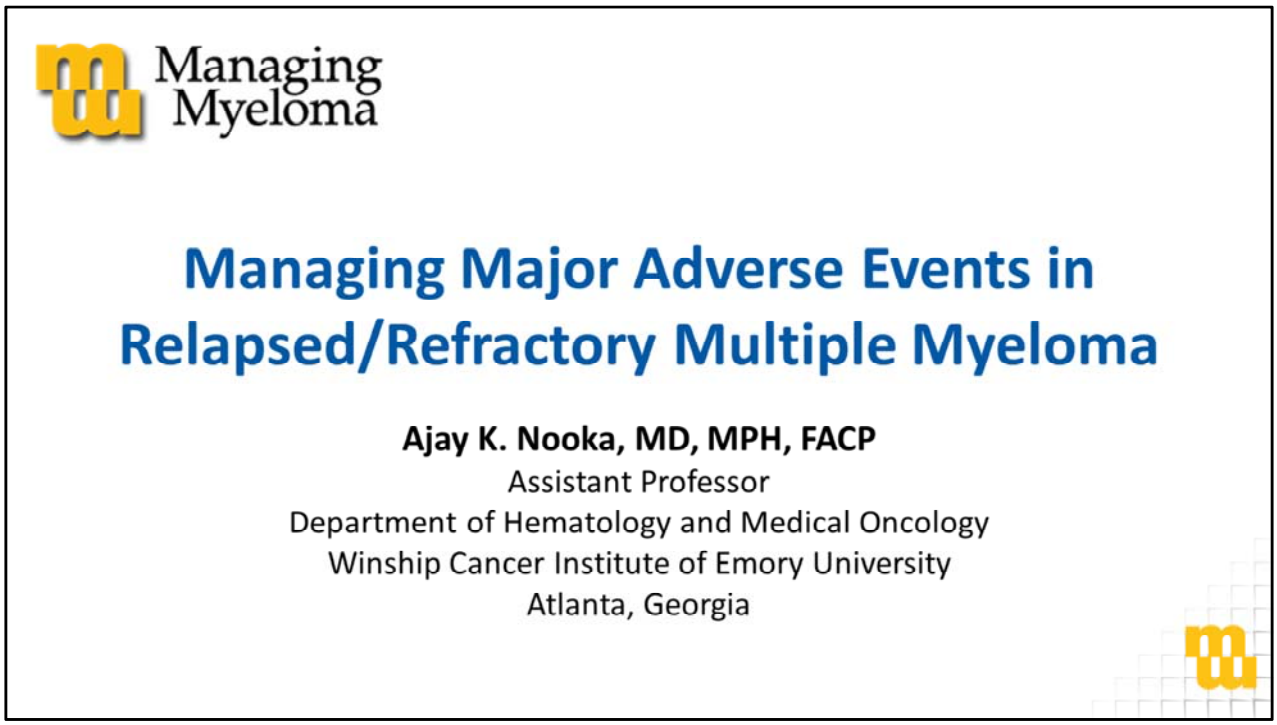
Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma



Welcome to *Managing Myeloma*. I am Dr. Ajay Nooka. In today's presentation, I will discuss managing major adverse events in relapsed/refractory multiple myeloma. In this video, I will provide you with information and tools necessary to develop strategies for managing baseline and treatment-emergent renal and hepatotoxicity from therapies used in relapsed/refractory multiple myeloma, recognize the risk of peripheral neuropathy and cardiovascular toxicity associated with specific agents and in specific populations, identify therapies associated with infusion reactions in relapsed/refractory multiple myeloma, and appropriate management strategies to mitigate these. Let's begin.

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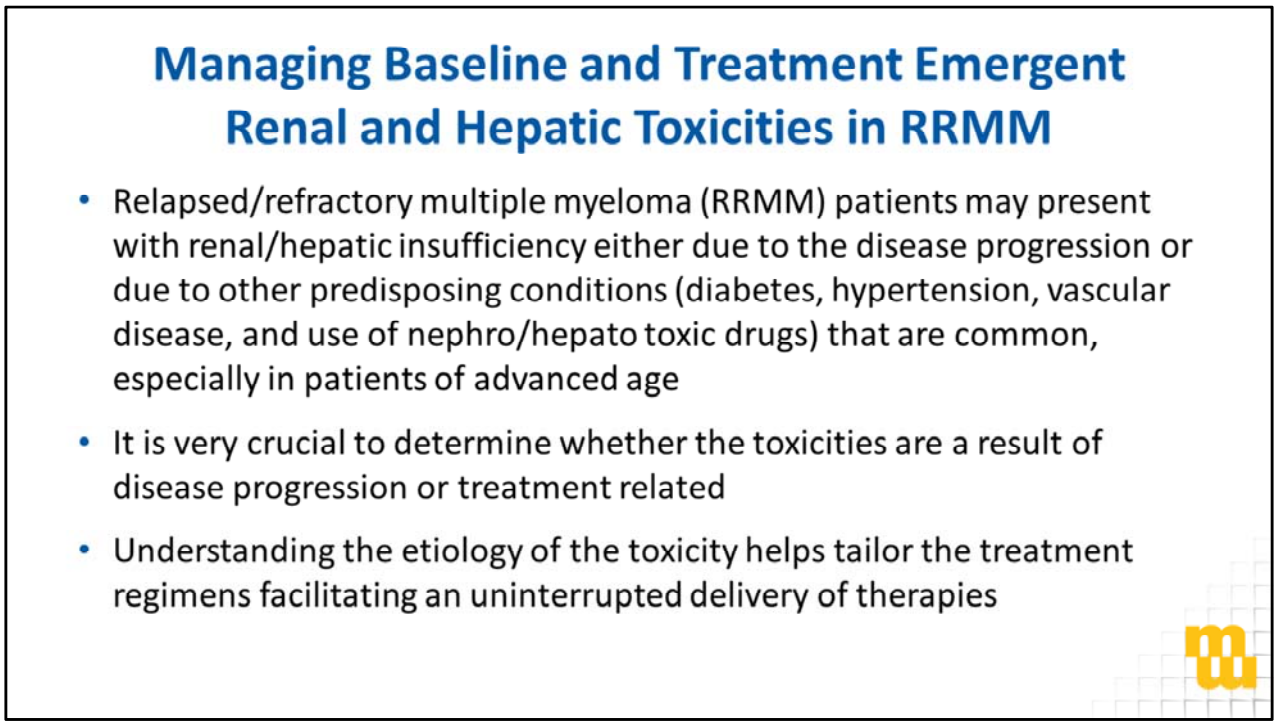

Relapsed/refractory multiple myeloma patients present with renal or hepatic insufficiency either due to disease progression or due to other predisposing conditions like diabetes, hypertension, vascular disease, and other use of nephrotoxic or hepatotoxic drugs that are more common in the advanced age. It is of extreme importance to determine whether the toxicities are myeloma related or treatment related. Understanding the etiology of this toxicity will help tailor the treatment regimens facilitating an uninterrupted delivery of these treatment strategies.

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Renal Dose Modifications: IMiDs

Drug	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Thalidomide[1] 50-200 mg PO q daily	100%	100%	100%	100%
Lenalidomide*[2] 25 mg PO q days 1-21/28 days	25 mg once daily	10 mg once daily	15 mg every alternate day	5 mg once daily
Pomalidomide[3] 4 mg PO q days 1-21/28 days	4 mg once daily	4 mg once daily	4 mg once daily	3 mg once daily

*Lenalidomide is primarily excreted unchanged by the kidney
IMiDs=immunomodulatory drugs; ESRD=end-stage renal disease; HD=hemodialysis; PO=by mouth
[1]Thalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020785s055lbl.pdf
[2]Lenalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf
[3]Pomalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf

We will talk about the renal and hepatic dose modifications. I will start with the three IMiDs that are currently FDA approved. The first one is thalidomide. Thalidomide is not cleared by the kidney, so it is perfectly fine to use at appropriate dosing, even among patients who are on end-stage renal disease and on hemodialysis. It is of extreme importance to realize this because a majority of the patients who present with renal dysfunction upfront may need a thalidomide-based regimen where thalidomide could be used without any dose reductions. Lenalidomide on the other hand is partially cleared by the kidneys, which needs dose reductions. Among patients who have creatinine clearance of greater than 60 mL per minute, the full dose can be used. Among patients who have moderate renal dysfunction with clearance between 30 mL to 60 mL per minute, a 10 mg per day dosing is used. Among patients on hemodialysis, 5 mg once daily is the recommended dosing. Pomalidomide is also kidney friendly. It does not need a huge amount of dose reductions, even among patients who have creatinine clearance of less 30 mL per minute. Those patients on hemodialysis are the ones that require dose reduction by 25% with 3 mg once daily on days 1 to 21, every 28 days.

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Hepatic Dose Modifications: IMiDs

Drug	Normal	Mild	Moderate	Severe
Thalidomide[1] 50-200 mg PO q daily	No dedicated study done			
Lenalidomide*[2] 25 mg PO q days 1-21/28 days	No dedicated study done			
Pomalidomide[3] 4 mg PO q days 1-21/28 days	4 mg once daily	3 mg once daily	3 mg once daily	2 mg once daily

*Lenalidomide is primarily excreted unchanged by the kidney

[1]Thalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020785s055lbl.pdf

[2]Lenalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021880s034lbl.pdf

[3]Pomalidomide Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204026lbl.pdf

When you look at the hepatic toxicity of the immunomodulatory agents, thalidomide or lenalidomide have not been adequately studied, but in pomalidomide it is very friendly, requiring dose reductions. At normal hepatic function, a full dose can be used. Among patients with mild-to-moderate hepatic insufficiency, 25% dose reduction is recommended at 3 mg once daily, and in patients who have severe hepatic insufficiency, 50% dose reduction is recommended.

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Renal Dose Modifications: PIs

Drug	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Bortezomib[1] 1.3 mg/m^2 days 1, 4, 8 and 11 every 21 days IV/SC	100%	100%	100%	100%
Carfilzomib[2] 20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16 every 28 days	100%	100%	Hold until renal functions stabilize and start at 1 dose level reduction	Hold until renal functions stabilize and start at 1 dose level reduction
Ixazomib[3] 4 mg PO days 1, 8, 15 every 28 days	4 mg	4 mg	3 mg	3 mg

PIs–proteasome inhibitors; IV–intravenous; SC–subcutaneous

[1]Bortezomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf

[2]Carfilzomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf

[3]Ixazomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf

Among the proteasome inhibitors, bortezomib which has been the first FDA-approved proteasome inhibitor, no toxicity and no dose reductions are recommended for renal toxicity. Even among patients who are on hemodialysis, a full dose of bortezomib can be used. Carfilzomib is also a potent proteasome inhibitor. I would suggest that when you are using carfilzomib, monitoring for tumor lysis syndrome is of extreme importance. Even though carfilzomib is very friendly to the kidneys, when it was first approved, as a good proteasome inhibitor it was able to give a huge amount of tumor response and subsequently resulted in tumor lysis syndrome. My suggestion would be to hold the carfilzomib until renal function stabilizes, if you are seeing a renal insufficiency, and start at one dose level reduction. Among patients on hemodialysis, hold until the renal function stabilizes and start at one dose level reduction. Ixazomib, the new oral proteasome inhibitor, is also friendly renally. Among patients who have creatinine clearance greater than 30 mL per minute, a full dose of ixazomib can be used. Among patients who have less than 30 mL per minute or patients on hemodialysis, a 25% dose reduction is recommended.

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Hepatic Dose Modifications: PIs

Drug	Normal	Mild	Moderate	Severe
Bortezomib*[1] 1.3 mg/m^2 days 1, 4, 8 and 11 every 21 days IV/SC	100%	100%	Reduce to 0.7 mg/m^2 in 1st cycle; escalation to 1 mg/m^2 in subsequent cycles based on tolerability	Reduce to 0.7 mg/m^2 in 1st cycle; escalation to 1 mg/m^2 in subsequent cycles
Carfilzomib[2] 20/27 mg/m^2 days 1, 2, 8, 9, 15 and 16 every 28 days	100%	75%	75%	Has not been studied in this population
Ixazomib[3] 4 mg PO days 1, 8, 15 every 28 days	100%	100%	75%	75%

*Bortezomib is metabolized by liver and clearance may decrease in patients with hepatic impairment

[1]Bortezomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf
[2]Carfilzomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202714lbl.pdf
[3]Ixazomib Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462lbl.pdf

Currently, the hepatic insufficiency, bortezomib can be given at full dosage among patients with normal or mild hepatic insufficiency. Among patients who have moderate-to-severe hepatic insufficiency, one dose level reduction should be considered and could be escalated at a later time at the return of baseline functions. Carfilzomib, there is no data for severe hepatic insufficiency, but certainly, it can be dose reduced in mild-to-moderate hepatic insufficiency by 25%. Ixazomib, similarly, no dose reductions are required for normal-to-mild hepatic insufficiency, but certainly dose reductions are needed for patients who have moderate-to-severe hepatic insufficiency.

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Renal and Hepatic Dose Modifications: Monoclonal Antibodies

Renal	CrCl >60 mL/min	CrCl 30-60 mL/min	CrCl <30 mL/min	ESRD or HD
Elotuzumab[1] 10 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	100%
Daratumumab[2] 16 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	100%

Hepatic	Normal	Mild	Moderate	Severe
Elotuzumab[1] 10 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	Has not been studied in this population
Daratumumab[2] 16 mg/kg days 1, 8, 15, 22 every 28 days	100%	100%	100%	Has not been studied in this population

[1]Elotuzumab Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761035s000lbl.pdf
[2]Daratumumab Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761036s000lbl.pdf

Coming to the other anti-myeloma agents, including the monoclonal antibodies, these are the friendliest agents in terms of the toxicities. Elotuzumab could be given renally, does not need any renal dose reductions, and could be given at full dosage even among patients on hemodialysis. Similar case with the daratumumab. We do not have data for both these agents for severe hepatic insufficiency, but no dose level reductions are required, even among patients with mild-to-moderate hepatic insufficiency.

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Renal and Hepatic Dose Modifications: Other (HDAC Inhibitor and Cyclophosphamide)

Renal	Mild CrCl ≥50 to <80 mL/min	Severe CrCl <30 mL/min	ESRD or HD	
Panobinostat[1] 20 mg days 1, 3, 5, 8, 10, 12 every 28 days	100%	100%	Has not been studied in this population	
Hepatic	**Normal**	**Mild**	**Moderate**	**Severe**
Panobinostat 20 mg days 1, 3, 5, 8, 10, 12 every 28 days	100%	75%	50%	Not recommended

Renal	CrCl >10 mL/min	CrCl <10 mL/min	ESRD or HD
Cyclophosphamide*[2] 300 mg/m^2 days 1, 8, 15 every 28 days	100%	75%	50%
Hepatic	**Serum bilirubin 3.1-5 mg/dL or transaminases >3 x ULN**	**Serum bilirubin >5 mg/dL**	
Cyclophosphamide*[3] 300 mg/m^2 days 1, 8, 15 every 28 days	75%	Avoid use	

HDAC=histone deacetylase
[1]Panobinostat Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf
*No dosing adjustments provided in the package insert. [2]Arnoff J, et al. *Euro J Cancer*. 2007;43:14-34. [3]Floyd J, et al. *Semin Oncol*. 2006;33(1):50-67.

One other drug which has gained FDA approval is panobinostat. Panobinostat is an HDAC inhibitor in combination with bortezomib and dexamethasone, and we do not have data about panobinostat usage in hemodialysis patients, but among the others with renal toxicity, it could be safely used. Cyclophosphamide requires 75% dose reduction among patients who have clearance less than 10 mL per minute, and among patients who are on hemodialysis, we recommend 50% dose reduction. The table notes the suggested dose reductions for hepatic insufficiency.

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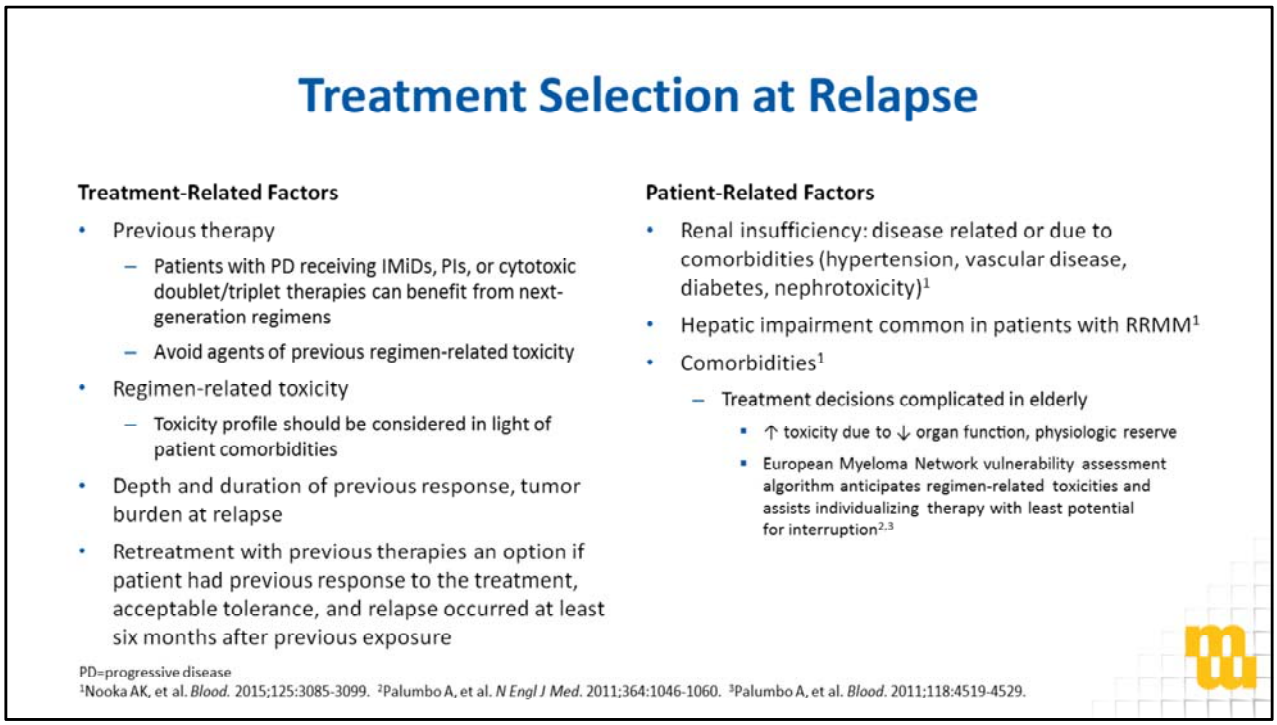

Once you understand the dose reductions that are needed and clearly what the toxicity is related to, it is very easy to understand the treatment selection at relapse based on the treatment-related factors, as well as the patient-related factors. Several factors come into account when you choose the treatment selection at relapse. Previous therapy, the regimen-related toxicity, the depth and duration of the prior response, tumor burden of the relapse, all these factor into the decision for the treatment choice at the time of relapse. Similarly, patient-related factors, as we discussed the renal insufficiency, hepatic insufficiency, and other comorbidities certainly play a role in choosing the right regimen that is friendlier to the patient.

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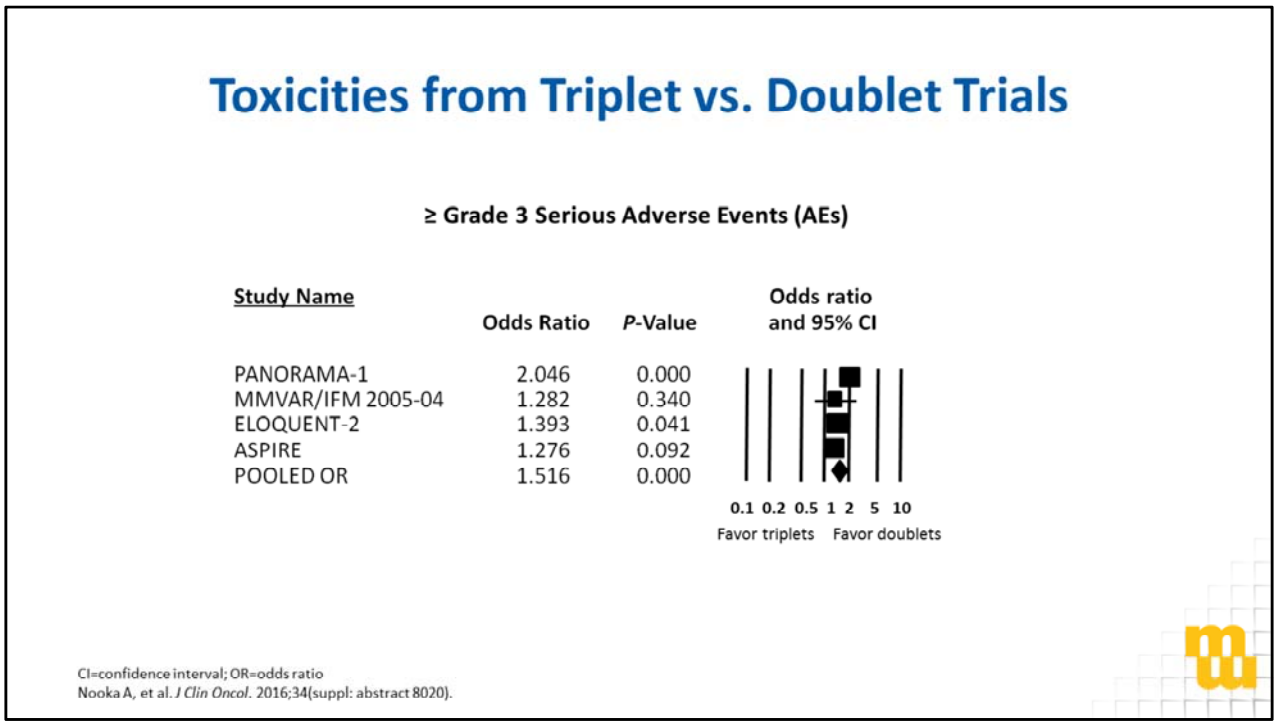

As we have seen a common theme over the last several years, there are six randomized controlled trials that have shown the benefit of the triplet regimen, compared to a doublet regimen. These six studies have used two different backbones. Two studies have used the bortezomib and dexamethasone backbone, and the other four studies have used lenalidomide and dexamethasone backbone. When you are adding a third agent, you are getting the benefit, but at the same time, you have to realize that the toxicity levels are higher too. We did a meta-analysis a few years ago including four trials that have been evaluated comparing a triplet regimen to a doublet regimen. We were able to show that the toxicity is not significantly overwhelming, but the odds ratio is 1.5 times compared to a doublet regimen in terms of a grade 3 toxicity. If you look at the slide, most of this toxicity is coming from one trial, which is a PANORAMA trial, which is skewing the farthest block to the right side.

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Adverse Events of Interest: TOURMALINE-MM1

Preferred terms	IRd (N=361), %			Placebo-Rd (N=359), %		
	All-grade	Grade 3	Grade 4	All-grade	Grade 3	Grade 4
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash*	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathies*	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism*	8	2	<1	11	3	<1
Neutropenia*	33	18	5	31	18	6

*Represents multiple MedDRA preferred terms.

IRd=ixazomib-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone
Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

If you look at the individual agents, the AEs of interest in the TOURMALINE-MM1 trial which basically compared the triplet regimen ixazomib-lenalidomide-dexamethasone versus lenalidomide and dexamethasone, the side-effect profile for this specific drug is very, very beautiful. The major side effects that you can see as a theme are the GI toxicity with diarrhea, constipation, nausea, and vomiting, and most of these are less than grade 3 toxicities. If you focus on the grade 3 toxicities, diarrhea is seen in 6% of the patients in the ixazomib-lenalidomide-dexamethasone arm compared to 3% in the placebo-lenalidomide-dexamethasone arm. This is a very well tolerated agent, an oral agent, and does not have longstanding toxicities of peripheral neuropathy. It could be mildly myelosuppressive, but these are very well tolerable. Especially, when you are combining it with the lenalidomide which has the side effect of myelosuppression, looking over the labs with a bit of vigilance is strongly recommended.

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Other Infrequent AEs: TOURMALINE-MM1 Trial

AE	IRd (N=361), %	Placebo-Rd (N=359), %
Arrhythmias*	16	15
Hypertension	6	5
Hypertension crisis	<1	0
Hypotension*	6	6
Heart failure*	4	4
Myocardial infarction*	1	2
Acute renal failure*	9	11
Liver impairment*	8	6
Interstitial lung disease*	1	2
Encephalopathy*	<1	1
Events of special interest		
New primary malignancy*†	5	4

*Represents multiple MedDRA preferred terms.
†Includes treatment-emergent AEs and new primary malignancies reported during follow-up period.

Moreau P, et al. *N Engl J Med*. 2016;374(17):1621-1634.

Other infrequent adverse events from the TOURMALINE-MM1 trial include hypertension in 6% of the patients compared to 5% of the patients in the lenalidomide-dexamethasone arm. Arrhythmias were common across both arms. The side- effect profile is almost similar to what you see with placebo plus lenalidomide-dexamethasone versus ixazomib-lenalidomide-dexamethasone.

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AEs of Interest: ASPIRE Safety Population (n=781)

AE, %	KRd (n=392)		Rd (n=389)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Dyspnea	19.4	2.8	14.9	1.8
Peripheral neuropathy*	17.1	2.6	17.0	3.1
Hypertension	14.3	4.3	6.9	1.8
Acute renal failure*	8.4	3.3	7.2	3.1
Cardiac failure*	6.4	3.8	4.1	1.8
Deep vein thrombosis	6.6	1.8	3.9	1.0
Ischemic heart disease*	5.9	3.3	4.6	2.1
Pulmonary embolism	3.6	3.1	2.3	2.3
Second primary malignancy*	2.8	2.3	3.3	2.8

*Grouped term
KRd=carfilzomib-lenalidomide-dexamethasone
Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.

Looking at the next trial, the ASPIRE trial. ASPIRE trial compared the triplet of carfilzomib-lenalidomide-dexamethasone versus lenalidomide-dexamethasone in relapsed/refractory patients. If you look at the all grade toxicity, dyspnea comes to the top of the list with almost 20% of the patients having an episode of dyspnea. Grade 3 toxicity was seen in 3% of the patients who have dyspnea in the carfilzomib-lenalidomide-dexamethasone arm compared to the lenalidomide-dexamethasone arm having 2% dyspnea. Peripheral neuropathy rates are similar. If you look in the third row, hypertension seems to be a common theme among the patients receiving carfilzomib-based regimens. The grade 3 toxicity with hypertension is close to 5% and this needs worth mention, we will talk more about this in a minute. Acute renal failure rates and the DVT rates, all these are almost similar to what you see with the lenalidomide-dexamethasone arm. The few AEs of interest that come to mind when you speak about carfilzomib-based regimens are: hypertension, non-pulmonary and non-cardiac dyspnea, cardiac failure. These seem to be slightly higher compared to the backbone of the lenalidomide and dexamethasone.

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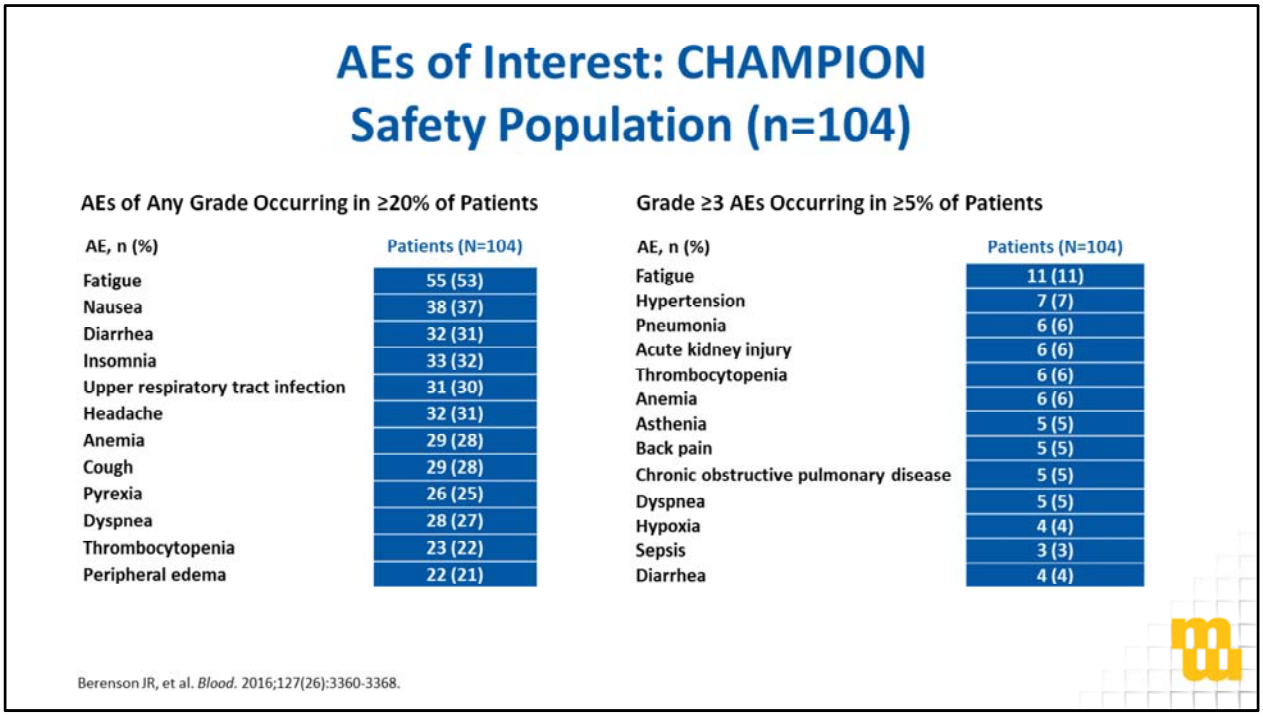

The main problem when you use a carfilzomib-based regimen is the schedule. Typically, the patients have to go for 6 days in a week on two consecutive days for three consecutive weeks and you get a week off, that is almost six visits. What CHAMPION trial tried to demonstrate is, how can we reduce the number of infusions? Can we do it on a weekly dosing instead of twice-weekly dosing? CHAMPION trial evaluated with a higher dose of carfilzomib at 70 mg/m^2 and evaluated in 104 patients on a weekly basis. What you see here are the adverse events that were seen in more than 20% of the patients, fatigue, nausea, and diarrhea being the most common side effects with carfilzomib and dexamethasone. More importantly, if you look at the grade 3 toxicities that are occurring in more than 5% of the patients, fatigue was seen in 11% of the patients, hypertension in 7% of the patients, and thrombocytopenia, anemia, all the symptoms of myelosuppression, as you can see, are seen in close to 3% to 7% of the patients.

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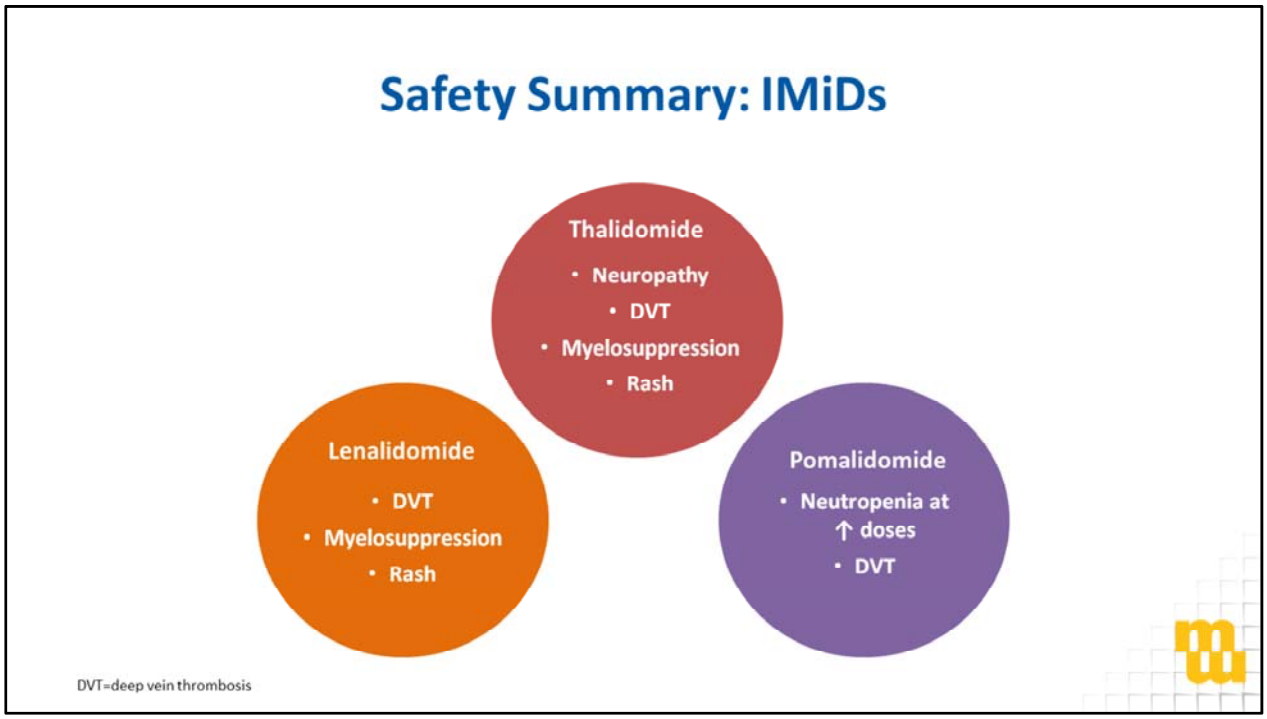

To summarize the safety of the immunomodulatory agents, there are three IMiDs that we currently have approved by the FDA: thalidomide, lenalidomide, and pomalidomide. The main side effects of thalidomide are neuropathy, DVT (deep vein thrombosis), myelosuppression, and rash. The main side effects with lenalidomide are DVT, myelosuppression, and rash. The main side effects with pomalidomide are neutropenia at higher doses and formation of DVTs. What you see commonly across the board is the formation of DVTs. It is not uncommon to see DVT in around 6% of the myeloma patient population that is receiving an IMiD. Appropriate usage of thromboprophylaxis with aspirin, or if the patient has more risk factors like a prior DVT or using steroids, or using in combination with any chemotherapeutic agents, certainly going on with a low molecular weight heparin certainly helps with thromboprophylaxis. Among all these three agents, myelosuppression is the least common with thalidomide. In somebody who has poor counts, that would be my IMiD of choice. The patients with rash could be re-challenged with lenalidomide and should not be completely withheld off an IMiD. They should be re-challenged, but one dose reduction recommendation that I make is changing the dexamethasone to prednisone, and giving it on an alternative day rather than giving it on a weekly basis certainly helps with the rash.

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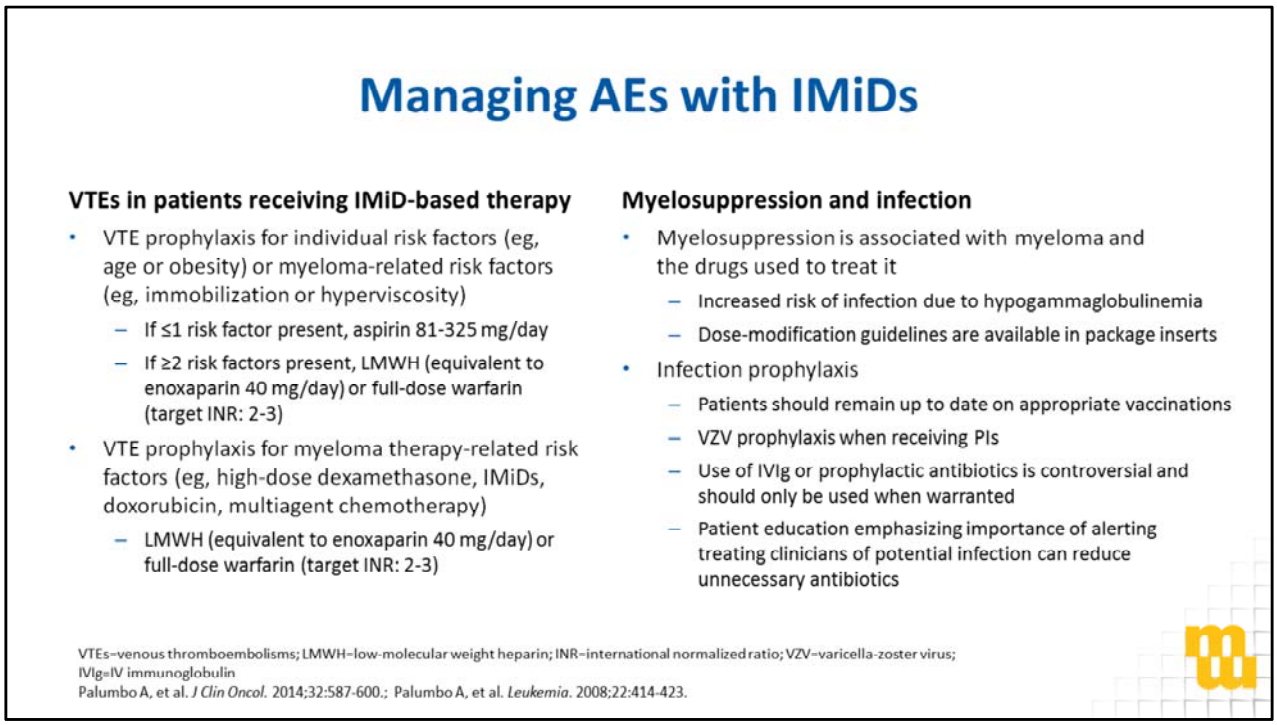

How do you manage these AEs for the venous thromboembolic events with the IMiD-based therapies? Basically, identifying the risk factors. Is the patient is receiving a single-agent lenalidomide? In such a case, in the absence of any other comorbidities, in the absence of any other risk factors, the patient could benefit with thromboprophylaxis from aspirin alone. If there is more than one risk factor, a low molecular weight heparin is indicated. Other side effects like the myelosuppression could be closely watched, and growth factors could be given if the patient needs to continue the treatment uninterrupted. You could also take the support of IVIG or take the support of anti-bacterials when you are using a dexamethasone-based, high-steroid based regimen so that you prevent the PCP pneumonias.

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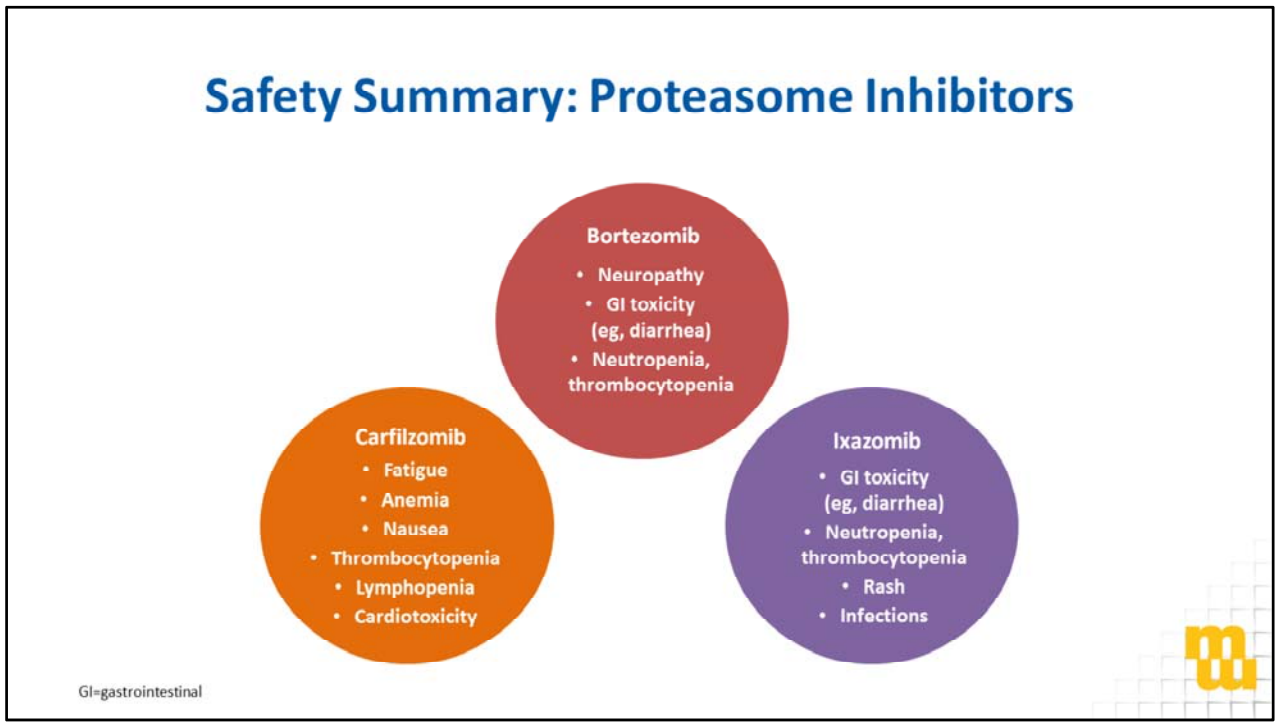

To summarize the proteasome inhibitors, the three proteasome inhibitors that we have currently are bortezomib, carfilzomib, and ixazomib. In bortezomib the main side effect is neuropathy. You also can see thrombocytopenia with myelosuppression with bortezomib-based therapies and GI toxicities. Appropriately identifying these patients who are at high risk for the neuropathy would certainly help us to monitor closely so that we make the proper dose reductions of the management strategies, otherwise specified. For carfilzomib, monitoring for fatigue, making appropriate dose reductions, monitoring for anemia, nausea, and thrombocytopenia, which is a class effect, are all things that could help us to mitigate these side effects if you watch closely so that we will be able to deliver these treatments without any interruptions. Similarly, ixazomib, the main side effects are the rash and GI toxicity. Appropriately treating these patients with anti-nauseants, treating them with a PPI, and appropriately treating them, monitoring for rash certainly can help with delivering this drug.

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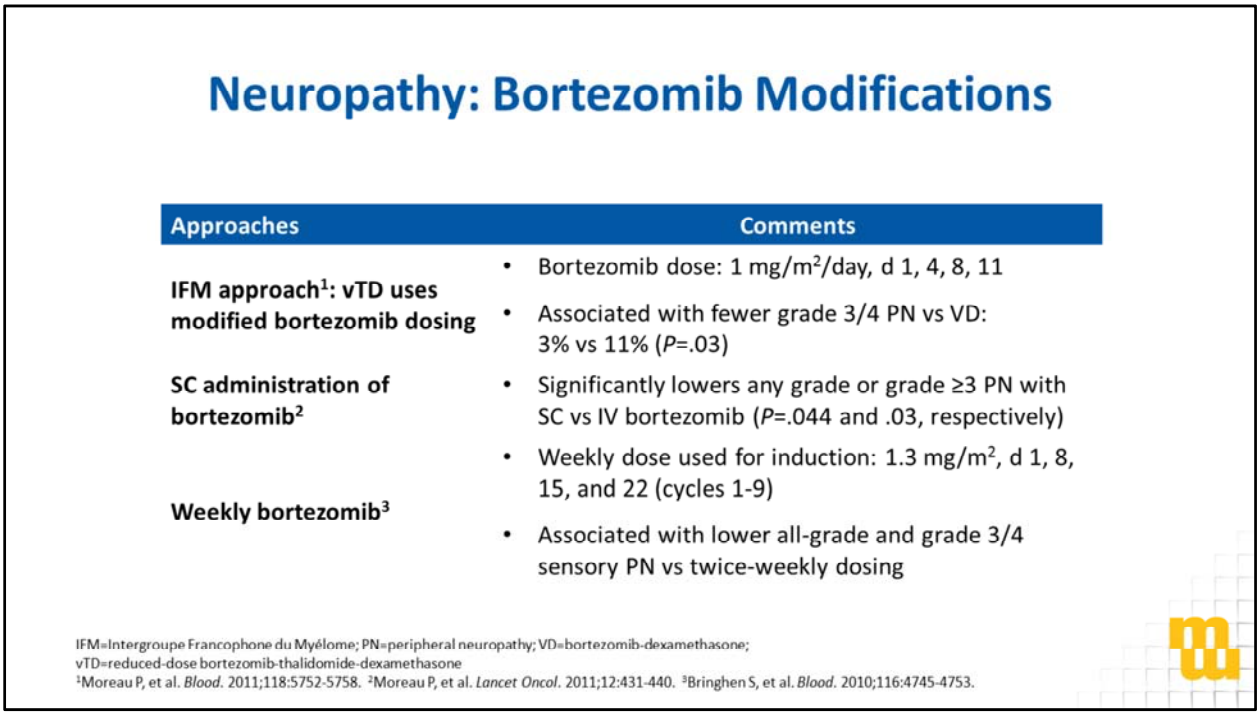

In neuropathy, for bortezomib, the dose modifications that were recommended are going down to one dose level to 1 mg/m^2 on an induction setting, days 1, 4, 8, 11. Using induction dosing or going back to a weekly regimen is appropriate. What we have seen over the last 5 years was when we moved from administering the IV bortezomib to subcutaneous administration of bortezomib, we have seen a significant decline in the grade 3 toxicities that we were used to seeing. It is a good move, and we are seeing lesser and lesser rates of neuropathy, and appropriate monitoring certainly helps.

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Cardiotoxicity of Proteasome Inhibitors in the Treatment of Multiple Myeloma

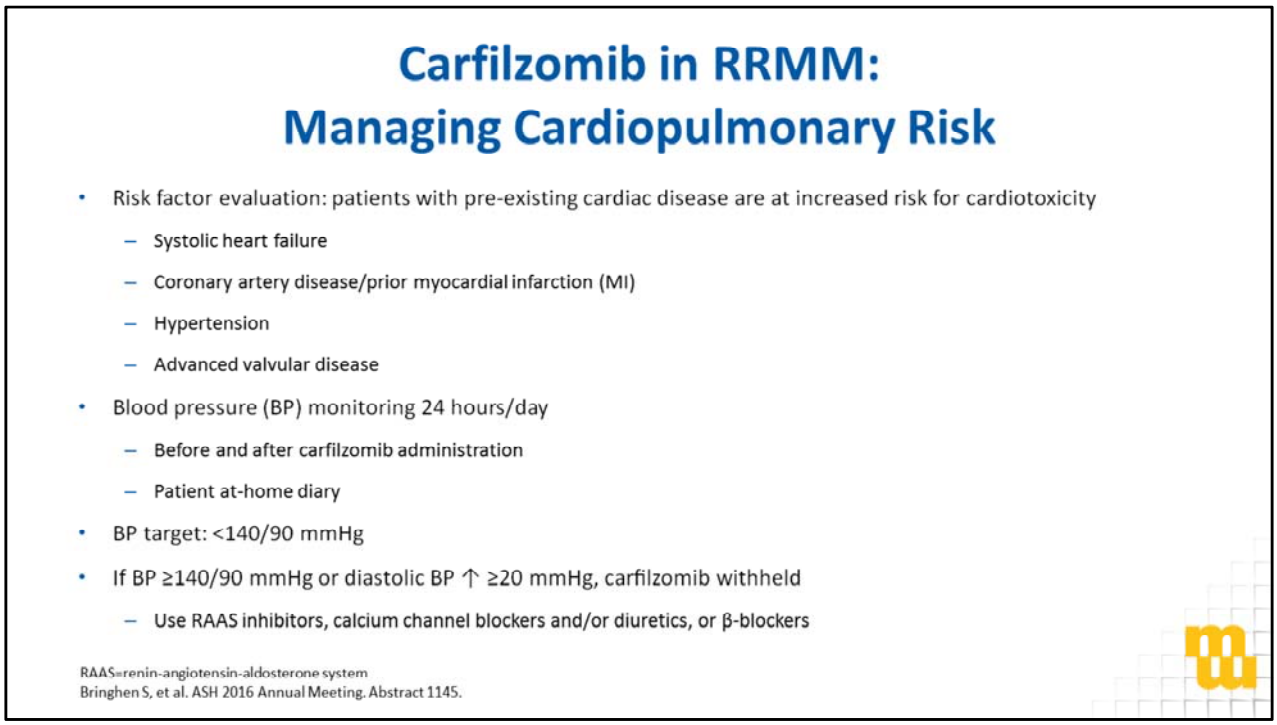
Special analysis of grouped-term organ system adverse events

Grouped adverse event, , (%)	Any AE	≥ Grade 3	SAE
Any cardiac	116 (22.1)	50 (9.5)	41 (7.8)
Cardiac arrhythmia	70 (13.3)	12 (2.3)	11 (2.1)
Cardiac failure	38 (7.2)	30 (5.7)	26 (4.9)
Ischemic heart disease	18 (3.4)	7 (1.3)	5 (1.0)
Cardiomyopathy	9 (1.7)	3 (0.6)	2 (0.4)
Any respiratory	363 (69.0)	54 (10.3)	34 (6.5)
Dyspnea	222 (42.2)	26 (4.9)	11 (2.1)
Cough	137 (26.0)	1 (0.2)	1 (0.2)
Pneumonia	67 (12.7)	55 (10.5)	52 (9.9)
Any grouped renal impairment	174 (33.1)	38 (7.2)	32 (6.1)
Increased serum creatinine	127 (24.1)	14 (2.7)	7 (1.3)
Acute renal failure	28 (5.3)	23 (4.4)	22 (4.2)
Renal failure	20 (3.8)	6 (1.1)	7 (1.3)

Richardson PG, et al *N Engl J Med.* 2005;352:2487-98. Siegel DS, et al. *Haematolgica.* 2013;98(11) :1753-1761.

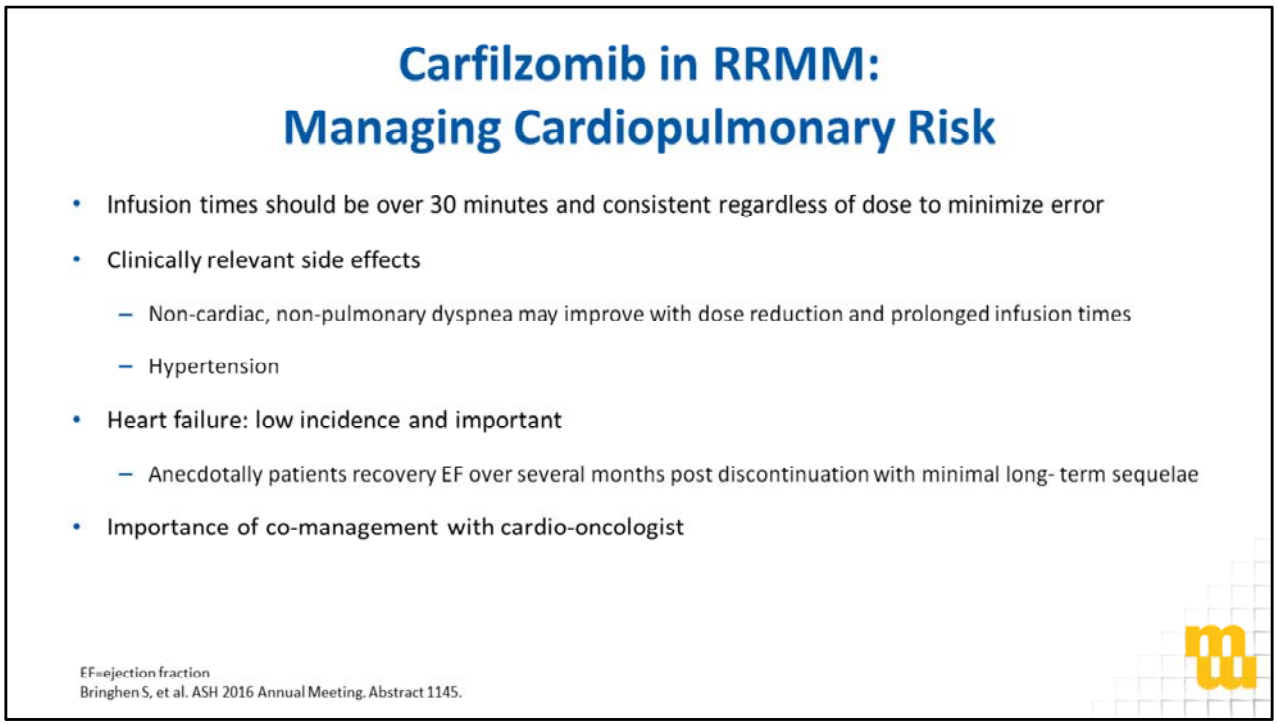
Coming to a completely different topic, the cardiotoxicity with the proteasome inhibitors. In my opinion, the real etiology is its class effect with the proteasome inhibition that could lead to cardiotoxicity, that could manifest as cardiac failure, uncontrolled hypertension, and sometimes dyspnea. What was seen in the past from the Richardson trial, the APEX trial, that was published very long ago, almost 10 years ago, was there was a signal of cardiac toxicity in those patients. What we have seen in recent years is we all know that carfilzomib is a better proteasome inhibitor based on the ENDEAVOR trial, that as the potency increases, so do the class effects, and so do the cardiotoxicity. It is not uncommon to see cardiotoxicity. Appropriate monitoring is what is of extreme crucial importance.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma

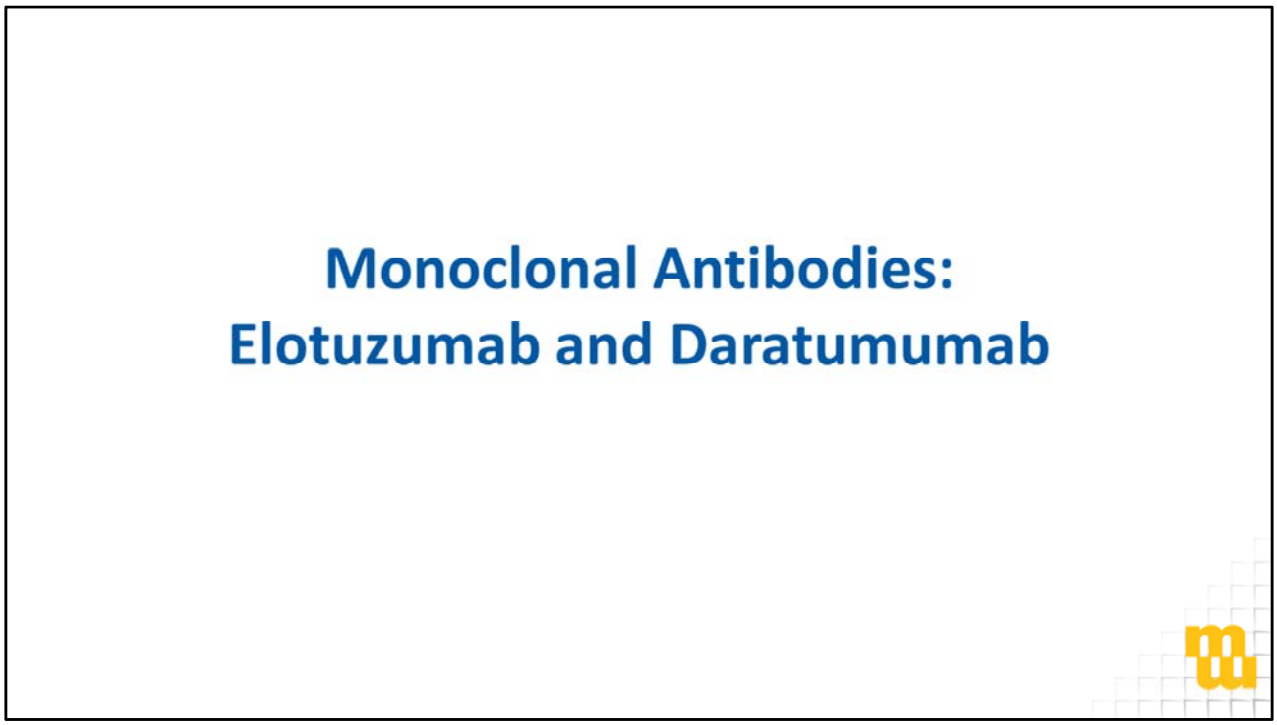


The way that I put this together is to identify and evaluate those risk factors (whether the patient has preexisting cardiac disease, whether the patient has any systolic heart failure, prior history of MIs, or any advanced valvular diseases), all these certainly would help us to identify those patients who are at risk for developing cardiac complications. Appropriate monitoring of blood pressure. Is the blood pressure getting out of control? Appropriately starting an anti-hypertensive regimen, and checking the blood pressures before and after carfilzomib administration. If their systolic blood pressure is greater than 20 mmHg, the carfilzomib dose can be withheld if the disease permits it. Using appropriate dose reductions would certainly help mitigate all these symptoms.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma



What you see with the infusion timings for 27 mg/m^2 is a 10-minute requirement of the infusion of carfilzomib. What we had seen practically is if you prolong this infusion time to 30 minutes, instead of giving it over 10 minutes, you mitigate a lot of these side effects that you normally see. Appropriately monitoring the patients and having counseling with them, saying that they can anticipate these non-cardiac and non-pulmonary dyspnea as a complication of receiving carfilzomib. They certainly will be prepared to have a similar side effect and there is no long-term toxicity that was seen with the side effect of dyspnea. In our institution, we certainly take the help of a cardio-oncologist, and certainly, their input is of extreme importance, especially when managing the hypertension and the cardiac failure.



Coming to a completely new set of agents, the monoclonal antibodies. The two drugs that fall into this category are elotuzumab and daratumumab.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma

Key Adverse Events Reported in ≥30% of Patients: ELOQUENT-2

Adverse event, n (%)	Elotuzumab-Ld (n=318)		Ld (n=317)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Common non-hematologic adverse events				
Fatigue	149 (47)	27 (9)	123 (39)	26 (8)
Pyrexia	119 (37)	8 (3)	78 (25)	9 (3)
Diarrhea	149 (47)	16 (5)	114 (36)	13 (4)
Constipation	113 (36)	4 (1)	86 (27)	1 (0.3)
Muscle spasms	95 (30)	1 (0.3)	84 (27)	3 (1)
Cough	100 (31)	1 (0.3)	57 (18)	0
Common hematologic toxicities				
Lymphopenia	316 (99)	244 (77)	311 (98)	154 (49)
Neutropenia	260 (82)	107 (34)	281 (89)	138 (44)
Infections	259 (81)	89 (28)	236 (74)	77 (24)

- Exposure-adjusted infection rate was 197 (incidence rate per 100 person-years of exposure) in both arms
- There was no detriment to overall health-related quality of life with the addition of elotuzumab to Ld

Ld=lenalidomide and dexamethasone
Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.

The ELOQUENT-2 trial which evaluated the benefit of combination of elotuzumab and lenalidomide-dexamethasone versus lenalidomide-dexamethasone. The ELOQUENT-2 trial is the one that had shown that this drug can be safely administered, even among relapsed/refractory patients without much change in the toxicity profile. If you see any grade toxicities, they are almost similar to what you see with lenalidomide and dexamethasone. The fatigue of 47% that was seen with elotuzumab, lenalidomide-dexamethasone any grade, is the most common side effect that you see with this combination. Similarly, with lenalidomide-dexamethasone, we see a 39% any grade toxicity with fatigue. What you also see is lymphopenia; the greater than grade 3 lymphopenia was significantly higher with elotuzumab, lenalidomide, and dexamethasone compared to lenalidomide and dexamethasone. Otherwise, the side-effect profile across the board does not appear to be any different between lenalidomide-dexamethasone and elotuzumab, lenalidomide-dexamethasone. What you commonly see is the infusion-related reactions with elotuzumab. It is a common theme for any monoclonal antibody. What has shown in our practice to mitigate these side effects are to give appropriate premedication with steroids, and certainly, this will decrease the rates of the infusion-related reactions.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma

Safety Daratumumab + Lenalidomide-Dexamethasone

Treatment-emergent AEs in >20% patients

	N=32	
	Any grade	Grade ≥3
Any event	32 (100)	28 (88)
Neutropenia	27 (84)	25 (78)
Cough	16 (50)	0
Diarrhea	14 (44)	1 (3)
Muscle spasms	14 (44)	0
Fatigue	11 (34)	0
Pyrexia	10 (31)	0
Thrombocytopenia	10 (31)	4 (13)
Hypertension	9 (28)	3 (9)
Nausea	9 (28)	0
Anemia	8 (25)	4 (13)
Peripheral edema	8 (25)	0
Upper respiratory tract infection	8 (25)	1 (3)
Peripheral sensory neuropathy	7 (22)	0

- Sixteen (50%) patients had serious AEs, eight (25%) of which were due to infections

Infusion-related reactions (IRRs) in >2 patients

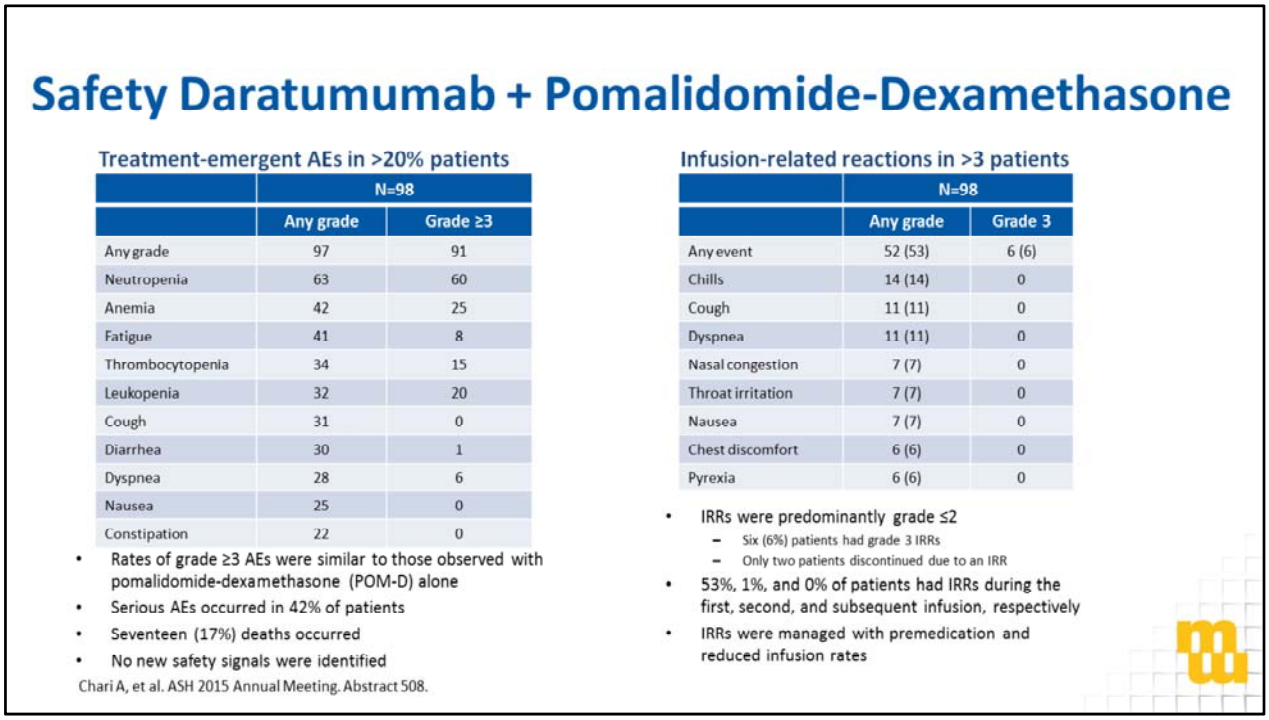
	N=32	
	Any grade	Grade 3
Any event	18 (56)	2 (6)
Cough	8 (25)	0
Allergic rhinitis	3 (9)	0
Nausea	3 (9)	0
Vomiting	3 (9)	0
Dyspnea	2 (6)	0
Nasal congestion	2 (6)	0

- Type and rate of IRRs were similar to those reported in studies of daratumumab monotherapy
- The majority of IRRs were grade ≤2
- All patients who experienced IRRs (n=18) had an IRR during the first infusion
  - Three patients had IRRs in the second or subsequent infusion
- Two patients had grade 3 IRRs; one patient had laryngeal edema and the other had hypertension
- No grade 4 IRRs were reported

Plesner T, et al. ASH 2015 Annual Meeting. Abstract 507.

The other drug is daratumumab, which is the CD38 monoclonal antibody that was recently approved in November of 2015 as a single agent. Recently, it was approved in combination with bortezomib and in combination with lenalidomide based on the CASTOR and POLLUX trials. This is data based on the trial combining daratumumab, lenalidomide, and dexamethasone showing the infusion-related reactions are the most common ones that you can see, seen in half of the patients. What is more striking is, if you look at the grade 3 toxicities, there are only 6% grade 3 toxicities in terms of infusion-related reactions. Again, going under the appropriate premedications and going along with a stable steady increase in the infusion rates, certainly can help counter these problems of infusion-related reactions. One important point is daratumumab certainly causes myelosuppression. When you are combining with another agent that could cause myelosuppression, it is of extreme importance to identify which of these combinations you could give and which of these combinations we should give with a dose reduction.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma



One example is daratumumab in combination with pomalidomide and dexamethasone. In our practice, what we commonly do is use pomalidomide at 3 mg as a starting dose. When you combine with daratumumab, if the patient does not have any side effects, we go for 4 mg at the next setting. Again, even from the daratumumab-pomalidomide-dexamethasone trial, we saw that infusion-related reactions are more common.

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma

Use of Montelukast* to Reduce IRR

Infusion-related reactions (N=348)	
Grade >3 IRRs	8%
Percentage of IRRs	
First infusion	56%
Second infusion	2%
All subsequent infusions	2%
Respiratory or thoracic symptoms	31%
Cough	14%
Dyspnea	9%
Throat irritation	6%
Nasal congestion	5%

Observed IRRs in patients with and without montelukast therapy		
	Montelukast 10 mg as pre-infusion (n=50)	No montelukast given as pre-infusion (n=298)
IRR rate at first infusion	38.0%	58.5%
Respiratory symptoms	20%	32%
Gastrointestinal symptoms	4%	11%
Chills	14%	14%
Median time for first infusion (hours)	6.7	7.6

Conclusions

- The findings of the Expanded Access Program (EAP) study in US patients with MM who had received >3 prior therapies including a PI and IMiD or were double-refractory observed an IRR rate and median infusion times that were similar to what were observed in the pivotal registration study MMY2002 in this patient population
- The observed IRR rate during the first daratumumab infusion was one-third lower in patients who received 10 mg of montelukast >30 minutes prior to the first daratumumab infusion than in patients who did not receive montelukast
- Respiratory and gastrointestinal symptoms were lower in patients who received montelukast, whereas chills were observed at a similar rate in both groups
- The median time for the first infusion was 0.9 hours shorter in patients who received montelukast
- Because the use of montelukast was limited to a small number of centers, the role of montelukast in reducing IRRs cannot be determined from these uncontrolled observations
- Additional studies to determine if montelukast mitigates the IRRs associated with the first infusion of daratumumab are indicated

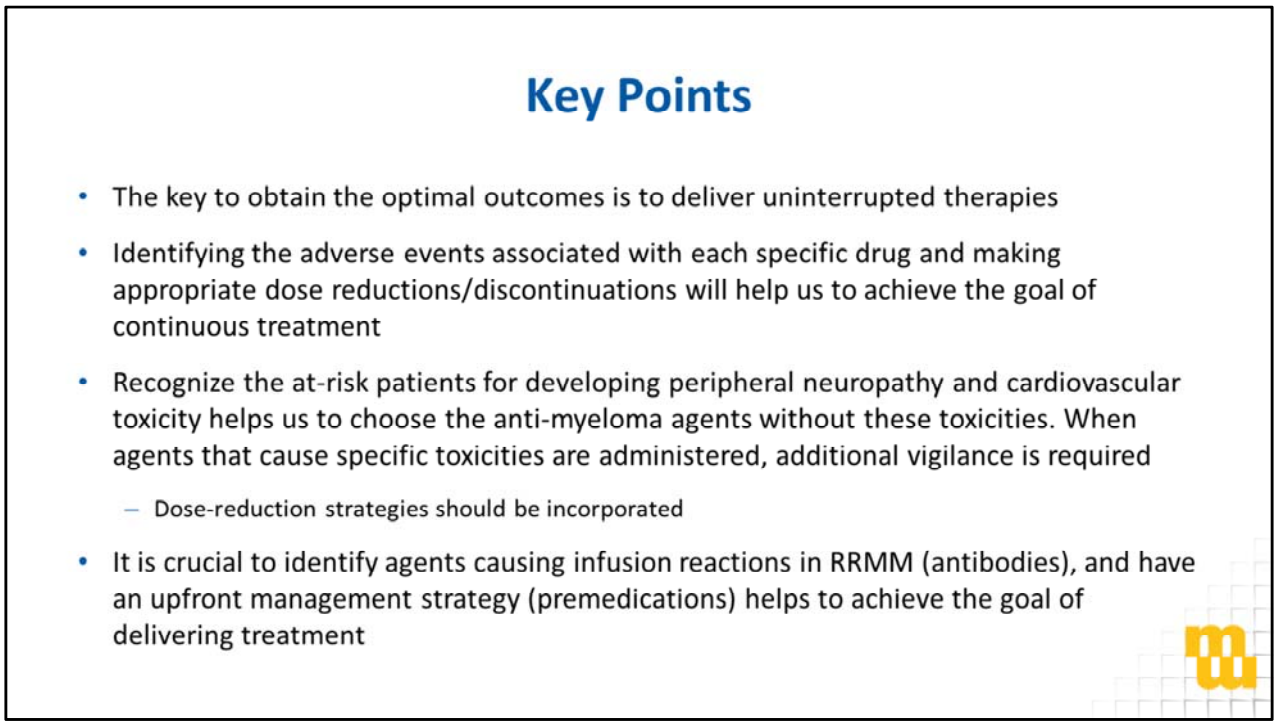
*Montelukast is not approved by the FDA for relief of IRR in patients receiving daratumumab

Chari A, et al. ASH 2016 Annual Meeting. Abstract 2142.

Another beautiful abstract that was presented at ASH of 2016, was using the montelukast* to reduce the infusion-related reactions. This was presented by Dr. Chari from Mount Sinai, basically showing that the first infusion times have significantly decreased by using montelukast as a premedication along with the steroids. This is very good; by giving the premedication, we are reducing the time of the first infusion and reducing infusion-related reactions.

**Montelukast is not approved by the FDA for relief of IRR in patients receiving daratumumab.*

Managing Major Adverse Events in Relapsed/Refractory Multiple Myeloma



The take-home points are, that it is of extreme importance to obtain the optimal outcomes by giving uninterrupted delivery of these therapies. How we can achieve this is by identifying the adverse events associated with each of these specific drugs. Making appropriate dose reductions and discontinuations whenever necessary will help us to achieve the goal of giving this drug continuously. Recognizing the at-risk patients for developing peripheral neuropathy and developing any cardiotoxicity will help us to choose the anti-myeloma agents that are very safe and specific for that patient population. Dose reduction strategies should be employed rigorously. It is of crucial importance to identify the agents that cause infusion-related reactions, most commonly antibodies, and to have an upfront management strategy by giving premedication of steroids and premedicating with montelukast. Also, having an appropriate strategy of what should be done when such a reaction happens will certainly help us to mitigate these toxicities.