression-free survival by prior therapies, interestingly noted here in patients with one line of prior therapy, there was no benefit in progression-free survival. However, in patients with two or three lines of prior therapy, in this subset analysis with all the caveats, we see a significant benefit in progression-free survival in this subset of patients.

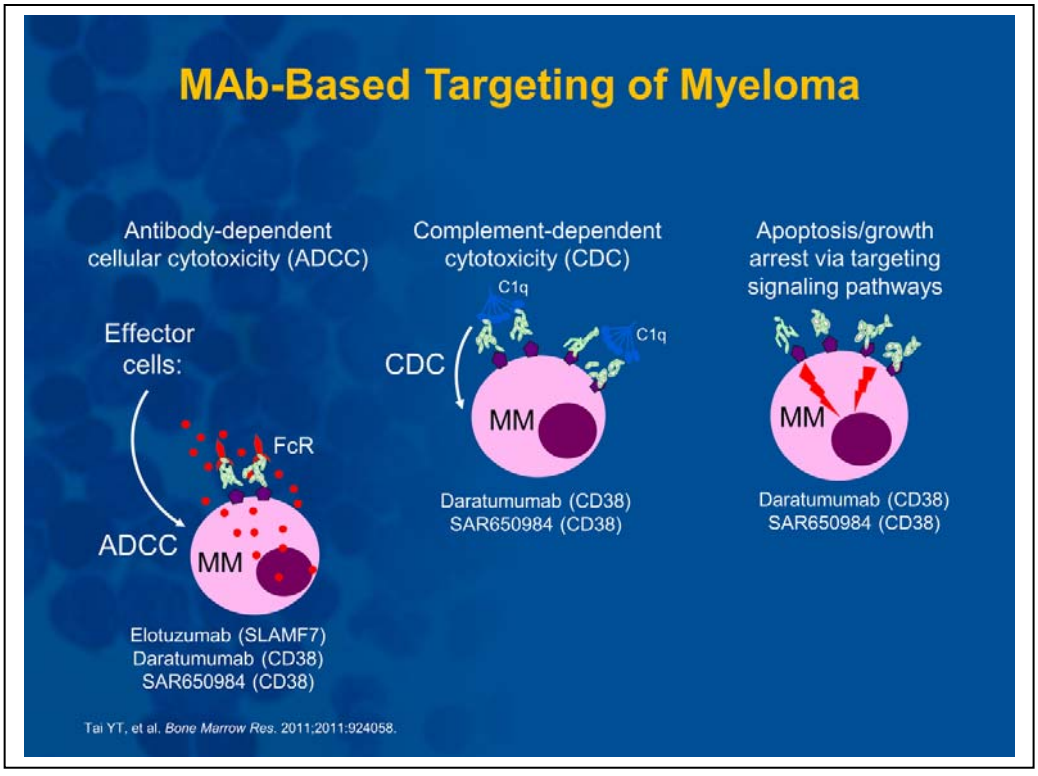


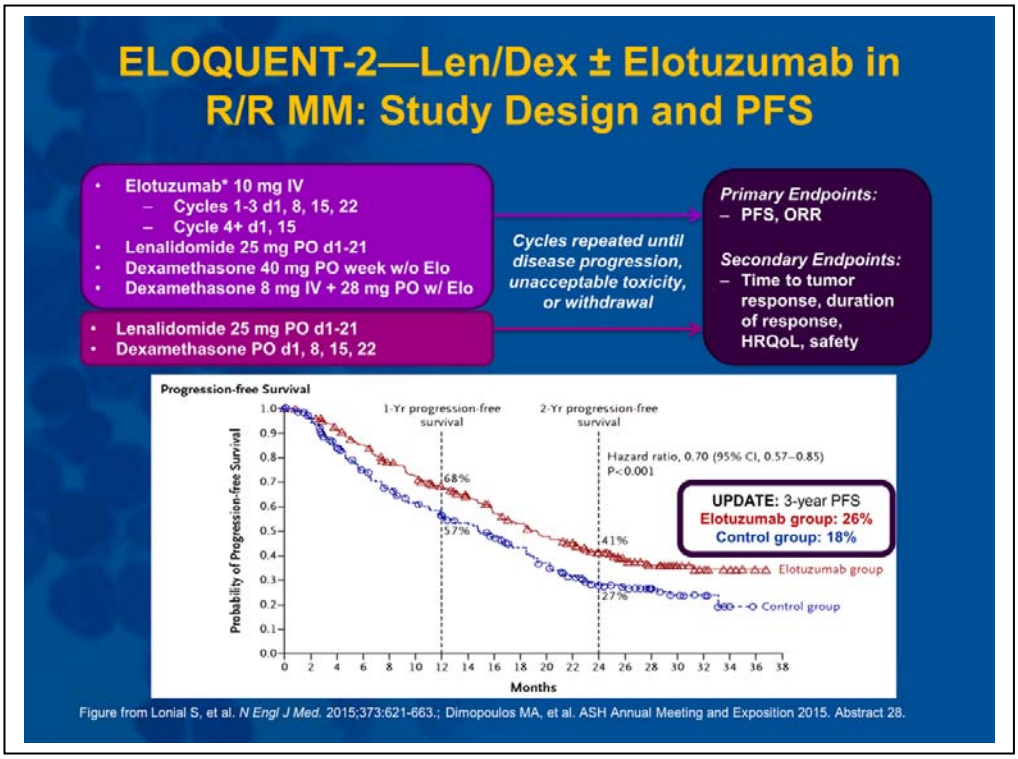


	IRd	Rd	HR/OR
Confirmed ORR, %	78.3	71.5	OR 1.44; *P*=.035
CR	11.7	6.6	OR 1.87; *P*=.019
≥VGPR	48.1	39.0	OR 1.45; *P*=.014
Median time to 1st response mos	1.1	1.9	
Median duration response, mos	20.5	15.0	

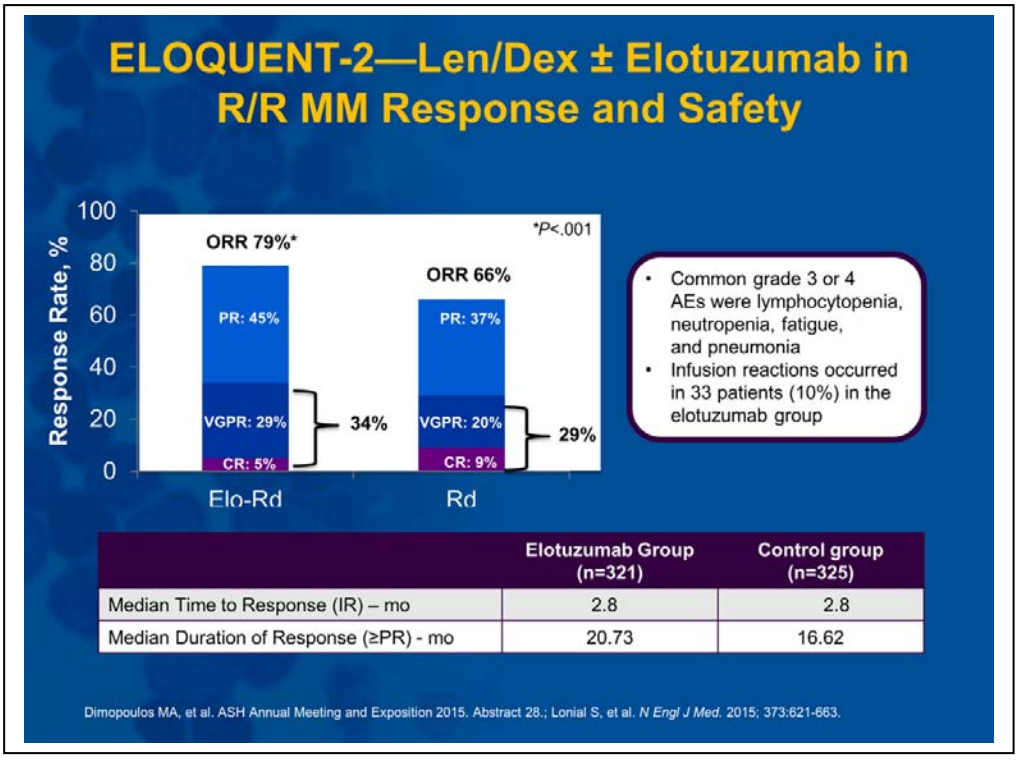
Here, you see the response rates that occur with the addition of ixazomib to lenalidomide and dexamethasone. Importantly, you see a 6% improvement in overall response rate, as well as an improvement in the complete remission rate from 6% to 12%.

As we move forward now, several other therapeutics have also been approved in relapsed/refractory myeloma, beyond carfilzomib and oral ixazomib or an oral proteasome inhibitor, and these include various monoclonal antibodies. When we look at monoclonal antibody-based therapy, it is very exciting. There are multiple mechanisms of action that we see, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), as well as apoptosis/ growth arrest through targeting signaling pathways.



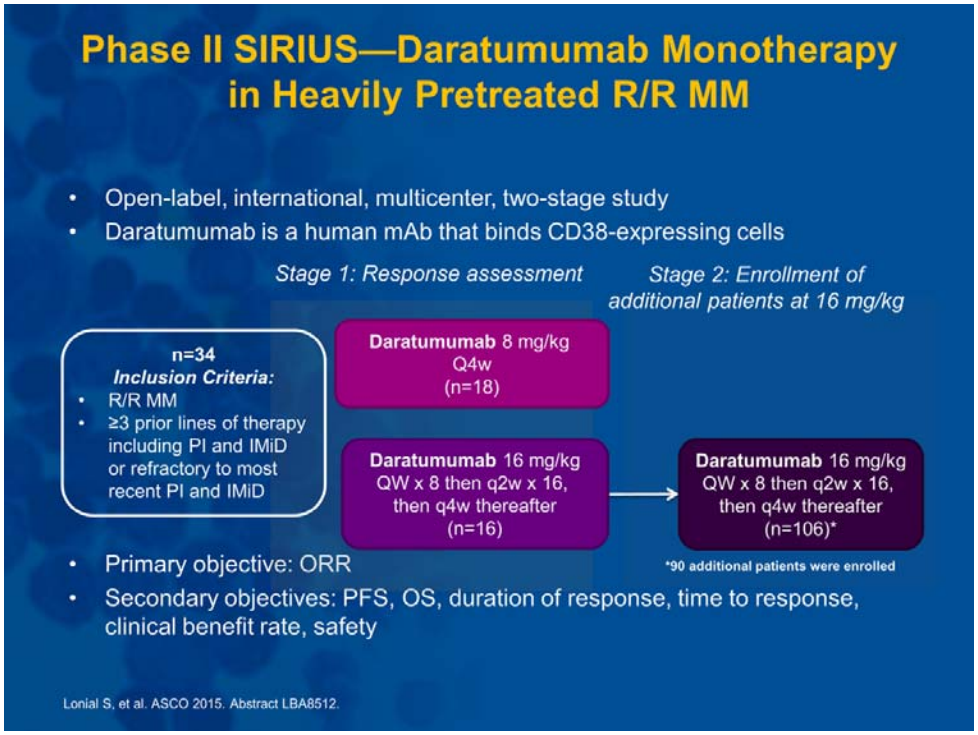


The next trial I would like to review with you is the ELOQUENT-2 study, which is the phase 3 trial of lenalidomide-dexamethasone plus/minus elotuzumab in patients with relapsed/refractory myeloma. Elotuzumab is a monoclonal antibody that targets SLAMF7. SLAMF7 is ubiquitously expressed on plasma cells and myeloma cells, as well as on natural killer (NK) cells. Elotuzumab works directly through both ADCC and CDC. Each of these pathways are typical for monoclonal antibodies; however, because it functions through a dual mechanism of action, we are very excited about elotuzumab.



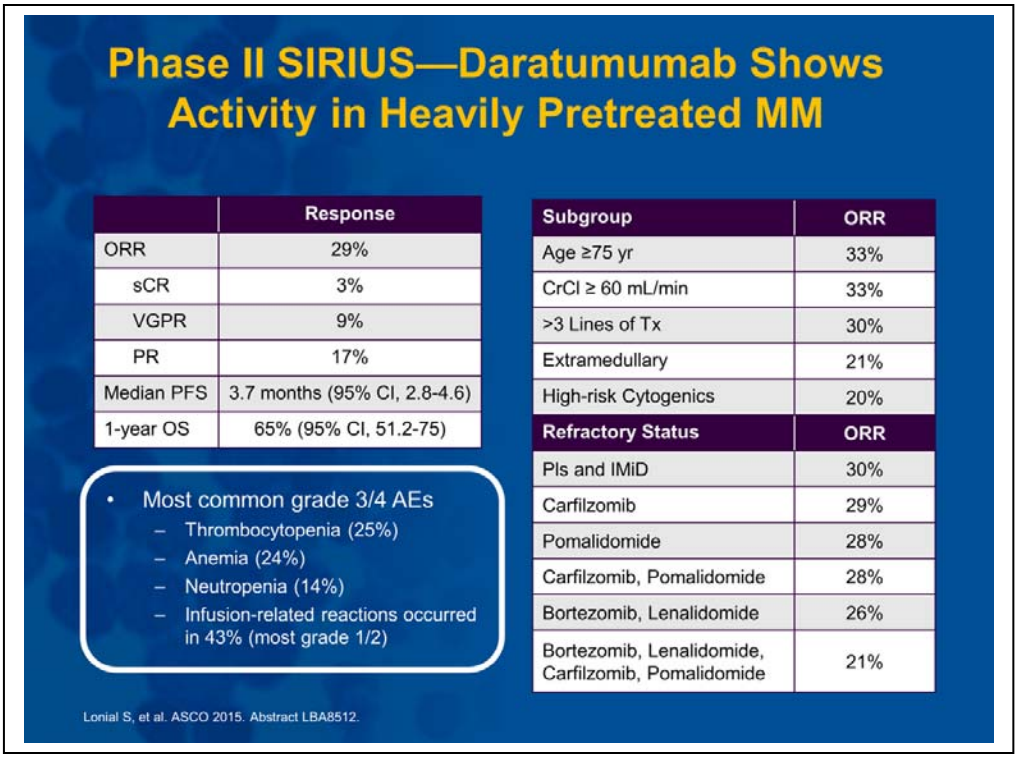
Importantly, in addition to the ADCC and the CDC that we see with typical monoclonal antibodies, we also see an immuno-stimulatory component to elotuzumab. Because we see SLAMF7 expression on NK cells, elotuzumab in fact, activates NK cells and this immuno-stimulatory component leads directly to plasma cell death, as well. Because of this dual mechanism of action that we see with elotuzumab, both with SLAMF7 expression

on plasma cells and NK cells, from direct cell death and plasma cells, as well as the immunostimulatory component, it is a very exciting time for immunotherapeutics in myeloma.



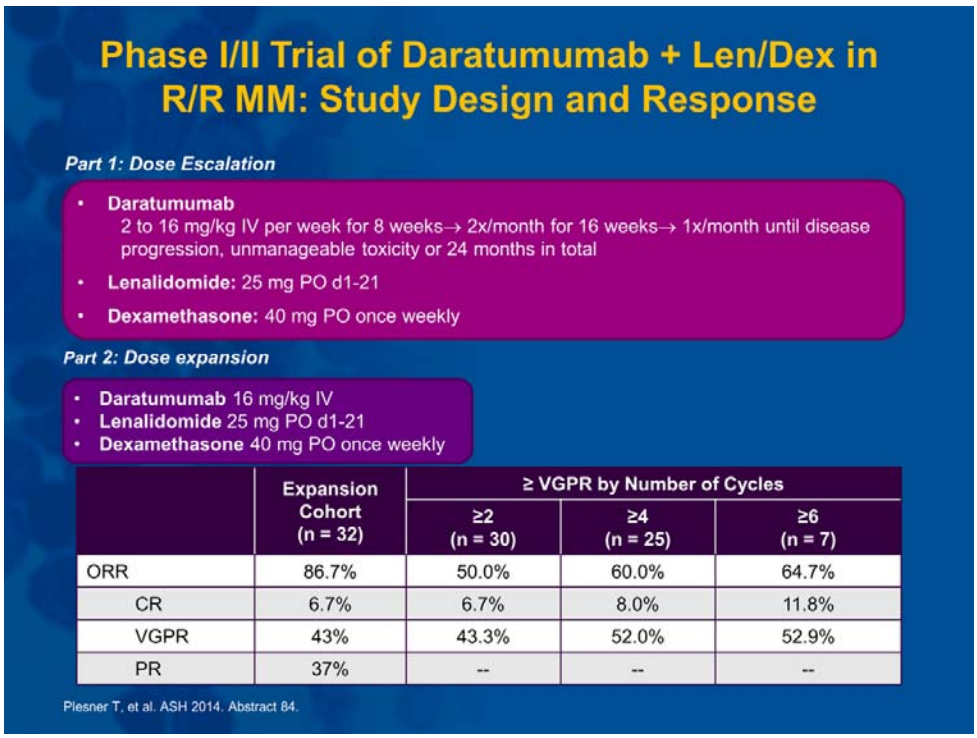
The next therapy I want to review with you and that is approved in the relapsed/ refractory myeloma setting is daratumumab. Daratumumab is another monoclonal antibody that is also approved for patients with relapsed/ refractory myeloma. Daratumumab targets CD38, and CD38 is also ubiquitously expressed on plasma cells.

Daratumumab was approved based on the SIRIUS trial, which was a single-arm phase 2 study. Patients with relapsed/ refractory myeloma had greater than three lines of prior therapy, including a prior proteasome inhibitor and an IMiD, or were refractory to their most recent proteasome inhibitor and IMiD.



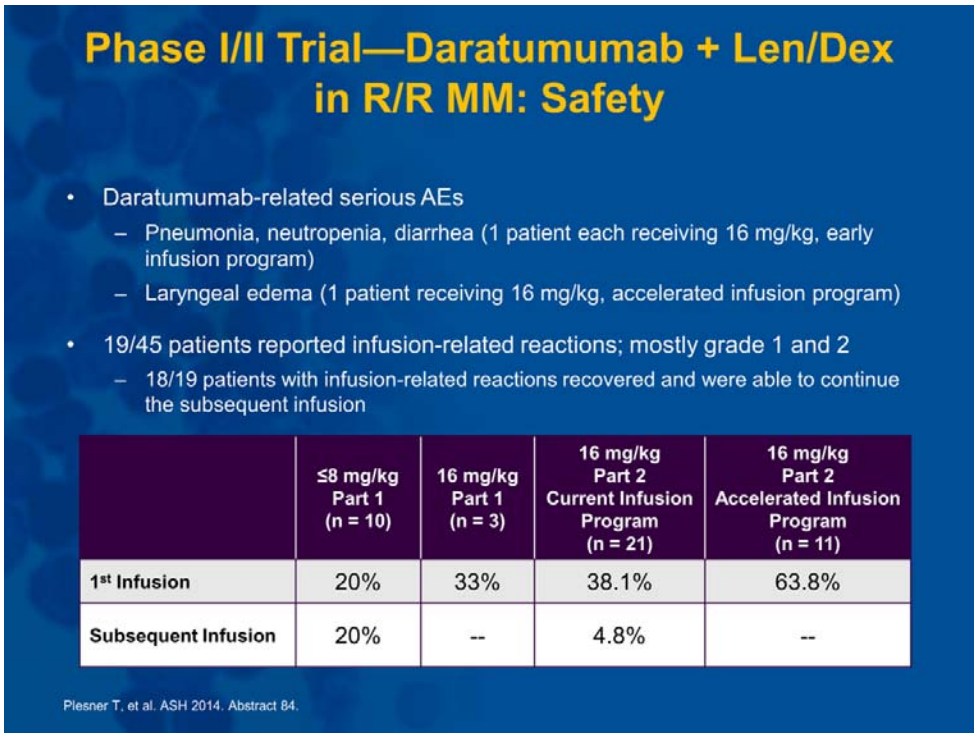
Here, 106 patients were treated, and what you will see is an overall response rate of 29%. These patients with heavily pretreated myeloma had a stringent CR (sCR) of 3%, a median progression-free survival of 3.7 months, and 65% 1-year overall survival.

The most common side effects that we saw with daratumumab are infusion-related reactions, although we saw some cytopenias with thrombocytopenia, anemia, and neutropenia in this single-arm study. The most common side effect practicing physicians need to be aware of is an infusion-related reaction which was seen in approximately 40% of patients in this trial, though most were grade 1 and grade 2. Infusion-related reactions can be seen, and need to be appropriately managed, similar to those seen with other monoclonal antibodies that we have previous experience with, such as rituximab.



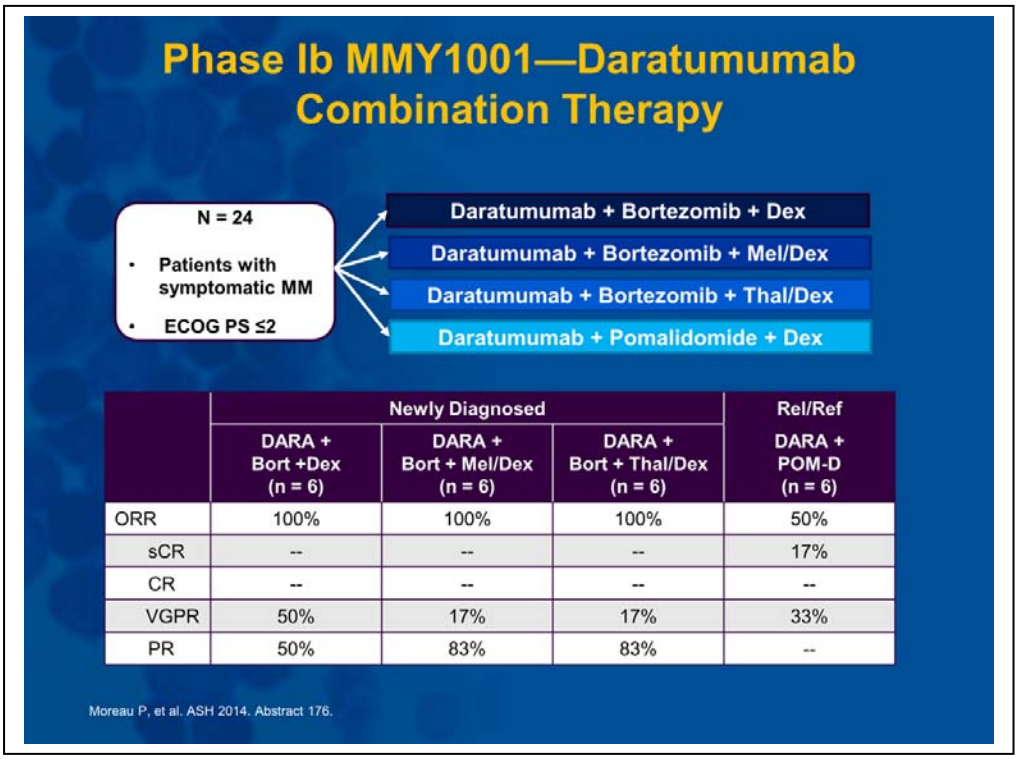
	Expansion Cohort (n = 32)	≥ VGPR by Number of Cycles		
		≥2 (n = 30)	≥4 (n = 25)	≥6 (n = 7)
ORR	86.7%	50.0%	60.0%	64.7%
CR	6.7%	6.7%	8.0%	11.8%
VGPR	43%	43.3%	52.0%	52.9%
PR	37%	--	--	--

Importantly, daratumumab can also be safely combined with other backbone therapies, including lenalidomide and dexamethasone. This is the phase 1/2 trial looking at the combination of daratumumab, lenalidomide, and dexamethasone in relapsed/refractory myeloma. What you see here is an expansion cohort, a very high overall response rate of 86%. As you see, patients stay on therapy longer; there is also a significant improvement in their depth of response, with a VGPR rate of 64% for patients who stay on therapy for more than 6 cycles.



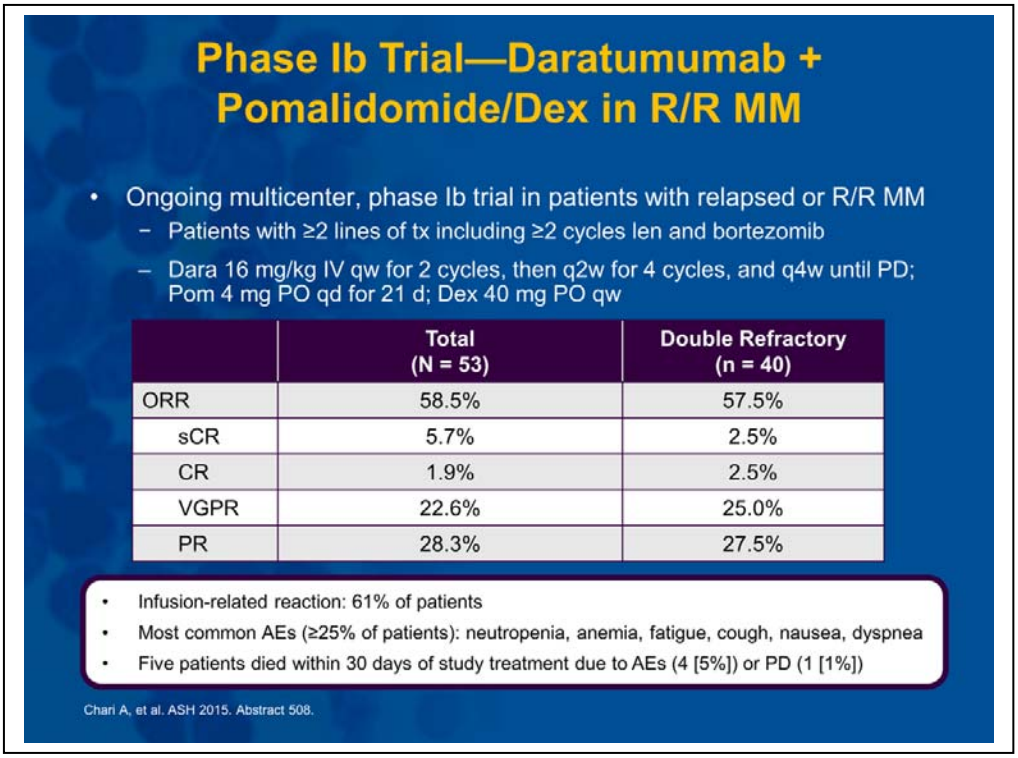
Importantly, the combination of daratumumab, lenalidomide, and dexamethasone is also very safe. Pneumonia, neutropenia, and diarrhea are the most common adverse events. However, importantly, 19 of the 45 patients in this study also had an infusion-related reaction, most of which were grade 1 and grade 2. These occurred in cycle 1 of therapy with the first infusions, and as the patient acclimated, these infusion reactions also diminished with time.

Daratumumab can also be combined with multiple other therapies. This slide summarizes the French experience, in which they combined daratumumab with bortezomib and dexamethasone; with the combination of bortezomib, melphalan and dexamethasone; with the combination of bortezomib, thalidomide and dexamethasone; and with pomalidomide and dexamethasone. As we can see here in this very early study with minimal numbers of patients, daratumumab was safely combined with all of



these various therapeutics. And you can see a very nice, high response rate in all of these different combinations, again highlighting that daratumumab can be safely combined with multiple different therapeutics.

In this phase 1 study, daratumumab was combined with pomalidomide and dexamethasone. In the ongoing phase 1B study, patients with relapsed/refractory myeloma had greater than 2 lines of prior therapy, including prior lenalidomide and dexamethasone. As you can see, the overall response is 58%.

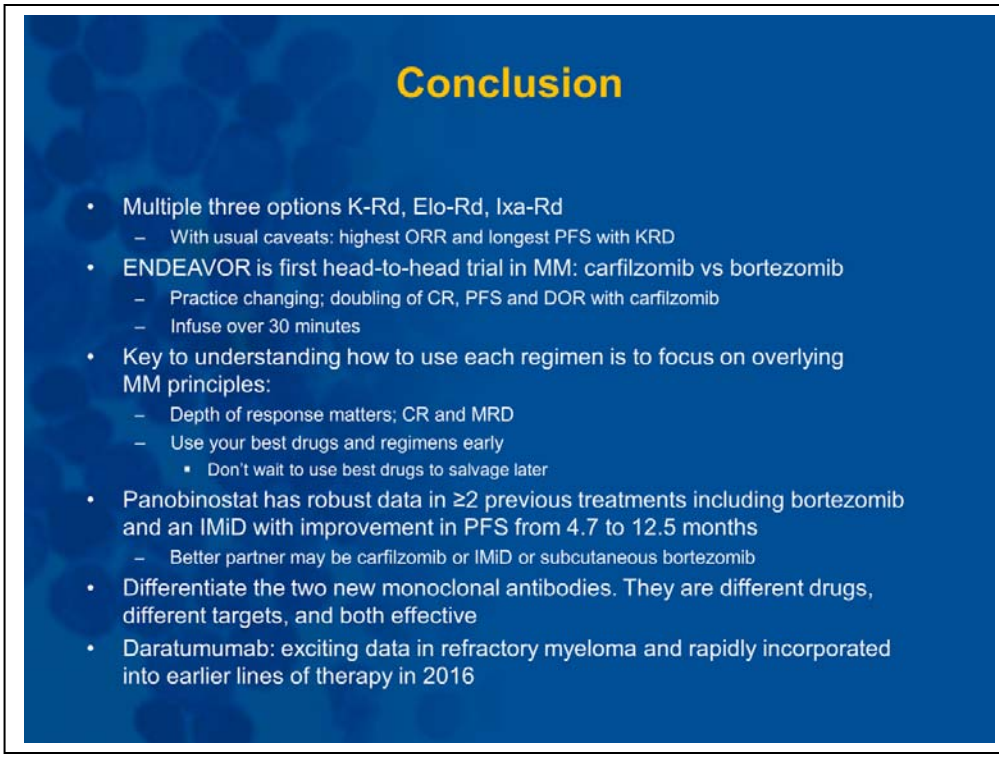


The most common reactions that were seen in this study were infusion-related reactions, similar to what was seen in previous daratumumab studies.

In conclusion, when we look at all of these therapeutic options in relapsed/refractory myeloma, how do we put all this together? We have multiple three-drug options, including carfilzomib, lenalidomide, and dexamethasone; elotuzumab, lenalidomide, and dexamethasone; as well as our oral proteasome inhibitor ixazomib, lenalidomide, and dexamethasone. With all the usual caveats of comparing across phase 3 studies, we see the highest overall response rate and longest progression-free survival with the combination of carfilzomib, lenalidomide, and dexamethasone in the relapsed/refractory setting.

I think ENDEAVOR is the most important practice-changing study, with the first head-to-head comparison in myeloma. In a direct comparison of carfilzomib to bortezomib, we see a doubling of the complete remission rate, as well as a doubling of the progression-free survival and the duration of response, with carfilzomib compared to bortezomib. I think this is an important practice-changing event, as we have now established the superiority of carfilzomib as the proteasome inhibitor of choice. Importantly, when using carfilzomib, it is critical to infuse carfilzomib over 30 minutes, and not use a 10-minute bolus infusion. I think this is important to the safe administration of carfilzomib.

Thinking about all of these therapeutic options can be quite challenging. It's always important to understand how to use these regimens, and to focus on the underlying myeloma and oncologic principles that have been proven time and time again. Number one: the depth of response matters. Our goal of therapy now is to get patients into complete remission, as well as minimal residual disease, and those therapies that can lead us to a complete remission are important options for patients.



Number two: we need to use our best drugs and use them early; don't wait to use our best drugs at salvage or a later time. Though historically in myeloma, we thought about retreatment or using therapies again or waiting to use our best drugs later in terms of salvage options, we have clearly shown that using our best drugs early is an important therapeutic principle to use in myeloma.

Panobinostat has robust data in patients with 2 or more lines of prior therapy, including bortezomib and an IMiD, with an improvement in progression-free survival from 4.7 to 12.5 months. The better partner drug, in fact, may be with carfilzomib or IMiDs or subcutaneous bortezomib. I think this is another important therapy to consider in our patients with relapsed/refractory myeloma.

Finally, it is important to differentiate our two monoclonal antibodies. Elotuzumab targets SLAMF7, which is expressed both on plasma cells, as well as NK cells, and has an immunostimulatory component, as well. Daratumumab targets CD38, which is also ubiquitously expressed on plasma cells. It is a very nice single-agent activity and is able to be combined very nicely with multiple therapeutic agents. You will see some very nice phase 3 data now from daratumumab, to be seen at both ASCO and EHA in 2016. However, it is important to realize that both of these monoclonal antibodies are very different. They work in different targets and have a different mechanism of action that we can see.

In conclusion, there are multiple therapeutic options available to our patients. We have our proteasome inhibitors with bortezomib, carfilzomib, and ixazomib. We have our immunomodulatory drugs with lenalidomide and pomalidomide. We have our new class of drugs with HDAC inhibitors with panobinostat, monoclonal antibodies with elotuzumab and daratumumab, as well as our standard alkylating-based therapy and steroids. These are all important therapeutic options for our patients.

I hope this has been helpful in understanding how we can combine these options, and how we can best use these options for our myeloma patients. Thank you.