Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

Welcome to *Managing Myeloma,* I am Dr. Beth Faiman. In today's presentation, I will be reviewing developing care plans for treatment-based patient monitoring in relapsed/refractory multiple myeloma. In this video, I will provide you with the information and tools necessary to understand updated diagnostic strategies for multiple myeloma, describe the rationale for the use of continuous or maintenance therapy with multiple myeloma patients, and develop a care plan for treatment-based monitoring in relapsed and/or refractory multiple myeloma. Let's get started.

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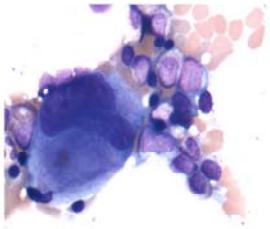
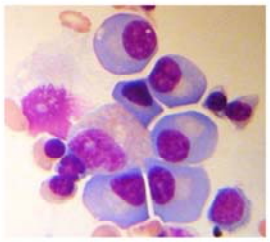
Multiple Myeloma: A Cancer of the Plasma Cells





- Healthy plasma cells produce immunoglobulins in response to foreign body invasion
- Myeloma cells produce abnormal immunoglobulin
  - 65% IgG; 20% IgA
  - 5% to 10% light chains (monoclonal kappa, lambda light chains, Bence Jones proteins)
  - Uncommon IgD, IgE, IgM, or nonsecretory disease

Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33.

Multiple myeloma is a cancer of the bone marrow plasma cells. Plasma cells are generally slow to divide, but when they become active, they can produce abnormal immunoglobulins. Healthy plasma cells produce immunoglobulins in response to foreign antigens. Myeloma cells produce abnormal immunoglobulins, and about 65% of them are IgG and about 25% are IgA type. These are the heavy chains. The heavy chains are accompanied by the light chains which are kappa and lambda. It is very uncommon to have IgD, IgE, or IgM type of myeloma or nonsecretory disease.

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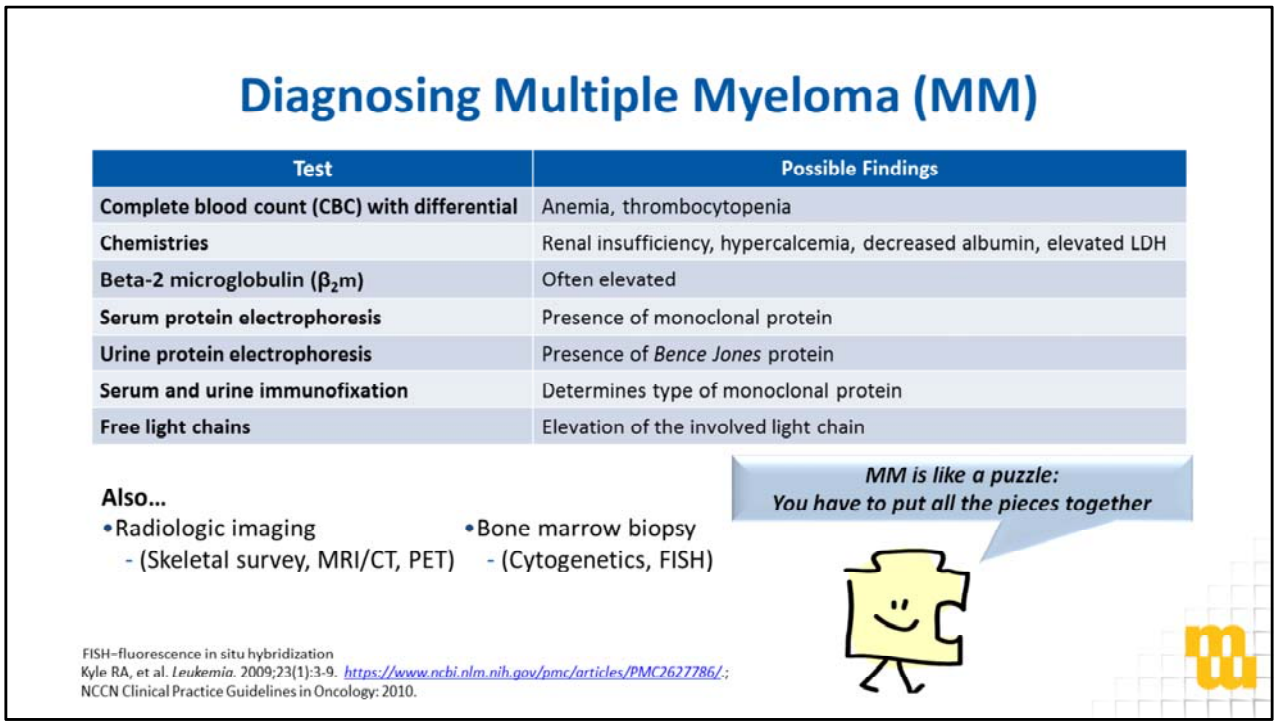

In order to correctly diagnose patients with multiple myeloma, there is a buffet of options that we want to check. This slide highlights the different tests to the left and the possible findings to the right. I often say that diagnosing multiple myeloma is like a puzzle. There are so many different pieces that you have to put together in order to make a correct diagnosis. A very important test is called a CBC, or complete blood count with differential. Patients with myeloma will often be anemic or have thrombocytopenia from the disease. The healthy bone marrow cells are crowded out by the abnormal cells. Chemistry panel is also important to assess organ function. Renal insufficiency or renal failure is very commonly found in patients with multiple myeloma at diagnosis or throughout. Elevated LDH levels are also found in patients with myeloma with very active disease. Beta-2 microglobulin is a nonspecific marker of inflammation in patients with myeloma. Beta-2 microglobulins can be elevated in patients who have sepsis or infections, but they can also be elevated in patients with active myeloma. The protein electrophoresis tests are very important as well. Serum and urine protein electrophoresis will look for the presence of a monoclonal protein. That is a clone of a normal protein which is causing damage to the organs. Serum and urine immunofixation are important to determine which type of protein is affected. Free light chains can also be elevated in patients with myeloma. A moment ago, I mentioned that there is a heavy chain and a light chain component to the immunoglobulin structure. The light chains can kind of fly off the structure; those are kappa or lambda. It is really important when you are diagnosing and monitoring your patients with myeloma to know whether they have kappa or lambda type of light chains, and follow those levels throughout the disease continuum. Those were the laboratory tests, and we want to add to that the radiologic imaging. Skeletal survey is a gold standard to screen for damage to bones from myeloma; however, you have to have about 30% to 40% bone loss present before it can be picked up on radiographs. Therefore, if the individual has suspicious areas of disease activity, an MRI, CT, or PET scan can be ordered. Finally, a bone marrow aspirate and biopsy is very important. Just like in other tumor types, we want to look at the characteristics of the tumor under the microscope, and it is best done on a bone marrow biopsy. From that, we can look at cytogenetics and FISH testing to look for their genetic risks.

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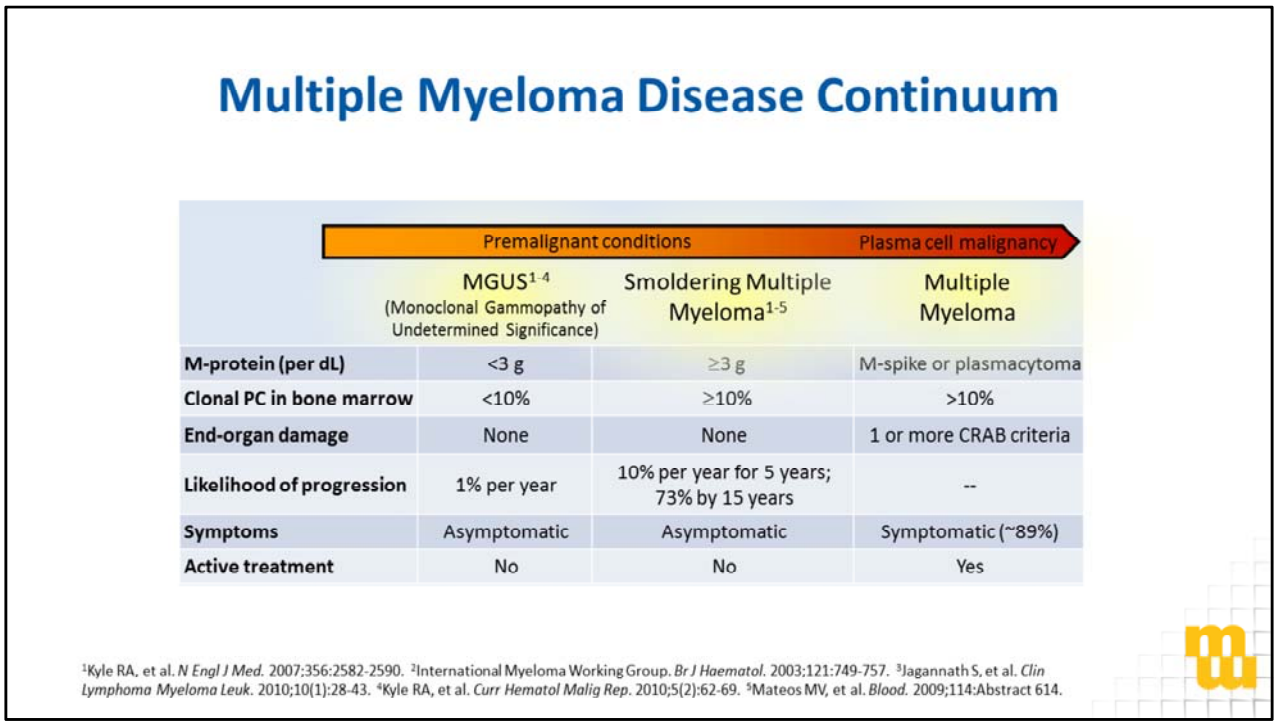

Not all patients with an abnormal protein have multiple myeloma; there is a disease continuum. There is a premalignant condition called monoclonal gammopathy of unknown significance (MGUS). Patients with MGUS have a low amount of abnormal paraprotein, they have a low amount of bone marrow plasma cell percentage, they have no evidence of end-organ damage – which we will talk about in a moment – and their likelihood of progression is very low, at a rate of about 1% per year over 30 to 40 years. The second category where patients with an abnormal paraprotein in the serum or urine will fall would be in the smoldering myeloma category. These individuals have a higher amount of monoclonal paraprotein in the blood or the urine. They have a higher percentage of clonal bone marrow plasma cells generally, and they still have no evidence of end-organ damage. The rate and likelihood of progression is higher in patients with smoldering myeloma. It is about 10% per year for 5 years, and then by 15 years, about 73% of those individuals will develop symptomatic myeloma requiring therapy. The third level in which patients are catapulted into the category of multiple myeloma is when the individual has any M-spike, or a collection of tumor cells called a plasmacytoma, bone marrow clonal plasma cell percentage of greater than 10%, and one or more CRAB criteria.

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Disease Progression in Smoldering Multiple Myeloma and MGUS Patients

10% per year risk of progression: first 5 years

Important to identify ones who will need treatment; no benefit if treatment too early

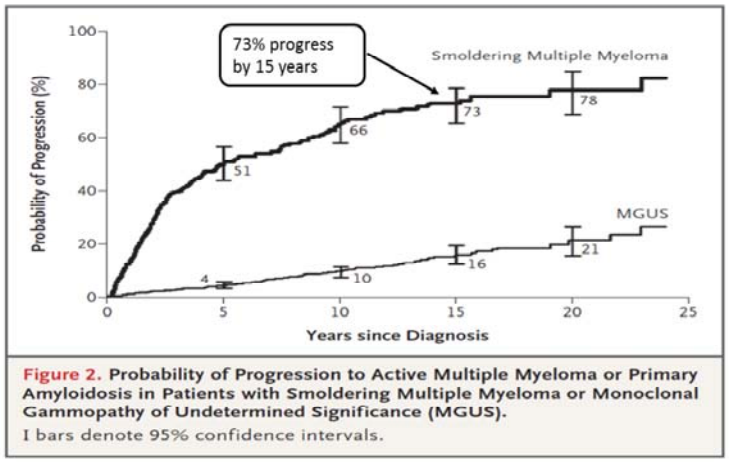

Figure 2. Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS).
I bars denote 95% confidence intervals.

Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590.

Now, I mentioned briefly a moment ago that patients with smoldering myeloma are more likely to progress to active myeloma. The trend today in multiple myeloma is to try to tease out those individuals with the higher risk characteristics that are more likely to require treatment, and intervene in the context of a clinical trial before that individual actually develops CRAB related criteria. We will discuss CRAB on a future slide, but it includes hypercalcemia, renal insufficiency, anemia, and bone lesions. As I mentioned, the risk of progressing is about 10% per year in the first 5 years among patients with higher levels of M-spike (about 3 g/dL of IgG), and it is important to find those ones that need treatment emergently as per the results mentioned.

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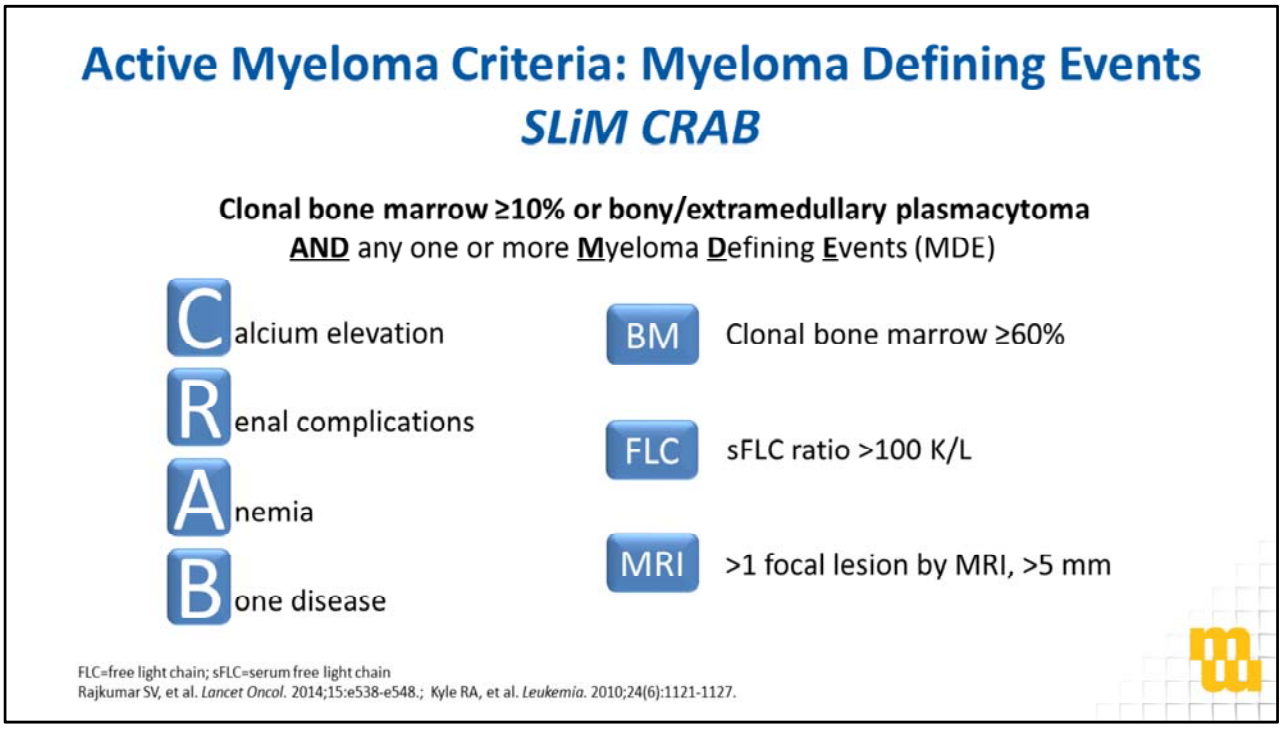

Those individuals with active myeloma have myeloma-defining events which we call SLiM CRAB criteria. In 2014, the International Myeloma Working Group wrote a paper. The lead author was Dr. Rajkumar from the Mayo Clinic, and it highlighted that our CRAB criteria are important (again, hypercalcemia, renal insufficiency, anemia, and bone disease), but then added three additional factors to look for. If the patients have a bone marrow clonal plasma cell percentage of greater than 60%, have a serum-free light chain ratio of kappa to lambda of greater than 100, and an MRI with more than one focal lesion greater than 5 mm, those patients need to be treated as multiple myeloma, because we want to delay worsening effects on the individual.

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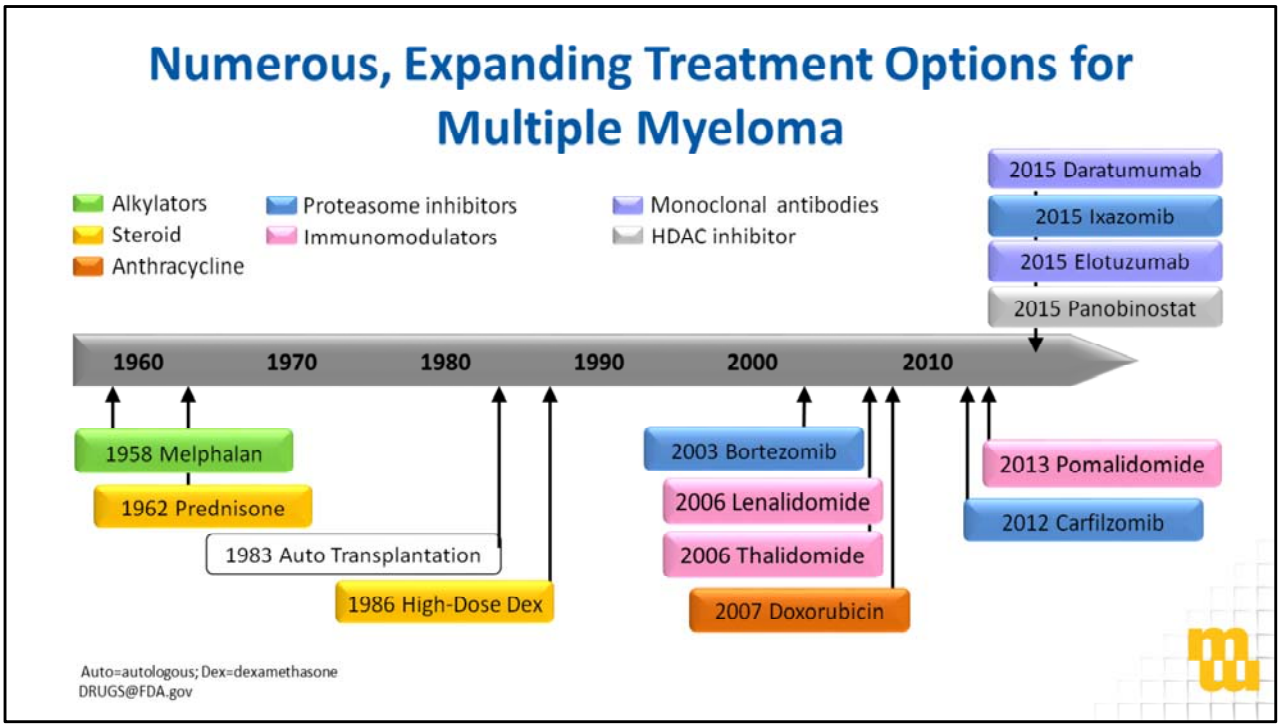

Once patients are diagnosed with multiple myeloma – that means that they have the abnormal paraprotein that is causing end-organ damage or impending end-organ damage – there are numerous expanding treatment options. When I first started managing myeloma patients in the mid-1990s, we had only a handful of treatment options, and now, we have a buffet of options. From the 1960s, we had prednisone and melphalan which is still used in some countries such as in Europe as a standard of care in many cases. Autologous stem cell transplant in the 1980s and 1990s became more commonplace. In the 2000s was when we had the explosions of new therapy starting with bortezomib, then thalidomide, and lenalidomide as well. In 2015, we had daratumumab, ixazomib, elotuzumab, and panobinostat, all approved by the FDA for use in patients with multiple myeloma, and in the last few years, we have had more expanding indications. As you can imagine, a patient with newly diagnosed myeloma has so many treatment options. The question is: how do we recommend treatment?

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Drugs and Drug Classes Approved for MM

Drug Class	Name	Abbreviations	Brand
Proteasome Inhibitor	Bortezomib	btz, V	VELCADE®
	Carfilzomib Ixazomib	Cfz, Car, K I	KYPROLIS® NINLARO®
Immunomodulatory Agent	Lenalidomide	len, R	REVLIMID®
	Thalidomide	thal, T	THALOMID®
	Pomalidomide	pom	POMALYST®
Alkylating Agent	Melphalan	mel, M	ALKERAN®, ALPHALAN®
	Cyclophosphamide	CTX, Cy, C	CYTOXAN®
Corticosteroid	Prednisone	pred, P	DELTASONE®
	Dexamethasone	D, d, Dex, DXM	DECADRON®
Bisphosphonate	Pamidronate	pmd	AREDIA®
	Zoledronic Acid	zol	ZOMETA®
Histone Deactylase Inhibitor	Panobinostat	P	FARYDAK®
Monoclonal Antibodies	Elotuzumab Daratumumab	ELO DARA	EMPLICITI® DARZALEX®

This next slide highlights the different drugs and drug classes approved for multiple myeloma. What is really nice is we are able to use drugs ranging from the IMiDs, which are the immunomodulatory drugs such as lenalidomide, thalidomide, and pomalidomide; the mAbs, the monoclonal antibodies; and the proteosome inhibitors such as bortezomib, carfilzomib, and ixazomib. Typically, in multiple myeloma these days, we mix and match one drug from each class to target the bone marrow stroma in that microenvironment in different ways. Remember the bone marrow microenvironment in patients with multiple myeloma is very complex. There are many different osteoclast-activating factors that dissolve bone, osteoblasts which rebuild bone are reduced, and we also have that VEGF and tumor necrosis factor and NF-kappa B, etc. We want to target each of these different areas in different ways with various drug classes. On this slide, I have abbreviations of each drug class which are something to remember in the future slides.

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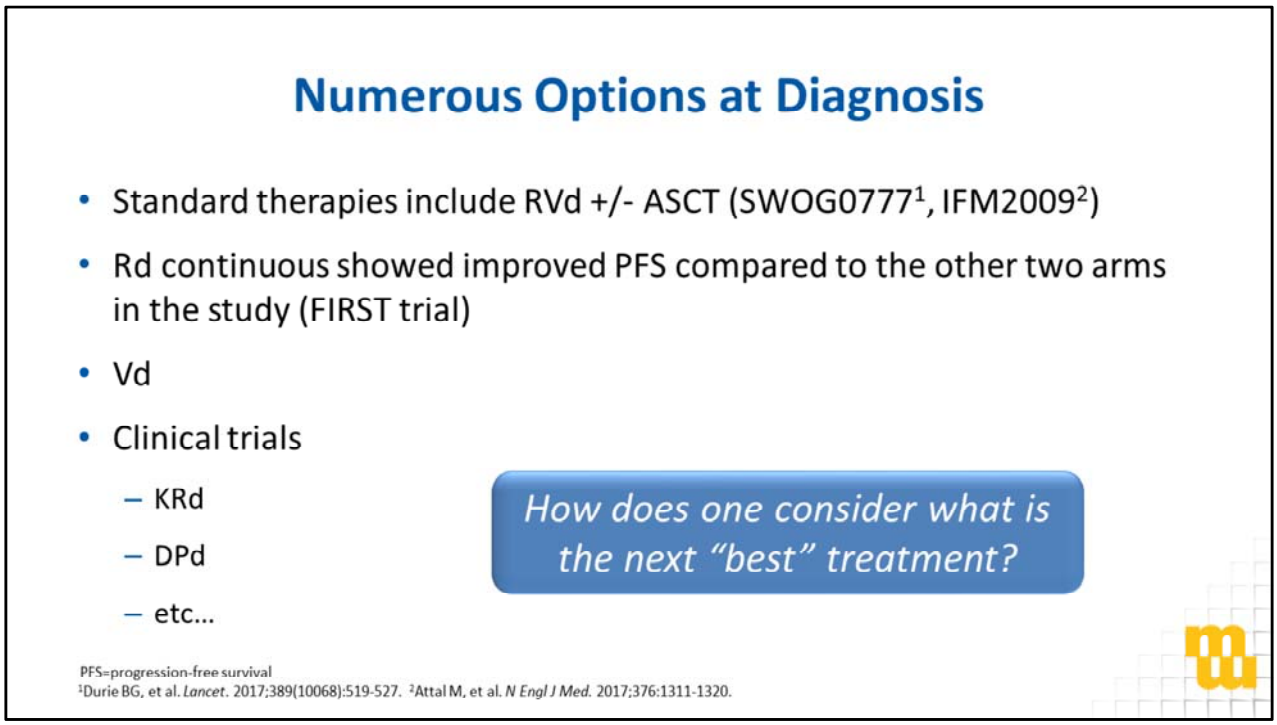

Again, there are numerous options in diagnosis. Standard therapies in myeloma today tend to focus on triplet therapies for healthier, fit individuals; typically, bortezomib, lenalidomide, and dexamethasone. That three-drug combination is given most commonly based on results of a SWOG trial, the SWOG777 study, which showed that the patients who had bortezomib for a period of 8 cycles and then went on to lenalidomide continuous therapy, those three drugs compared to those who had two drugs had a longer progression-free survival and overall survival without stem cell transplant. We also know from the IFM 2009 study, which was a collaboration between the French Myeloma Group and the Dana Farber Cancer Institute, that patients who had a transplant and a three-drug induction (bortezomib, lenalidomide, and dexamethasone) had a longer remission or progression-free survival rate. We know that the three-drug is a very effective regimen as long as you can minimize toxicities. Namely, the biggest toxicity in the SWOG777 study was peripheral neuropathy. If we are aware of this and we can assess our patients' risk for neuropathy, ask them if they have any changes to the nerve function when they are receiving bortezomib for example, then we can address and intervene those symptoms accordingly. The FIRST trial was a study where patients were randomized to three different arms. Lenalidomide and dexamethasone continuous was the first arm. The second arm was lenalidomide and dexamethasone for a fixed dose, and that was for 18 cycles. Melphalan, prednisone, and thalidomide comprised the third arm.

What was nice about this study is that it was an all-oral regimen in patients who were not transplant candidates, and we saw that continuous lenalidomide and dexamethasone had improved progression-free survival compared to the other two arms. Based on this, your patients can either get three drugs or two drugs at diagnosis, and those were the studies to support the most common regimens that we give. There are some studies that use bortezomib and dexamethasone in newly diagnosed patients. Primarily patients that you want to bring into the clinic or cannot afford the oral agents to be used at diagnosis would be considered. You would also consider bortezomib-dexamethasone in those patients with compromised renal function because bortezomib is very safe in patients that have compromised renal function without those reductions necessary. There are numerous clinical trials with carfilzomib, lenalidomide, and dexamethasone, as well as daratumumab, pomalidomide, and dexamethasone among many others. The take-home point is that when patients are diagnosed with multiple myeloma, they have numerous treatment options available and we are still learning best practices as to how to best use those treatments. If a clinical trial is available in that person's area, we want to encourage clinical trial participation so that we can find the best way to use the drugs that we currently have in our armamentarium, or find better ways to treat myeloma.

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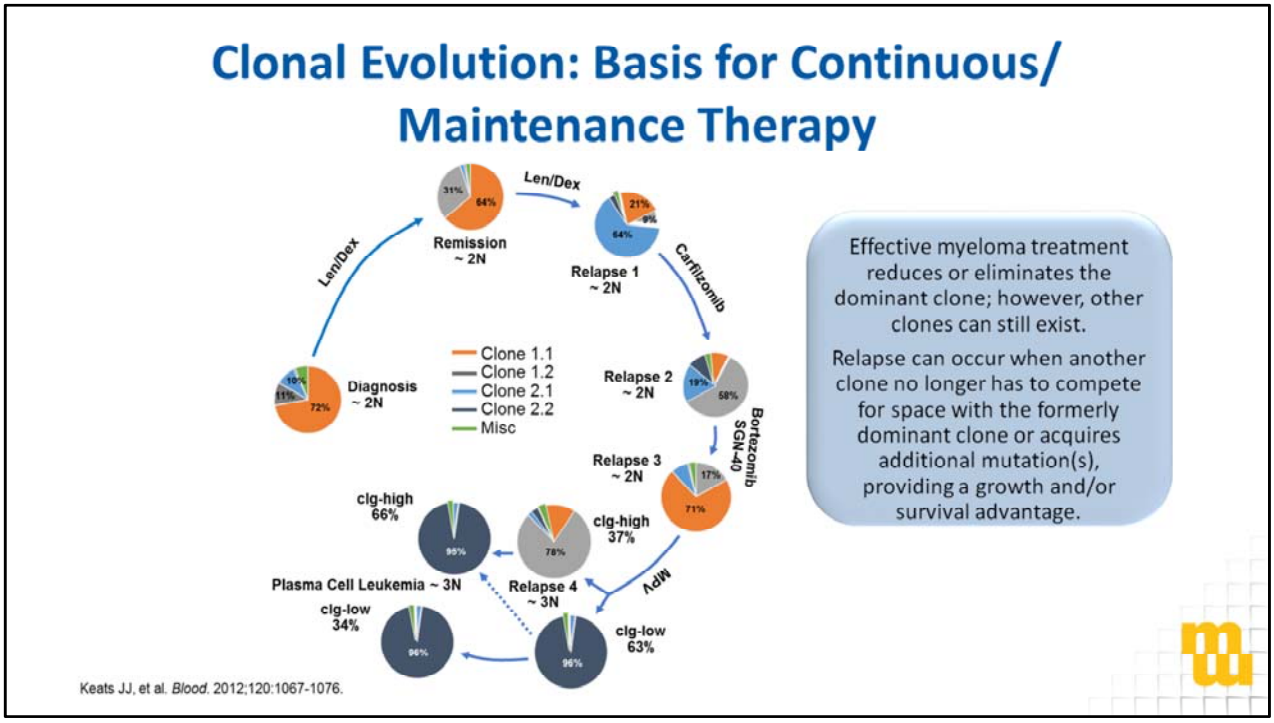

For those patients that are treated with newly diagnosed myeloma on a variety of therapies, again the trend is continuous therapy with or without stem cell transplant. We can improve one's progression-free survival and overall survival with three drugs, but we do not necessarily need to use three drugs in all individuals. However, it is important to know that these are abnormal clones of normal cells and those clones change over time. Effective myeloma treatment reduces those abnormal clones, but new dominant clones can recur. This slide was based on a study from Keats and it was reported in *Blood* in 2012, and the idea is still the same. The clone that is the dominant one at diagnosis that is suppressed will be essentially eliminated and then new clones can take over. Eventually at the end of one's treatment, when they become relapsed and refractory to treatment, the clone that you are treating is entirely different oftentimes than the clone that they presented with.

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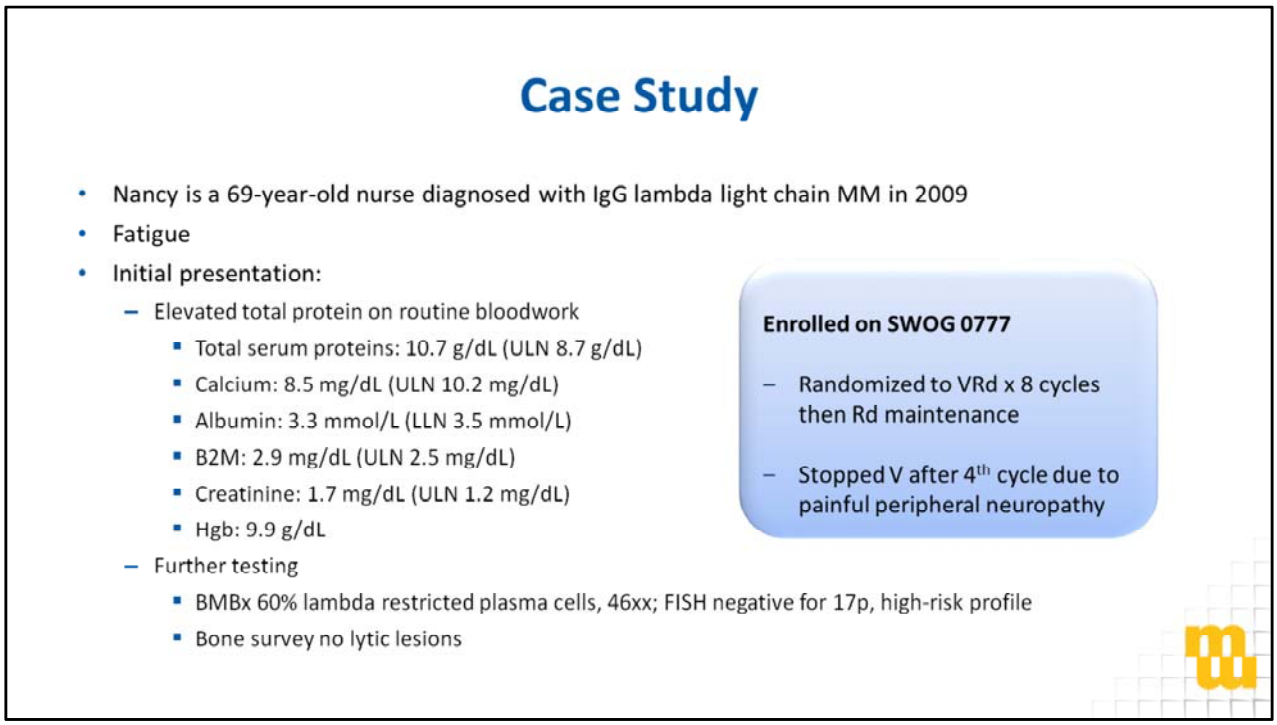

I wanted to give you a case study to kind of wrap your heads around how we best manage relapsed myeloma these days, and I wanted to start with Nancy nurse. Nancy is a 69-year-old nurse, and she was diagnosed with IgG lambda light chain multiple myeloma in 2009. Remember, IgG is one of the most common types of multiple myeloma. She presented with fatigue, and initial presentation showed an elevated total protein, normal serum calcium, a mildly lowered albumin, beta-2 microglobulin kind of in the normal range, maybe some mild renal insufficiency with a creatinine of 1.7, and she had anemia with a hemoglobin of 9.9. Further testing showed 60% lambda-restricted plasma cells. She had good cytogenetics (normal) and the FISH was negative for high-risk characteristics. She had pretty "standard-risk disease." She had a bone survey that showed no lytic lesions. She opted to participate in a SWOG777 study. That was the study I mentioned that randomized individuals to either receive bortezomib, lenalidomide and dexamethasone, or lenalidomide and dexamethasone alone. There was no transplant option in the study. The bortezomib (listed as V) was stopped after the fourth cycle due to painful peripheral neuropathy. Back when the study started, we typically gave bortezomib intravenous on schedule of days 1, 4, 8, and 11 on a 21-day cycle. Nowadays, we know that it is evidence when you administer bortezomib subcutaneously, and on a sometimes reduced schedule based on the peripheral neuropathy, it is much less likely to occur, and more reversible as well.

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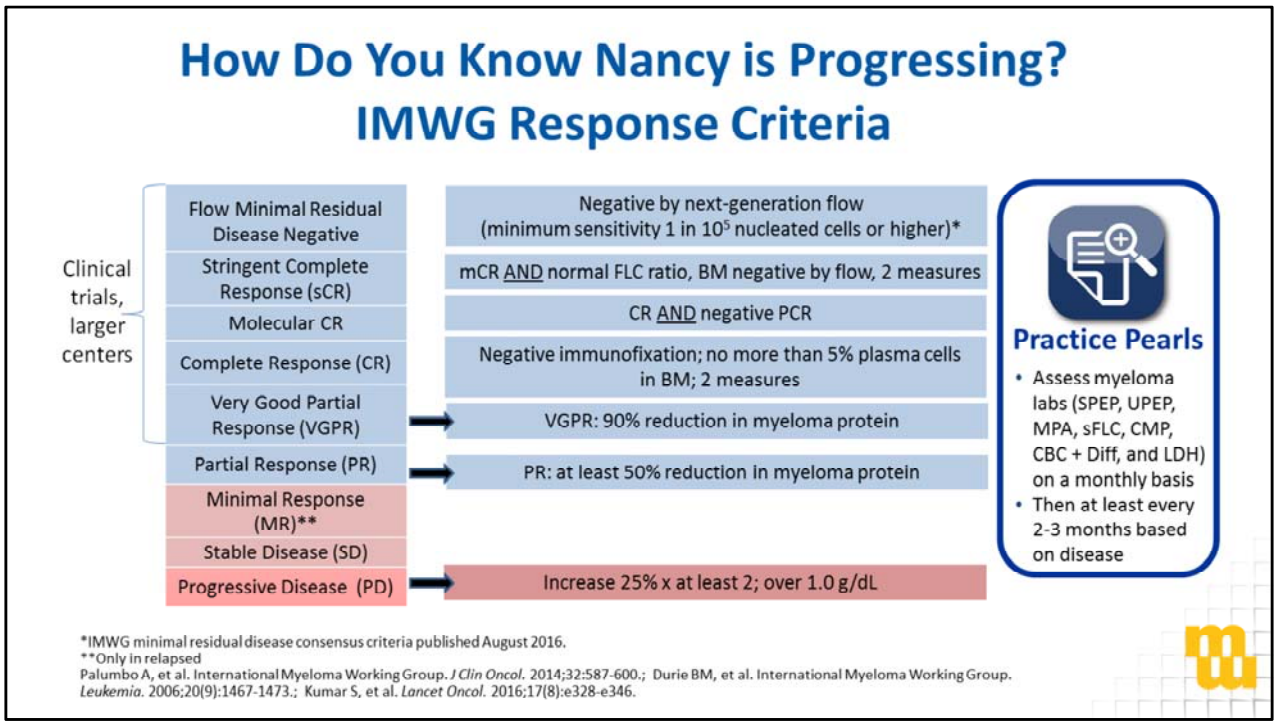

When Nancy started treatment on the SWOG777 study in 2009, how do we know that she is actually responding to treatment? This slide highlights the International Myeloma Working Group criteria for response. On this slide, I would like to highlight a couple of factors. Most commonly in most centers, we want to achieve the best response as possible. Within the first 2 cycles, you can expect a patient to achieve at least partial response with a 50% reduction in the myeloma paraprotein. The next level that we would like to see patients achieve would be a VGPR, or very good partial response, which is a 90% reduction of paraprotein. Imagine that Nancy has an M-spike of 5 g/dL. We want to see that go down by at least 2.5 g at the first evaluation and then subsequently see that go as low as possible. There is a concept of myeloma called minimal residual disease. Many different studies are being conducted to determine the significance. We now have immunophenotypic ways of measuring for very low levels of 10 to the -6 clones in the bone marrow, and so, the updated myeloma response criteria reflect this. This is mostly used in larger centers and clinical trials, and the PR, VGPR, or CR, where you have negative immunofixation, is typically what we strive for in the community or outside the clinical study setting. Once we achieve a response, we want to make sure that paraprotein does not go up. Let's assume that Nancy had achieved a complete response, where she has normal immunofixation and low level of bone marrow plasma cells (less than 5%) by two different measures. Now, we see the protein come back. It was 0 and now it is back to 0.25, 1.0, and now 1.5. That would be criteria for disease progression for Nancy. The interval of assessing the myeloma labs is variable according to your institution. Basically in my practice, I will assess myeloma parameters every month during the first year of therapy. Once the individual is on a maintenance setting, I will make that every 2 months, or even every 3 months if they are extremely stable disease, especially if they are in a complete response.

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Flowsheet – Rising Serum Free Light Chain

	Kappa Free, Serum	Lambda Free, Serum	K/L Ratio, Serum
2009	3.30 - 19.40 mg/L	5.7 - 26.3 mg/L	0.26 - 1.65
	<2.7 (L)	**1386.0 (H) - At Diagnosis**	0.00 (L)
	<2.7 (L)	315.7 (H)	<0.01 (L)
	5.9	177.5 (H)	0.03 (L)
	5.9	73.3 (H)	0.08 (L)
	13.6	60.2 (H)	0.23 (L)
	8.9	22.4	0.40
	10.6	17.7	0.60
	9.3	17.8	0.52
	3.3	17.6	0.19 (L)
	9.8	15.3	0.64
	13.1	20.8	0.63
	11.2	29.6 (H)	0.38
	15.0	47.8 (H)	0.31
	13.4	48.2 (H)	0.28
	<3.3 (L)	**132.3 (H)**	<0.02 (L)
	3.5	**134.4 (H) slow biochemical PD**	0.01 (L)
	<3.3 (L)	**124.7 (H) over 1 year**	<0.02 (L)
	<3.3 (L)	**133.8 (H)**	<0.01 (L)
2017	7.1	**839.9 (H)**	0.02 (L)
	6.7	**1280.2 (H)**	0.02 (L)

Now, Nancy had a lambda light chain type myeloma, and you can see on this slide in 2009 her lambda-free serum level was 1386. She was kind of a nonsecretor. She did not secrete an intact paraprotein, it was mostly a lambda type, and it went down nicely to the normal range. However, she lost her excellent response and over time she had this slow biochemical progressive disease over one year.

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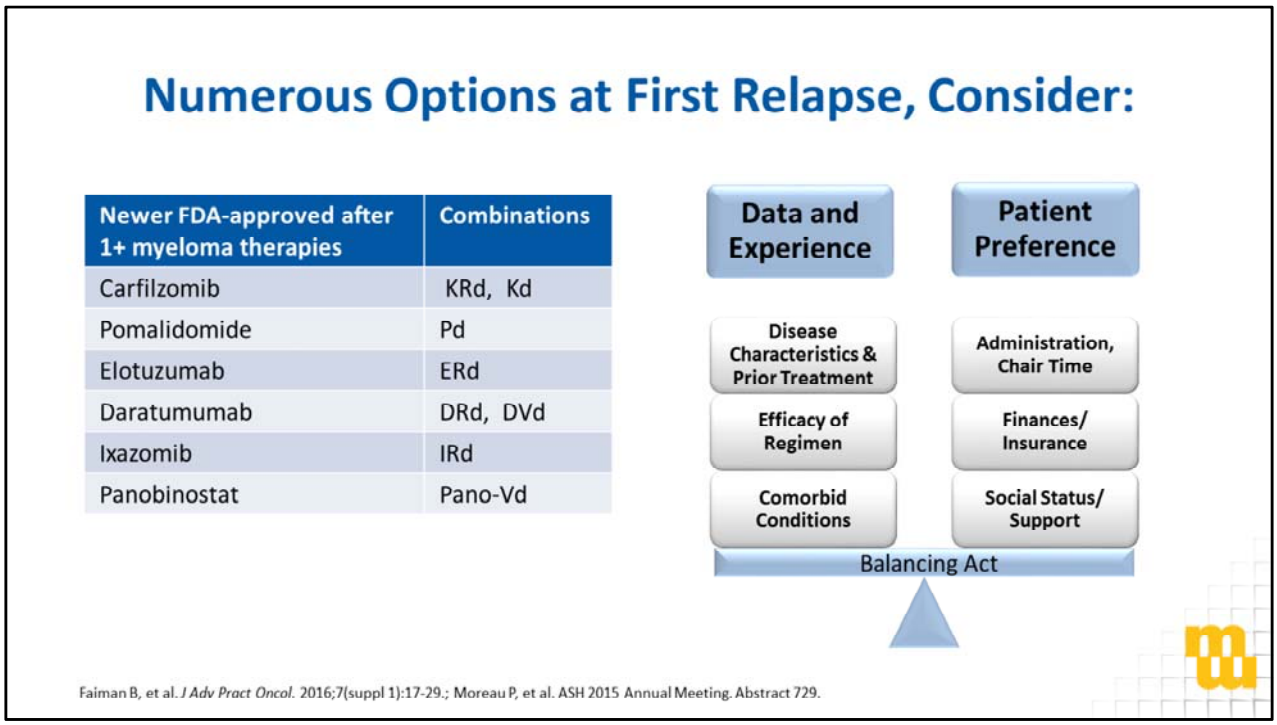

What would you consider for Nancy at relapse with all these numerous treatment options? Well, we know that there are numerous therapies available that are FDA approved at relapse. Carfilzomib can be given with lenalidomide and dexamethasone pills; pomalidomide-dexamethasone is an all-oral regimen with two drugs; elotuzumab and daratumumab are monoclonal antibodies that are FDA approved in combination with either lenalidomide-dexamethasone or bortezomib-dexamethasone with daratumumab; ixazomib-lenalidomide-dexamethasone which is an all-oral regimen of three drugs; and panobinostat-bortezomib-dexamethasone as well. Generally when we consider what to give the patient next, you want to use your data and experience. What do the clinical trials say in patients like Nancy? She had a three-drug regimen and stopped bortezomib for neuropathy at the time, but maybe her neuropathy is resolved. Then we can consider even just restarting the bortezomib or similar drugs such as ixazomib from that drug class. We want to take into account patient preference, the financial and the insurance issues, as well as social status and support. Some people you might want to bring to the clinic so you can eyeball them and see how they are responding, and make sure that they have appropriate resources. If you are worried about adherence in taking oral medications, maybe intravenous would be better for them (or if the individual working or caring for a loved one and cannot travel to the clinic). Take into consideration all of these patient-related factors, disease-related characteristics, and their type of relapse. For Nancy, it was a slow biochemical relapse. It was not a rapid symptomatic, new bone lesions anemia relapse. You want to take that into consideration as well.

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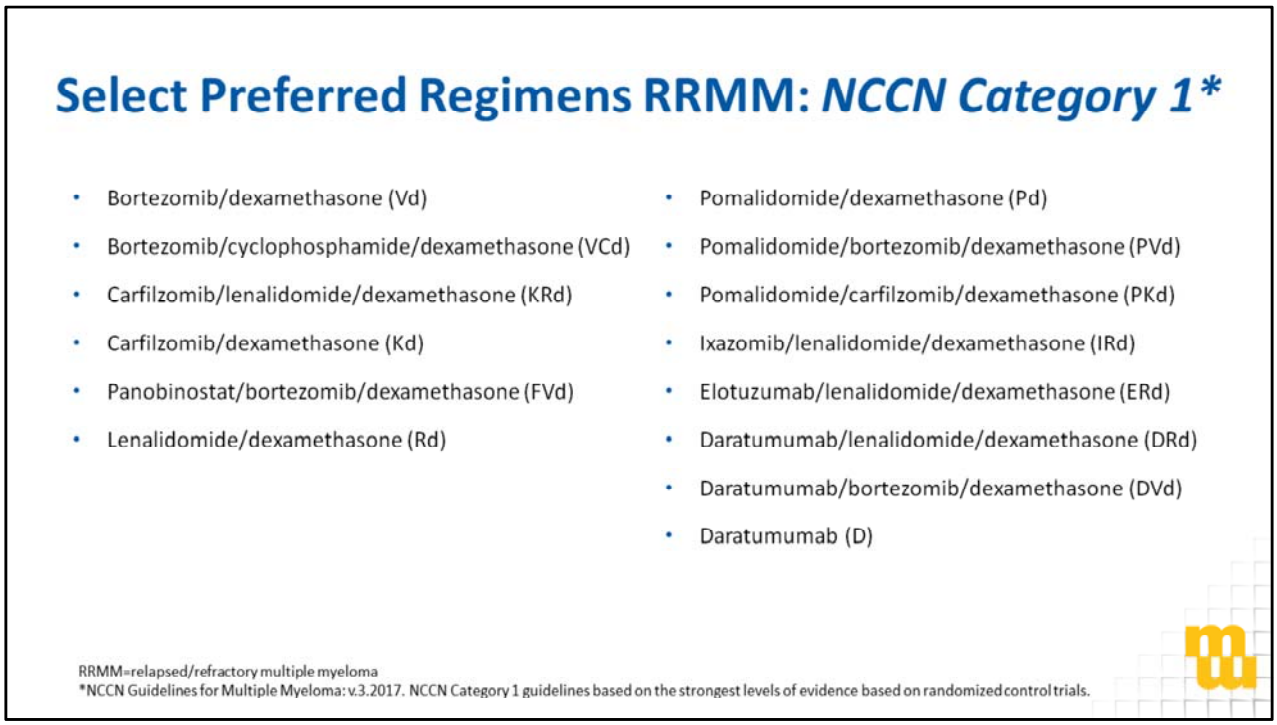

One of the areas where I look for guidance when I am making recommendations would be the National Comprehensive Cancer Network. They are grade guidelines as to the strength of the evidence. Category one are the strongest levels of evidence, based on randomized controlled trials. Bortezomib-dexamethasone, bortezomib-cyclophosphamide-dexamethasone etc. are all listed on this slide and are all reasonable considerations. Just because they are in the NCCN category, however, that does not always give us good counsel as to what to do.

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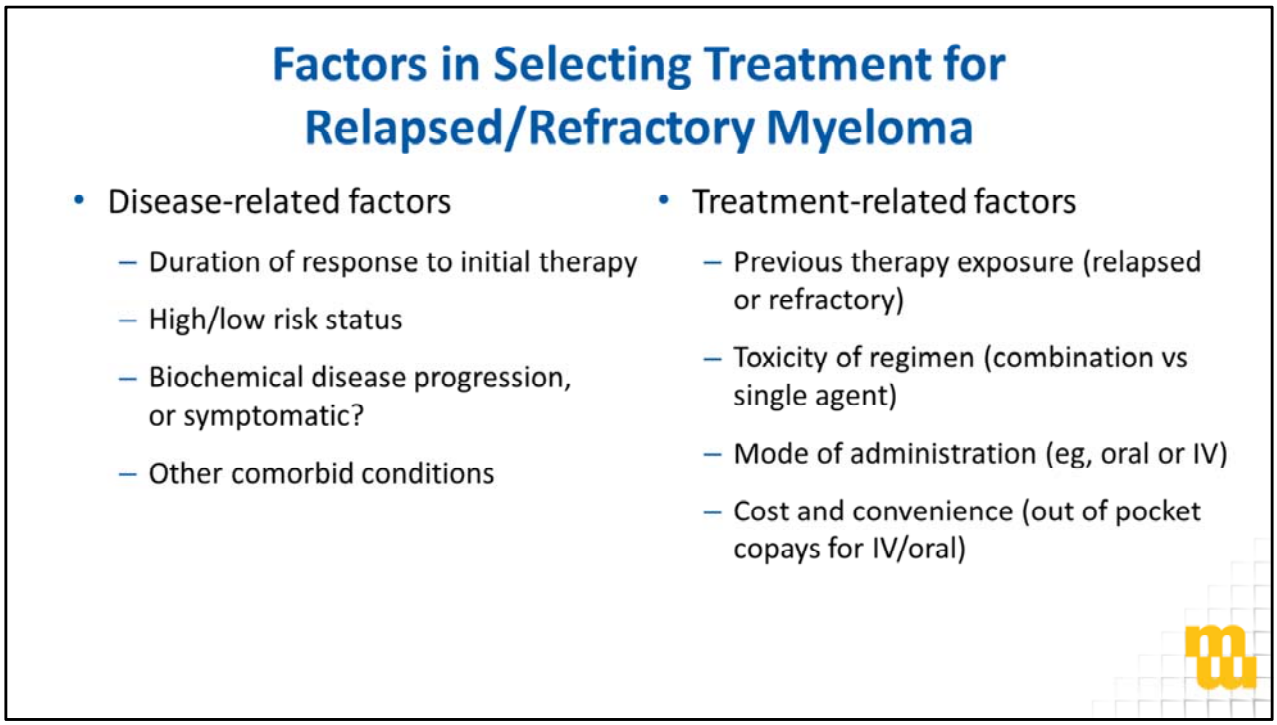

Factors in selecting treatment for relapsed myeloma patients or refractory myeloma patients are listed on the slide, and they are similar to what I mentioned before. Disease-related factor such as how do they respond to their earlier therapy, high- and low-risk status, was it a biochemical disease progression or symptomatic and they are very sick, and what are their other comorbid conditions? Do they have uncontrolled diabetes which makes corticosteroids a challenge to administer? What are the treatment-related factors such as previous therapy exposure or the toxicity of the regimen as well?

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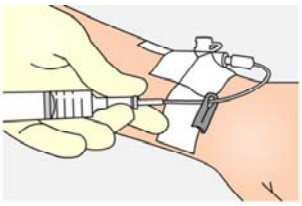
Carfilzomib: IV Administration 2 Days/Week

Approved for RRMM in the US at two dose levels:

1) 20/27 mg/m^2 with len/dex, or
2) 20/56 mg/m^2 monotherapy

Carfilzomib 28-day Cycle						
1	**2**	3	4	5	6	7
8	**9**	10	11	12	13	14
15	**16**	17	18	19	20	21
22	23	24	25	26	27	28

Cycle 1, week 1: **20** mg/m^2
Cycle 1, week 2+: **27 or 56** mg/m^2

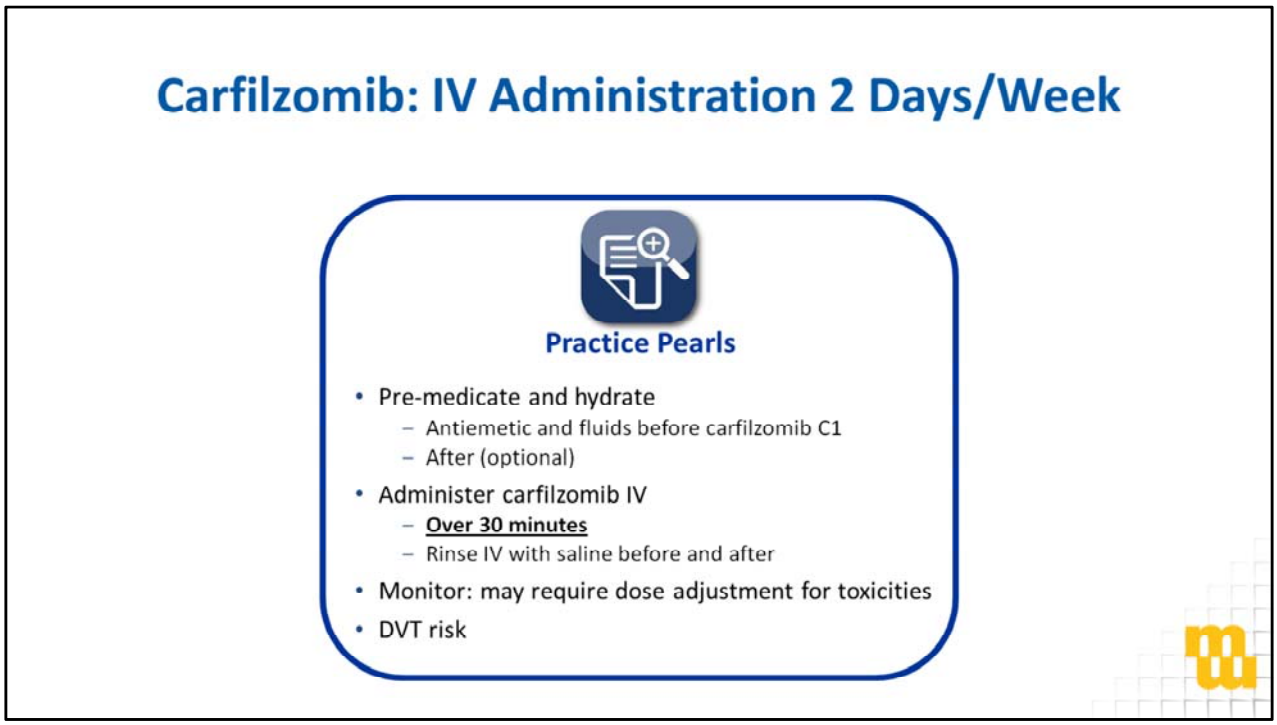


- ASPIRE: 792 patients randomly assigned to carfilzomib/len/dex or len/dex; median PFS 26.3 months, vs. 17.6 months
- ENDEAVOR: 929 patients randomly assigned to carfilzomib/dex or bortezomib/dex median PFS 18.7 months, vs. 9.4 months

Carfilzomib Prescribing Information, 2016.

Carfilzomib is an intravenous proteasome inhibitor which is administered in the vein and is approved by the FDA for use in relapsed and refractory multiple myeloma at two dose levels. The first dose level starts at 20 mg/m^2 and increases to 27 mg/m^2 (with lenalidomide and dexamethasone; ASPIRE trial) or it can be at 20/56 mg/m^2 as monotherapy. On the slide, I have a calendar that highlights the days 1, 2, 8, 9, 15, and 16 of a 28-day cycle administration schedule. It is back-to-back. The drug is given typically over about 10 minutes. However, some patients experience better outcomes when they have it administered over 1/2 hour, especially the higher dose of 56 mg/m^2 twice weekly. I will review in a moment the ASPIRE and the ENDEAVOR studies. However, these two studies had large amounts of patients and showed improved progression-free survival compared to the comparator arms and possibly an overall survival benefit compared to the regimen.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

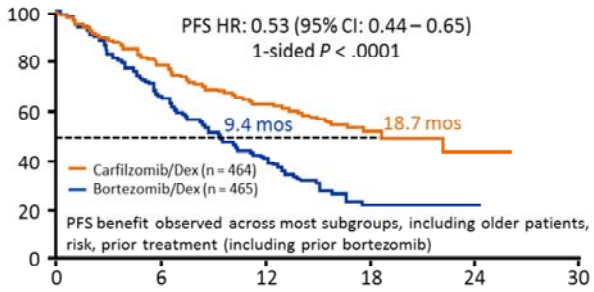


It is important for nurses to know how to pre-medicate and hydrate the patients. Pre-medicating patients with antiemetics and IV fluids from 250 mL to 500 mL of saline before the first infusion is very important. When carfilzomib was FDA-approved in 2012, we had more of a propensity to give higher doses of saline pre and post. Unfortunately, many of our patients developed shortness of breath and cardiopulmonary issues, and we now have more experience to show that they do not need the pre and post hydration as much as we used to. As nurses, we should monitor the lung sounds, making sure that they do not have any cardiorespiratory distress, swelling in the ankles, and be more liberal with diuretic use if need be. Patients are actually at an increased risk of deep vein thrombosis with the high-dose carfilzomib as seen in the ENDEAVOR trial. ENDEAVOR compared carfilzomib-dexamethasone to bortezomib-dexamethasone, and patients in a carfilzomib-dexamethasone arm had a higher risk of deep vein thrombosis. Educate your patients for strategies to minimize that risk, such as walking around, ambulation, and hydration. Assess for symptoms of deep vein thrombosis, such as swelling of the unilateral extremity or cyanosis or coolness of the skin.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

ENDEAVOR: Kd vs Vd -2-fold Increase in Median PFS vs Vd in Relapsed MM

- *Patients with symptomatic RRMM after 1-3 prior treatments with ≥ PR to ≥1 prior regimen (N = 792)*
- Significant PFS improvement and higher response rates with carfilzomib/dex vs bortezomib/dex in relapsed MM; ORR: 77% vs 63% (*P* < .0001), respectively

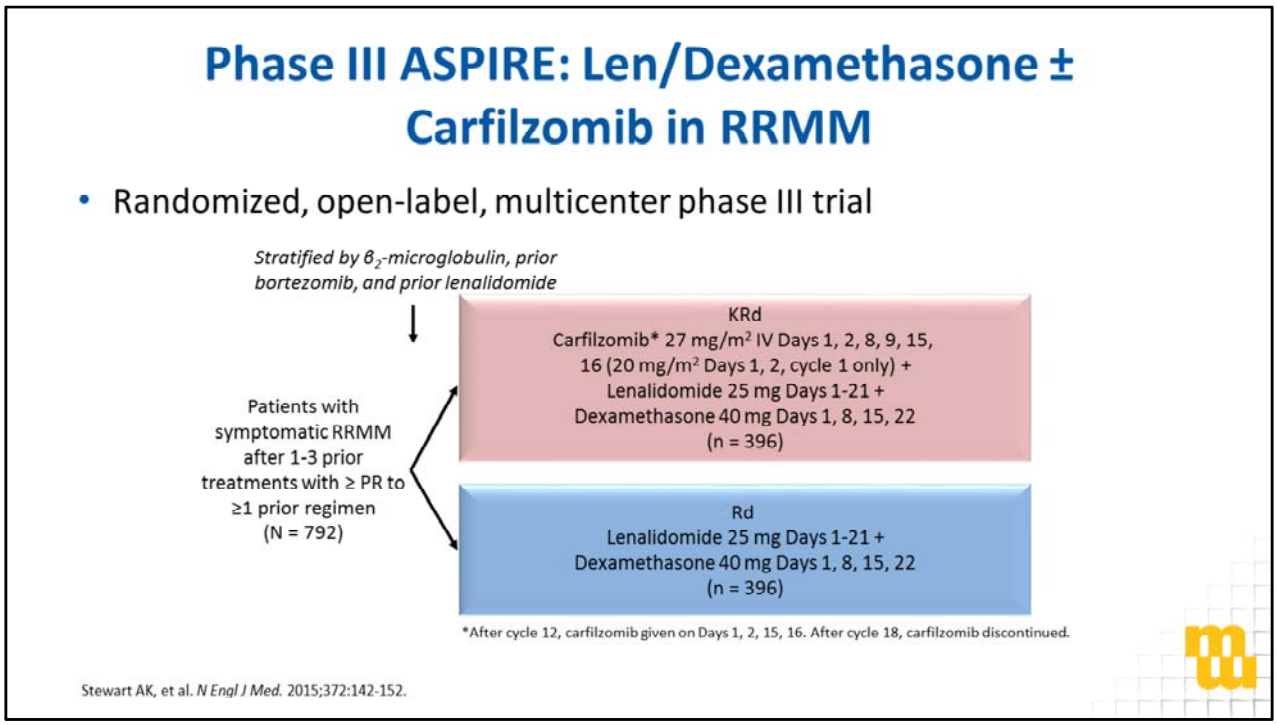


- Rates of d/c to due AEs similar (14% vs 16%), but rates of grade ≥3 hypertension (25% vs 9%), dyspnea (5% vs 2%), and heart failure (5% vs 2%) increased with carfilzomib vs bortezomib; rates of grade ≥2 peripheral neuropathy increased with bortezomib/Dex vs carfilzomib/dex (32% vs 6%)

d/c=discontinuation; AEs=adverse events
Dimopoulos MA, et al. *Lancet Oncol.* 2016;17(1):27-38.

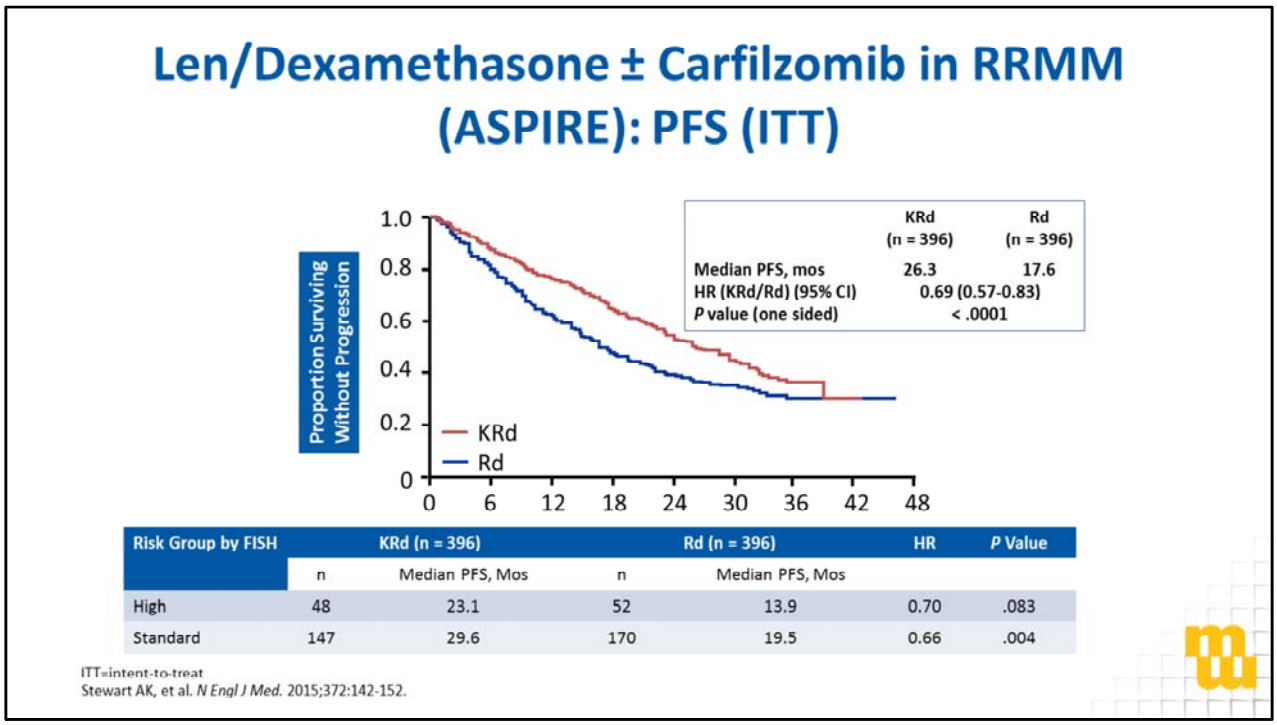
This next slide is the ENDEAVOR study that I referenced a moment ago. It compared carfilzomib-dexamethasone versus bortezomib-dexamethasone. The results of the study showed that there was a two-fold increase in the median progression-free survival, which means patients did better in the carfilzomib-dexamethasone arm versus the bortezomib-dexamethasone arm. These are both proteasome inhibitors, it is a two-drug regimen. Bortezomib can be given subcutaneously, but this was an intravenous carfilzomib dose. This would be one reasonable option especially for somebody who is a slow progresser.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



The phase 3 ASPIRE trial compared lenalidomide and dexamethasone plus or minus carfilzomib in patients with relapsed or refractory multiple myeloma. This study that was published in the *New England Journal of Medicine* in 2015

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



Risk Group by FISH	KRd (n = 396)		Rd (n = 396)		HR	*P* Value
	n	Median PFS, Mos	n	Median PFS, Mos		
High	48	23.1	52	13.9	0.70	.083
Standard	147	29.6	170	19.5	0.66	.004

ITT=intent-to-treat
Stewart AK, et al. *N Engl J Med.* 2015;372:142-152.

showed that there was an improved progression-free survival among those patients who received the three drugs versus the two-drug regimen. The median progression-free survival was 26.3 months versus 17.6 months, and patients with high-risk cytogenetics actually benefited more from the carfilzomib-lenalidomide-dexamethasone arm than the lenalidomide-dexamethasone arm.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

ASPIRE: Select Adverse Events

Select Adverse Events	KRd (n = 392) All Grades, %	Rd (n = 389) All Grades, %
Nonhematologic AEs occurring in ≥25% of patients		
▪ Diarrhea	42.3	33.7
▪ Fatigue	32.9	30.6
▪ Cough	28.8	17.2
▪ Pyrexia	28.6	20.8
▪ Upper respiratory tract infection	28.6	19.3
▪ Hypokalemia	27.6	13.4
▪ Muscle spasms	26.5	21.1
Hematologic AEs occurring in ≥25% of patients		
▪ Anemia	42.6	39.8
▪ Neutropenia	37.8	33.7
▪ Thrombocytopenia	29.1	22.6
Other AEs of interest		
▪ Dyspnea	19.4	14.9
▪ Peripheral neuropathy	17.1	17.0
▪ Hypertension	14.3	6.9
▪ Acute renal failure	8.4	7.2
▪ Cardiac failure	6.4	4.1
▪ Ischemic heart disease	5.9	4.6

Practice Pearls

Implications

- Monitor blood counts
- Monitor for infection
- Cardiac
  - EKG for patients with cardiac history, ECHO baseline
  - **Diuretics, inhalers, minimize fluids, longer infusion time (30 minutes)**
- Advise patient on
  - Shortness of breath (dyspnea)
  - Fatigue
  - Cytopenias
  - Infection prevention
  - VTE prophylaxis

Carfilzomib Prescribing Information.; Stewart AK, et al. *N Engl J Med.* 2015;372:142-152.

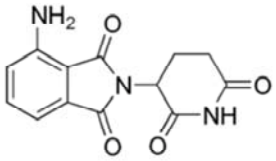
This next slide highlights the serious select adverse events. Again, with lenalidomide, we want to make sure that we monitor for blood clots and we want to watch blood counts. In terms of carfilzomib, an EKG monitoring, especially for patients with a cardiac history, is important. I mentioned briefly earlier the importance of hydrating but not drowning your patients, meaning that we want to assess the fluid volume status in a routine manner. We also want to ask them questions such as have you been more short of breath or sleeping on pillows, to assess if they are having any fluid volume overload. Despite these adverse events, this regimen is generally well tolerated and effective at treating patients with relapsed myeloma.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

Pomalidomide

Pomalidomide

- Class: IMiD
- Indication: patients with MM
  - Have received at least two prior therapies
  - PD within 60 days of last therapy
- FDA approval: February 8, 2013
- Administration: oral
- Metabolism/clearance
  - Liver via CYP1A2 and CYP3A4
- Can be ± low-dose dex
- REMS Program

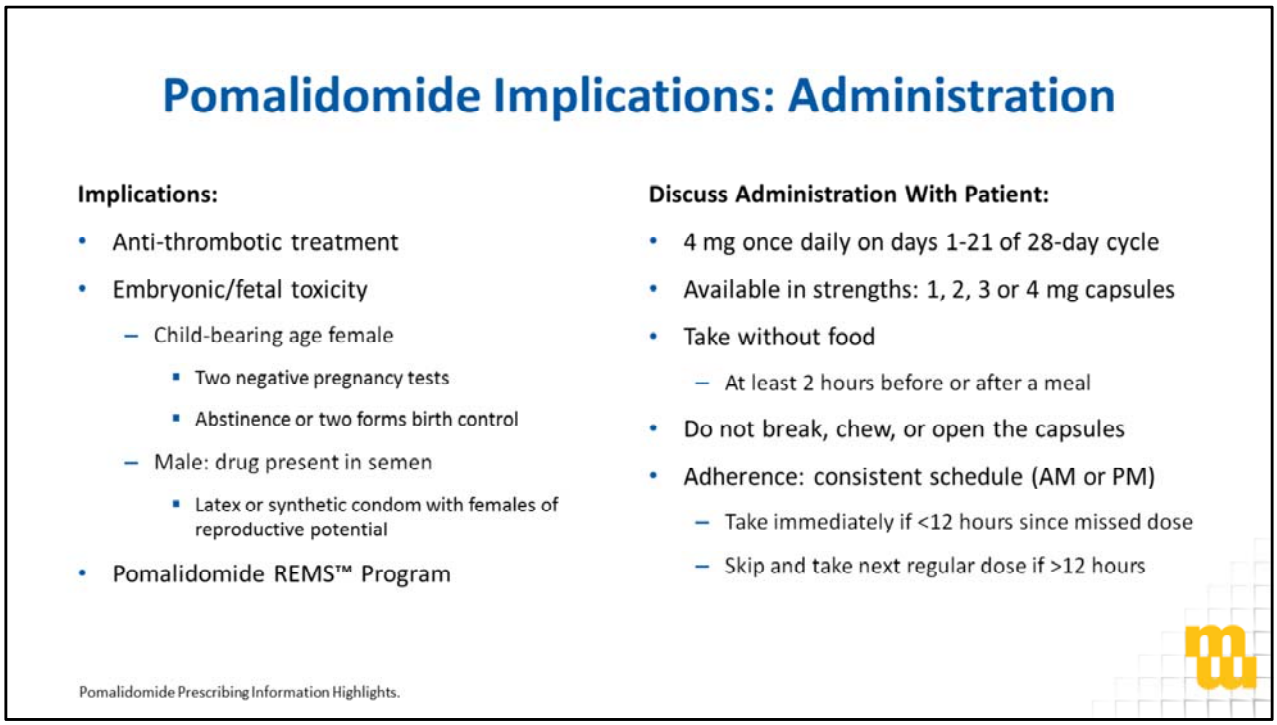


- Pomalidomide prolongs survival
- Pomalidomide has a manageable safety profile with few discontinuations due to AEs
- Pomalidomide maintains quality of life and provides oral convenience for patients

Pomalidomide Prescribing Information Highlights.

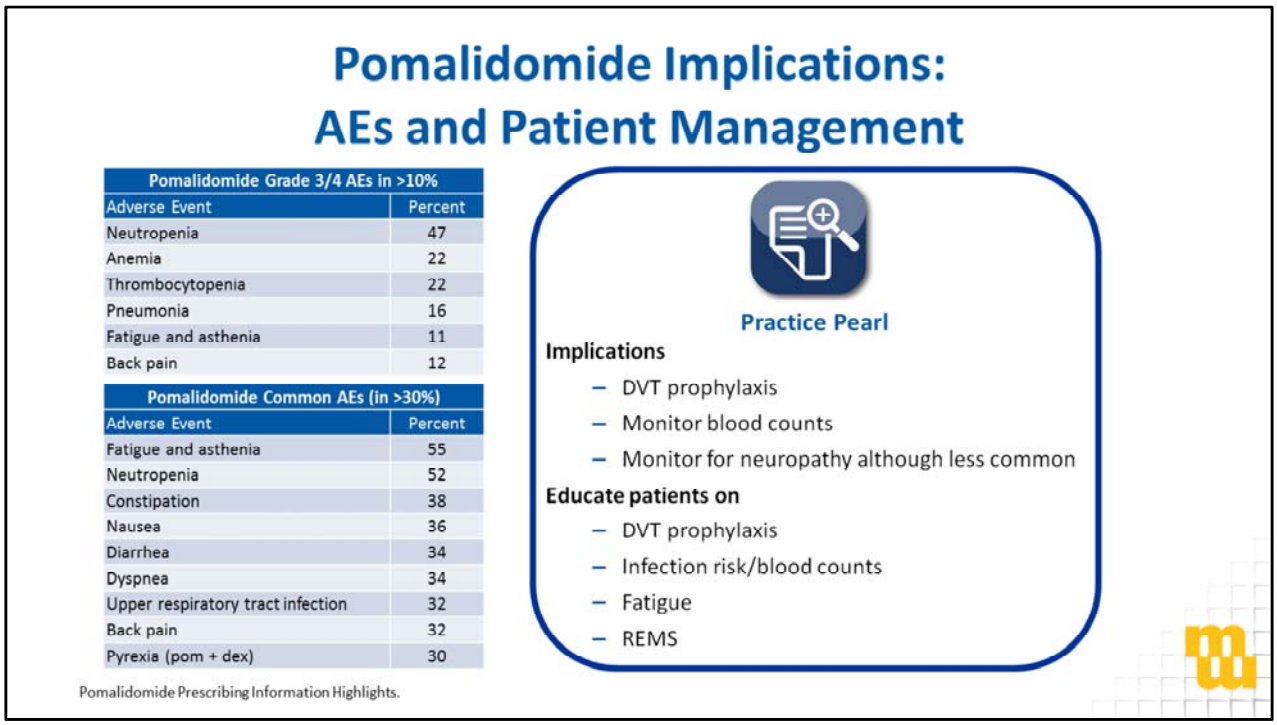
Pomalidomide is an oral immunomodulatory drug that is very similar in chemical structure to lenalidomide and thalidomide. It is oral and it is cleared by the liver, and it is more commonly given with low-dose dexamethasone. It does not have as great of a single-agent benefit, so it is better when it is combined with dexamethasone.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



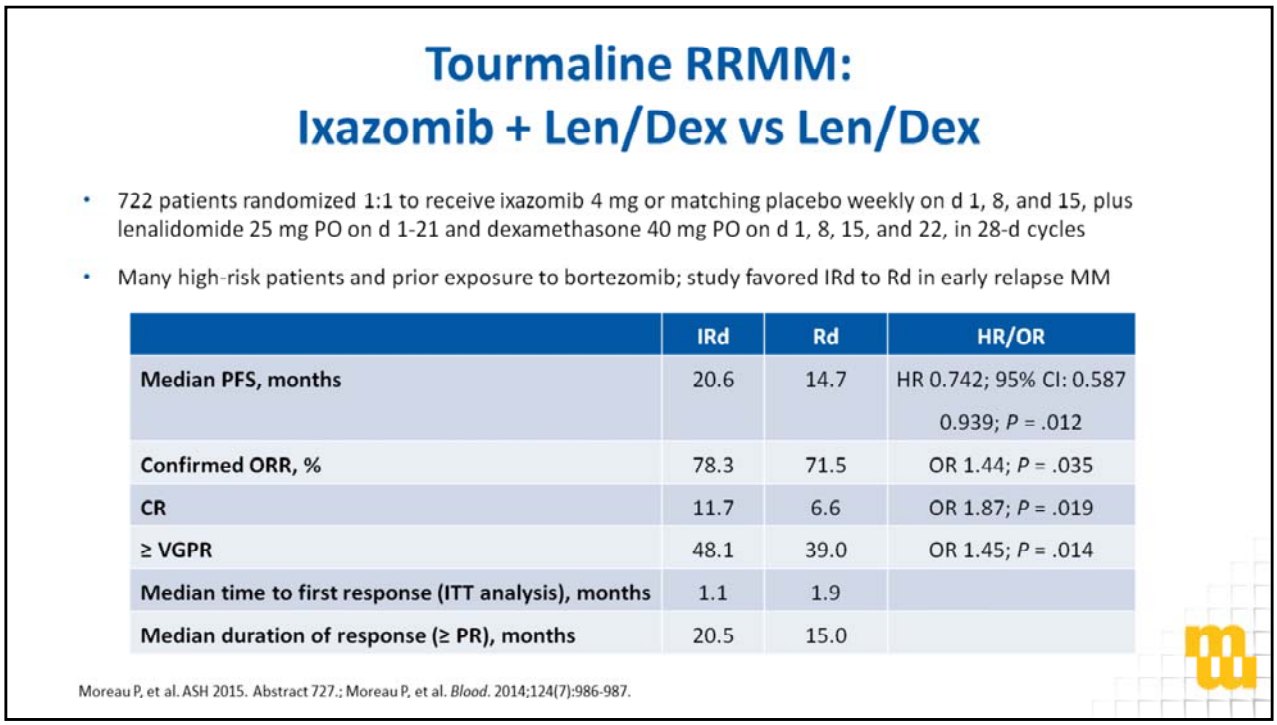
Anti-thrombotic therapy is important when patients are receiving pomalidomide, because they all receive DVT prophylaxis in the form of aspirin or, if they were at a high-risk for blood clots, low-molecular-weight heparin in the studies. The drug is started at 4 mg orally days 1 through 21 of a 28-day cycle, and the capsule strengths are 1, 2, 3, or 4 mg. It is important to take pomalidomide without food, so 2 hours before or after a meal, and I tend to recommend to administer it at nighttime. Basically they would have dinner and then they can take it just right before bed. It is important to have a consistent schedule, and if they miss a dose, not to take the next dose within 12 hours.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



These are the top three side effects that I educate my patients on with pomalidomide (I provide the same type of education for lenalidomide): It can affect your blood counts, so we want to monitor the blood counts routinely. It can cause an increased risk of blood clots, so as mentioned before, strategies for preventing deep vein thrombosis are ambulation and hydration. Risk factor for blood clots can increase if patients are immobilized, undergoing surgery, and if they have any cardiac or renal problems. Also ask your patient if they had a prior blood clot because that is important information. During the first 3 cycles, they should have prophylactic low-molecular-weight heparin if there is no contraindication to prevent that risk of recurrent DVT during the initial treatment stages. Again, there is an increased risk of infection in all patients with multiple myeloma. Again this is a cancer of the immunoglobulins, and the immunoglobulins are essential to our humoral immune system to protect us from getting sick. Looking for factors to minimize infection are important, such as adequate immunizations and making sure that they wash hands and use hand sanitizer, and avoid people with known colds.

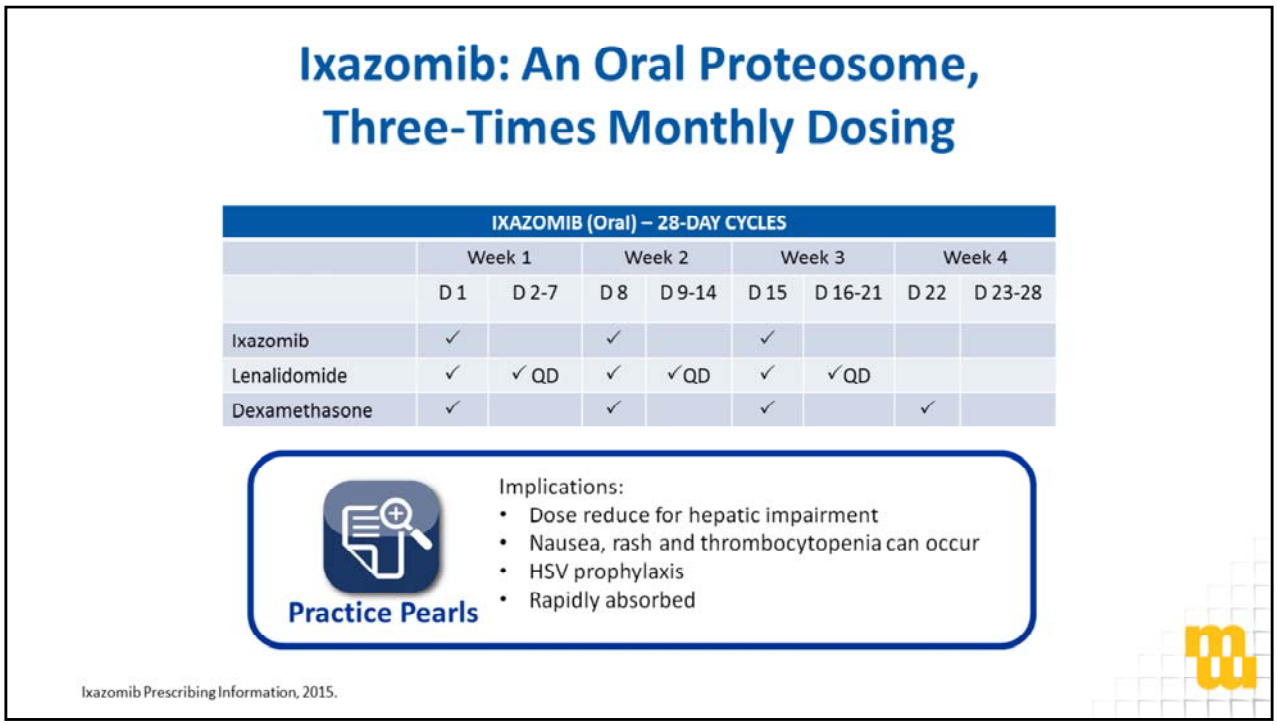
Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



	IRd	Rd	HR/OR
Median PFS, months	20.6	14.7	HR 0.742; 95% CI: 0.587 0.939; *P* = .012
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 first response (ITT analysis), months	1.1	1.9	
Median duration of response (≥ PR), months	20.5	15.0	

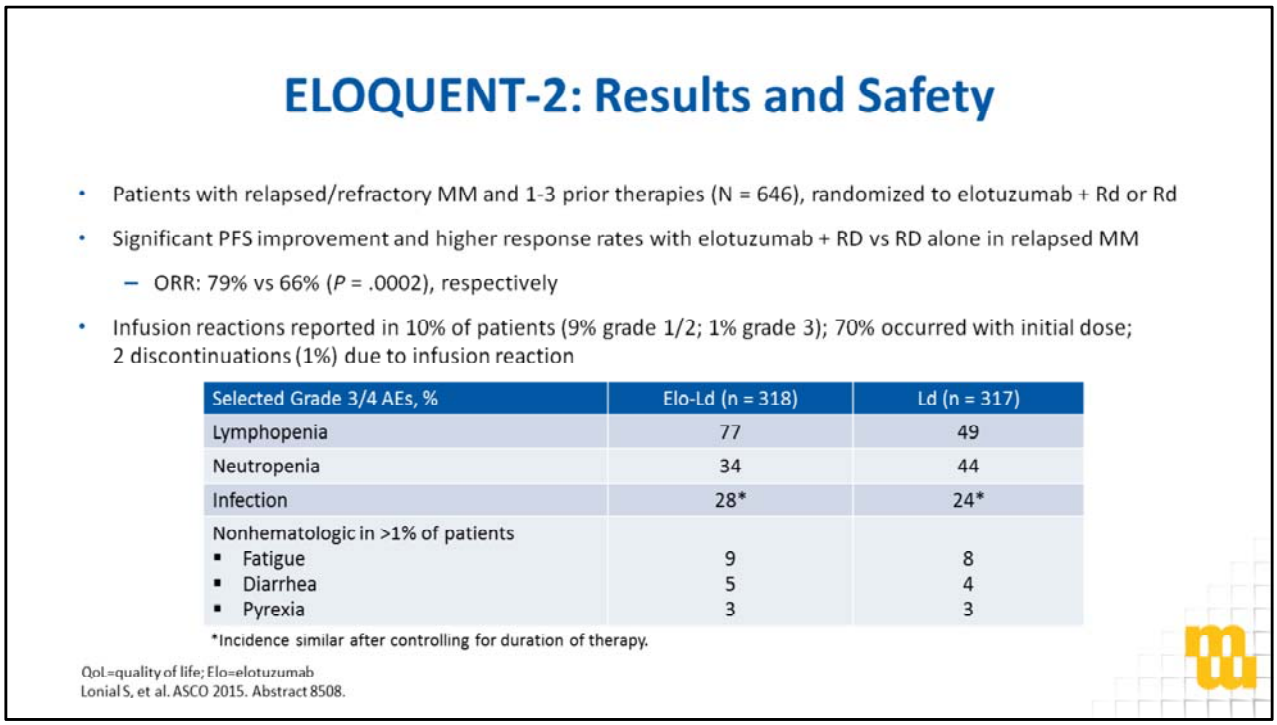
The next study is ixazomib, lenalidomide, and dexamethasone versus lenalidomide-dexamethasone. This is called the TOURMALINE study and this was the pivotal study that gained FDA approved for patients to have this drug in combination with one prior therapy. There were 722 patients in this study and they were randomized one to one to receive either ixazomib-lenalidomide-dexamethasone or just lenalidomide and dexamethasone pills. The median response time was really interesting in this study. It only took 1.1 months for the patients to respond, and the progression-free survival was longer with the three drugs versus the two-drug therapy. I think that is really important. This is an all-oral regimen that patients can receive and expect to have almost an immediate response in the first month, and it was very well tolerated.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



The dosing schedule is a little bit complicated, meaning that the ixazomib is only 3 days a cycle. I tell people to pick the day that they want to take the dexamethasone and ixazomib (because they are taken on the same day) and I make a calender for them. I like to pick Monday since it is the start of the week and so maybe Monday, Monday, Monday with the week off would be the ixazomib. Lenalidomide would be days 1 through 21 of a 28-day cycle, and then dexamethasone would be the week off. It is important to know that with proteasome inhibitors, all patients are at an increased risk for shingles reactivation or herpes zoster virus. All of these patients, even if they got the zoster vaccine back in the day, need to be receiving acyclovir or valacyclovir to minimize the risk of shingles. It is important to know that nausea can occur and some GI side effects, but ixazomib needs to be taken without food. Typically, I like to instruct patients to wake up on a Monday morning, have dexamethasone and ondansetron on the first dose to minimize your risk of nausea, 2 hours later they take their ixazomib, and about an hour after they can have lunch. Keeping this schedule in mind is something that can help especially with the drug exposure and for it to work more effectively.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



ELOQUENT-2: Results and Safety

- Patients with relapsed/refractory MM and 1-3 prior therapies (N = 646), randomized to elotuzumab + Rd or Rd
- Significant PFS improvement and higher response rates with elotuzumab + RD vs RD alone in relapsed MM
  - ORR: 79% vs 66% (*P* = .0002), respectively
- Infusion reactions reported in 10% of patients (9% grade 1/2; 1% grade 3); 70% occurred with initial dose; 2 discontinuations (1%) due to infusion reaction

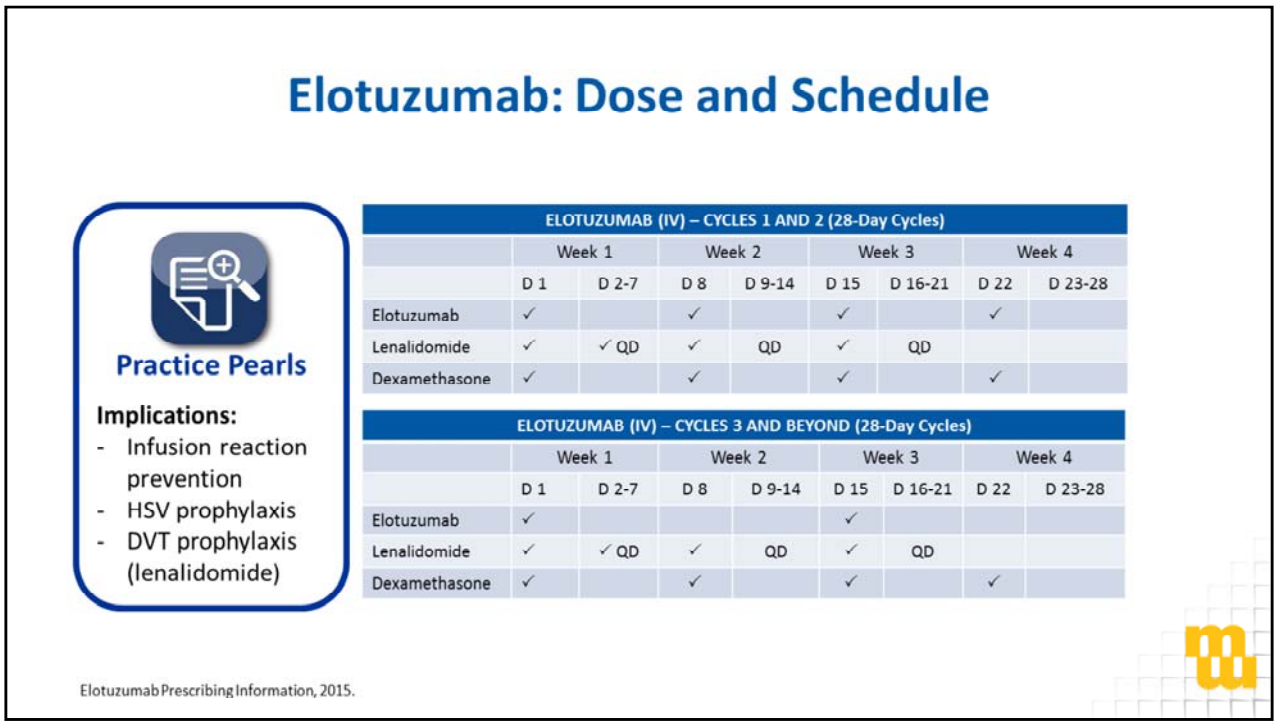
Selected Grade 3/4 AEs, %	Elo-Ld (n = 318)	Ld (n = 317)
Lymphopenia	77	49
Neutropenia	34	44
Infection	28*	24*
Nonhematologic in >1% of patients		
▪ Fatigue	9	8
▪ Diarrhea	5	4
▪ Pyrexia	3	3

*Incidence similar after controlling for duration of therapy.

QoL=quality of life; Elo=elotuzumab
Lonial S, et al. ASCO 2015. Abstract 8508.

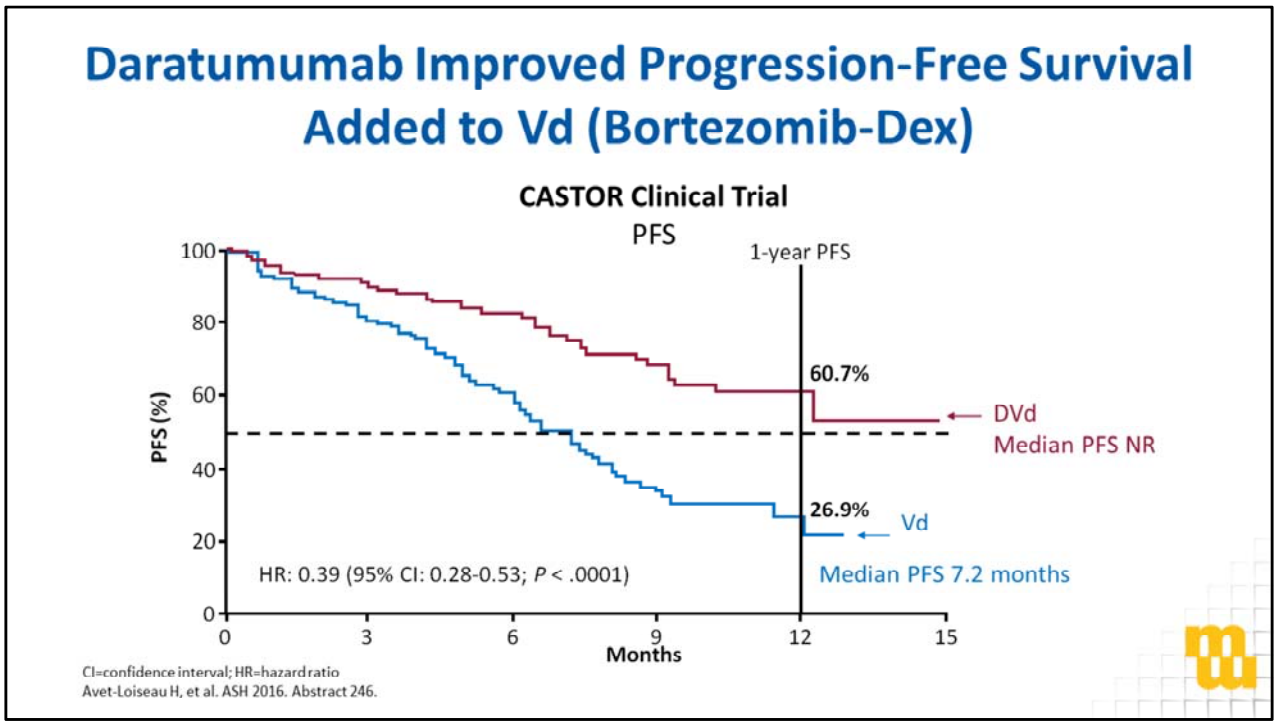
The ELOQUENT-2 study used elotuzumab. Elotuzumab is a monoclonal antibody targeted against SLAMF7, and elotuzumab is a smart bomb. Elotuzumab enhances natural killer cell activity, which is something that we lose over time with myeloma patients. The most important thing when you administer elotuzumab is to educate patients that it is given weekly for 8 weeks, and then days 1 and 15 as long as they are responding. Elotuzumab is approved in combination with lenalidomide and dexamethasone, and patients did better with their response rate when they received elotuzumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone alone. Infusion reactions are the biggest thing to worry about. It was only reported in 10% of the patients, but 70% occurred with the initial dose, and these tend to be a little bit more mild, especially if you are premedicating according to the manufacturer's instructions. We recommend an H1 blocker, H2 blocker, an antihistamine, and an antipyretic such as acetaminophen before each infusion, and then once your body recognizes this antibody, you can lengthen the infusion time. It typically starts at 0.5 mL per minute and then it can be increased to 5 mL per minute infusion rate. Whereas a long infusion starts over 4 to 6 hours, once your body is used to it, it can go in over about an hour.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



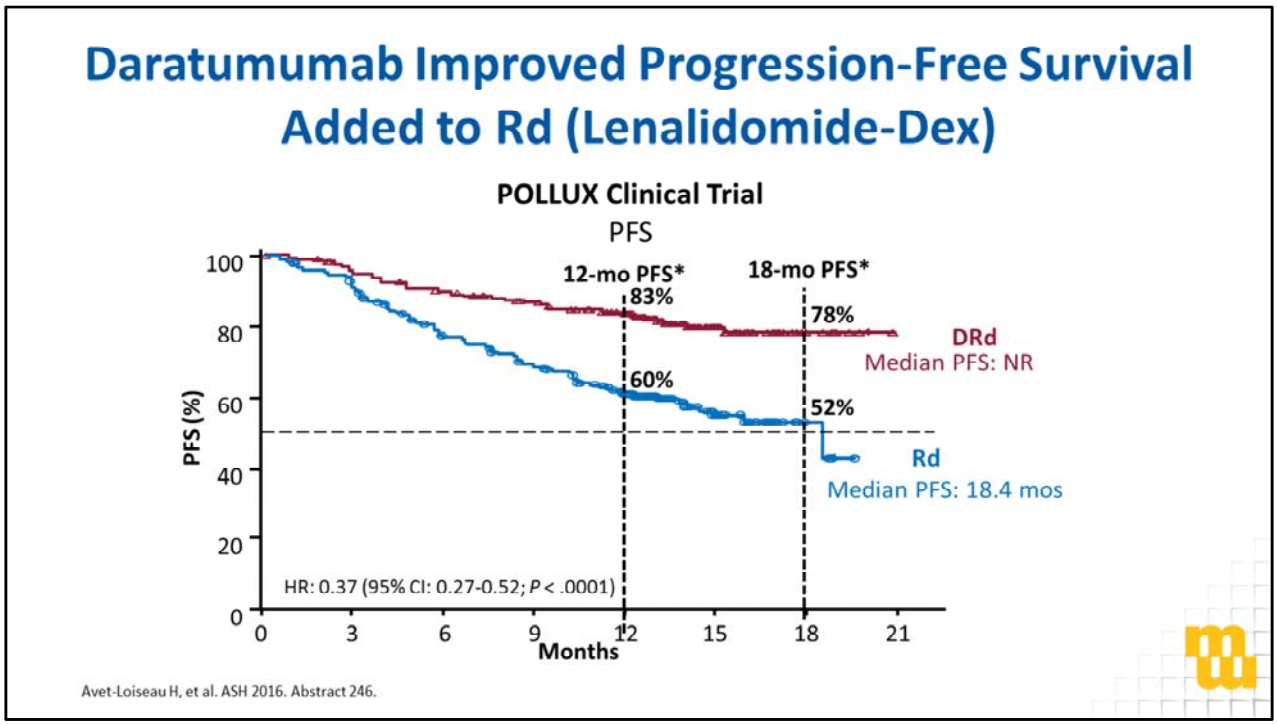
This is the elotuzumab dosing schedule as I mentioned and it is days 1, weeks 1, 2, 3, and 4. Again cycles 1 to 2 it is weekly, and then it goes to every other week. The lenalidomide is standard scheduled for 21 out of 28 days, and the dexamethasone is weekly no break. There is a similar risk of infusion reaction, and shingles prevention and blood clot prevention with the baby aspirin or full aspirin is recommended.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



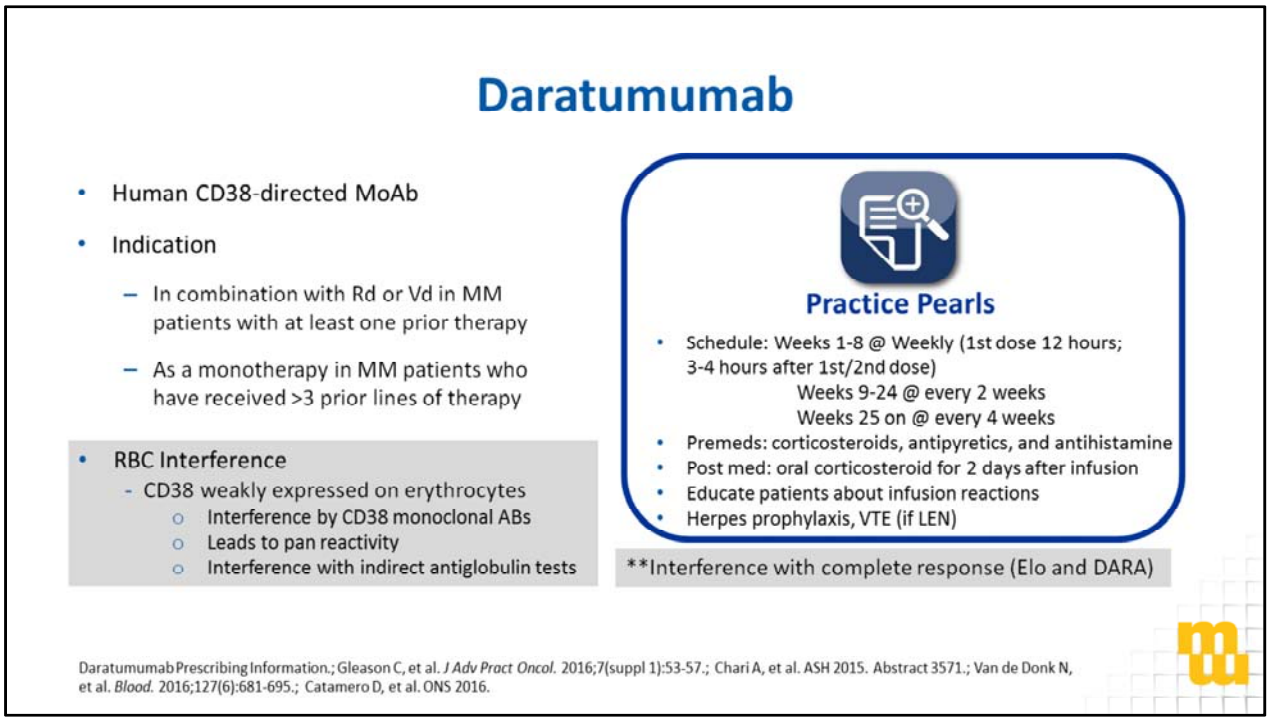
Daratumumab is a monoclonal antibody that is targeted against CD38. CD38 sits on the red blood cells, and it also sits on myeloma cells. When we had the CASTOR clinical trial, we observed improved progression-free survival when bortezomib was added to daratumumab and dexamethasone, a 60.7% progression-free survival versus 26.9% progression-free survival on that study. The three drugs are quite effective, and again, daratumumab is something that we worry about as the infusion reaction which I will go over in a moment.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



Daratumumab in the POLLUX studies actually showed an improved progression-free survival when lenalidomide and dexamethasone was added. Here, you can see on this slide, the improved progression-free survival with the daratumumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone alone. Again, you have all these different drugs combined with either a lenalidomide-dexamethasone or bortezomib-dexamethasone that are now added to our treatment armamentarium.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



Daratumumab is a monoclonal antibody targeted against CD38, and it is FDA approved as monotherapy by itself, or in combination with lenalidomide-dexamethasone or bortezomib-dexamethasone. It is important to know a couple of things about daratumumab, and elotuzumab for that matter. The first thing about daratumumab is the red blood cell interference. CD38 is weakly expressed on erythrocytes or red blood cells. What happens when patients get daratumumab, is they need to have a baseline type and screen, and then if a blood transfusion is anticipated, they need to have type and cross matching according to the blood bank. It will look like there are antibodies to the red blood cells because it leads to pan reactivity and direct antiglobulin blood test interference. Patients should know what blood type they are before they start, and then if there is an emergency, the blood bank can transfuse Kell-negative blood. If we have a planned transfusion, we recommend taking two pink-top tubes and sending it to your American Red Cross so they can wash the daratumumab off of the red blood cells and get an accurate type and cross match among those patients on daratumumab. The clinical pearls for this one are that we need to make sure that the daratumumab is given weekly for 8 weeks, and then weeks 9 to 24 every 2 weeks, and then every month. The premeds consist of corticosteroids and antipyretics and the infusion time is long, especially for the first dose. They are in the treatment area for about 10 hours oftentimes, and so depending on the institution, they might have a short stay bed or go to a larger institution with a treatment area that might be open a longer period of time. The treatment infusion reactions tend to occur when they are in the chair and once the B memory cells recognize the daratumumab, then you are less likely to have a reaction. Another thing that I wanted to mention that refers to elotuzumab and daratumumab is interference with complete response. Basically when you are receiving these monoclonal antibodies, sometimes there can be an inference and it can look like there is an M-spike especially because it is an IgG kappa agonist, and so, that could be measured in the blood in low levels.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

Adverse Events Commonly Associated with MM Therapeutic Agents

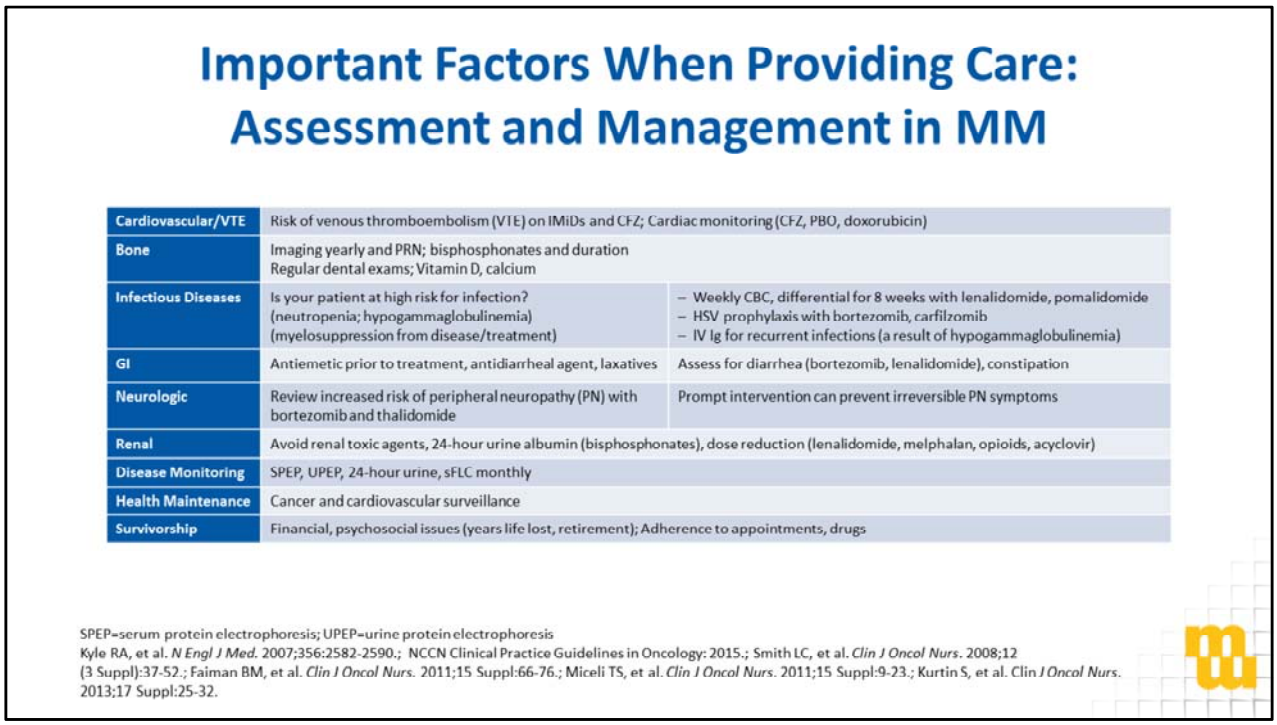
		PN	Myopathy	VTE	Thrombocytopenia	Neutropenia	Lymphopenia	Anemia	Decreased NK cells	Infection	Pneumonia	Fatigue	Nausea	Diarrhea	Constipation	2° primary malignancy	High blood glucose	Infusion reaction	Osteoporosis	Rash	Edema	Mood disorders
PIs	Bortezomib	X			X					X		X	X	X	X							
	Carfilzomib				X	X	X	X			X	X	X	X							X	
IMIDs	Thalidomide	X		X		X						X	X		X					X	X	
	Lenalidomide			X	X	X		X		X		X	X	X	X	X				X	X	
	Pomalidomide			X	X	X		X				X	X		X					X		
Chemotherapy	Cyclophosphamide				X	X		X		X			X			X						
	Melphalan				X	X		X					X	X		X						
Corticosteroids	Dexamethasone		X	X						X			X				X		X		X	X
	Prednisone		X	X						X			X				X		X		X	X
DACis	Panobinostat				X	X	X	X			X	X		X									
	Vorinostat				X			X				X	X	X									
mAbs	Elotuzumab							X			X	X	X	X			X	X					
	Daratumumab				X				X									X					

NK natural killer, *PN* peripheral neuropathy, *VTE* venous thromboembolism

Colson K. *Support Care Cancer.* 2015;23(5):1431-1445.

These drug classes – the proteasome inhibitors, immunomodulatory drugs, corticosteroids, and chemotherapies such as cyclophosphamide and melphalan – have really changed the landscape of multiple myeloma. We know that there are various side effects of each, which are listed on this slide. Peripheral neuropathy is more common with bortezomib and thalidomide, blood clot risk is more common with the immunomodulatory drugs and higher doses of carfilzomib, and so on. It is important to make sure you know what the drug is that your patient is receiving, and what the side effects are so that you can educate them as to what to look for, such as the blood clot signs.

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma

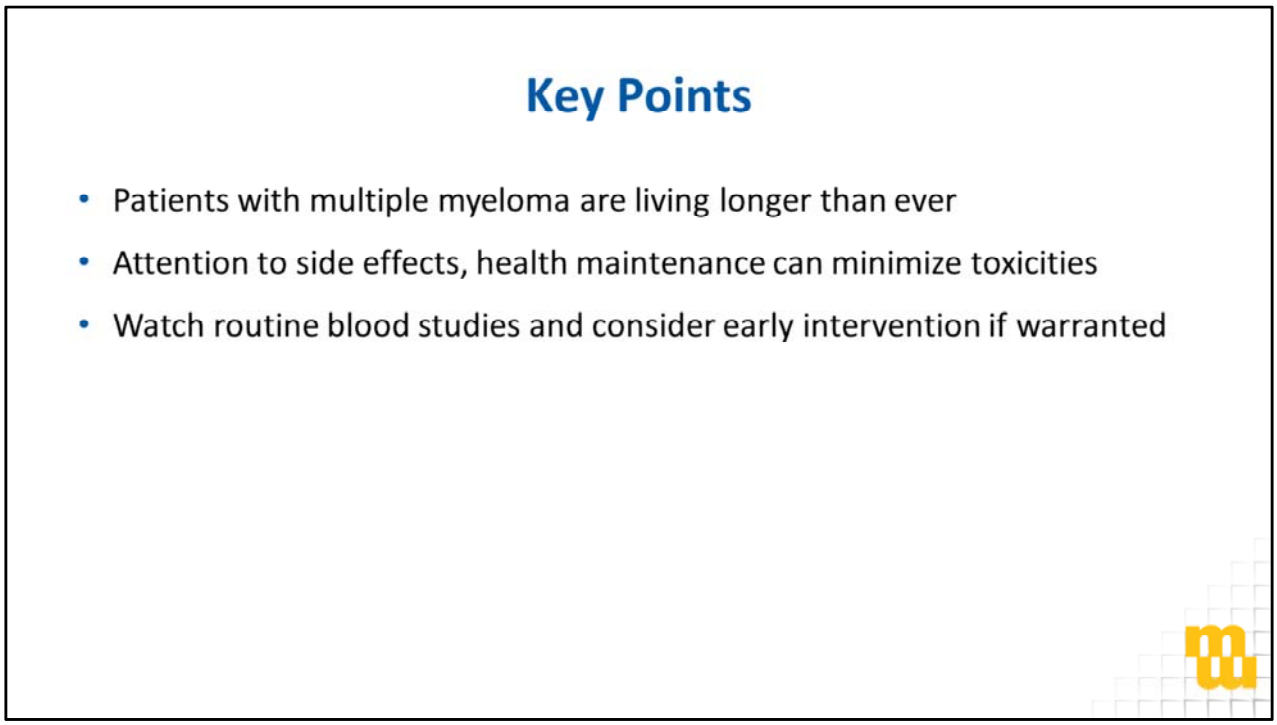


Because I think it is important for nurses to develop care plans, I wanted to share with you a care plan that I use for patients in my practice. This next slide focuses on important factors when providing care to patients with myeloma. It is important to take into consideration the disease-related factor and the treatment-related side effects we are looking for, because things change over time. When patients have myeloma, we know the cardiovascular system is important to look for including the risk of blood clots. That might be fluid, so for example, at diagnosis, the patient had normal kidney function and never had a blood clot, but now, they are having kidney failure, they are hospitalized, they are going through surgery. That person should be receiving more thromboprophylaxis. Bone is something that is so important. I did not fully go over the importance of bone monitoring, but a baseline skeletal survey is important for all patients, and surveillance skeletal surveys are also important on a 1- to 2-year basis and as needed. Remind your patients to have regular dental exams and adequate vitamin D and calcium exposure as well. In terms of infectious disease, we want to make sure that they know that they are at an increased risk for infection. Signs and symptoms of shingles should be reviewed because most of these drugs cause an increased risk of shingles. Make sure that they understand they need to take acyclovir, valacyclovir, or similar drugs to minimize their risk. Shingles vaccine is not indicated right now because it is a live virus which we think can reactivate in patients with hematologic cancers. In terms of CBC monitoring, many of these drugs can cause thrombocytopenia or anemia or leukopenia. Capturing a CBC test weekly for at least the first 8 weeks and then according the manufacturer's recommendation is also important. Intravenous immunoglobulin can be administered for patients with life-threatening and recurrent pneumonias if they have hypogammaglobulinemia or lower IgG levels, which typically are lower than 400 in some patients, especially with light chain disease.

The gastrointestinal system needs to be assessed, such as the diarrhea which can happen long term on lenalidomide or with bortezomib antiemetics, before each exposure to the medications that might be causing nausea is important as well.

The neurologic system should be evaluated for patients who are on bortezomib and carfilzomib, as many of these drugs have an increased risk (albeit low sometimes) of peripheral neuropathy. Educate patients to look for numbness and tingling in the fingers or extremities, especially pain, because one can hold the drug and reduce the dose and that neuropathy should improve at least to one level. We know that from research. In terms of renal, we want to avoid nephrotoxic agents such as NSAIDs, and contrast dyes if possible. Make sure that if patients are on prolonged bisphosphonates that the albumin in the urine is assessed as well to look for tubular dysfunction, which can occur over time. Dose reductions of medications need to be taken care of if patients develop worsening renal disease. For example, acyclovir is typically dosed at 400 mg twice daily; however, if patients develop new renal insufficiency that dose can go down to 400 mg daily or even 200 mg in some instances. Disease monitoring and health maintenance should also be important: encourage a healthy lifestyle. This is a chronic illness. Most patients are living a long time. I know that this current statistics with the older medications are showing by the SEER data a 49% survival of 5 years, but many internal studies from Mayo Clinic and other institutions are showing that most patients will live actually 10 years. Making sure that they stay fit for the next therapy, decrease cardiovascular risk factors, and lead a "healthy lifestyle" is important. Assessing the survivorship component of financial, and psychosocial issues is also important as well. We have a lot of abstracts these days that are focusing on that. Physicians and sometimes the nurses do not necessarily address financial issues as much as we should, and that is a topic that many patients do not want to talk about. Realizing that there might be a financial burden, look for copays for provider visits. Some people have $30 to $40 copay each time they see a provider. Do they need to come in every month to be seen or can they be seen virtually through telehealth visits or other mechanisms as well?

Developing Care Plans for Treatment-based Patient Monitoring in Relapsed/Refractory Multiple Myeloma



To conclude, I would like to leave you with these key take-away points. Patients with multiple myeloma are living longer than ever. Attention to key side effects, health maintenance can also minimize toxicities. It is important to watch routine blood studies and consider early intervention if warranted on either the treatment of myeloma or adjusting the dose of the medication as well. I want to take a moment to thank you for viewing this activity.