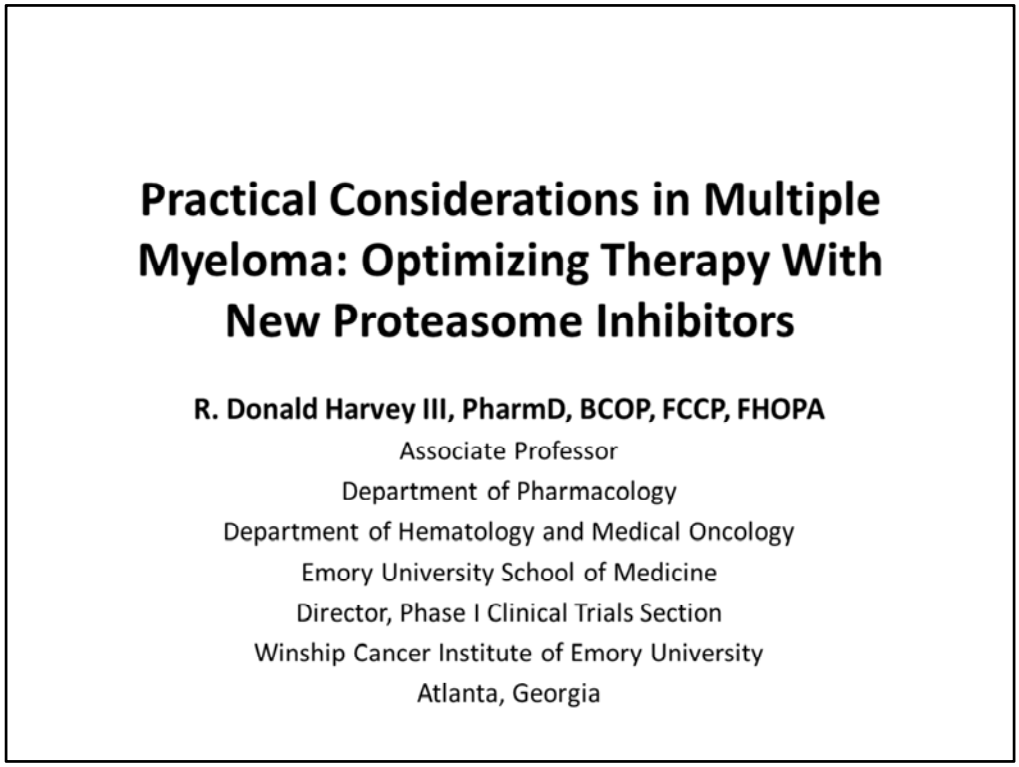
Practical Considerations in Multiple Myeloma:
Optimizing Therapy With New Proteasome Inhibitors



Welcome to *Managing Myeloma*. My name is Dr. Donald Harvey. I am Director of Phase 1 Clinical Trials Section and an Associate Professor in Hematology, Medical Oncology, and Pharmacology at the Winship Cancer Institute at Emory University. Today, I will be discussing "Practical considerations in multiple myeloma: Optimizing therapy with new proteasome inhibitors."

Learning Objectives

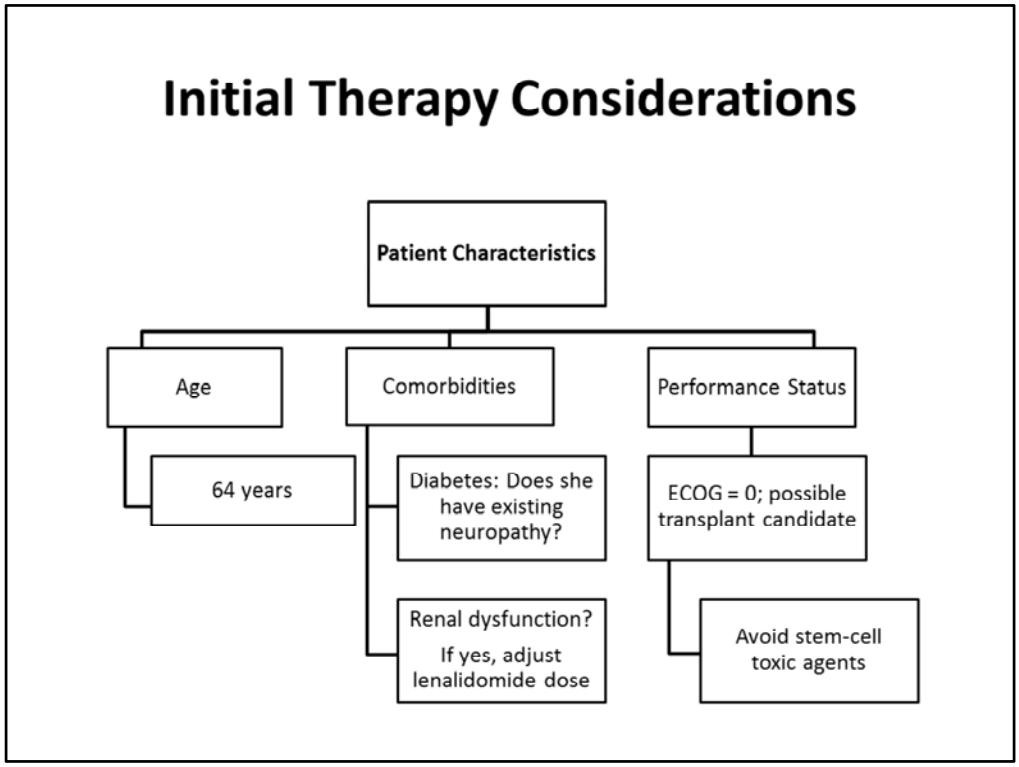
- Identify and differentiate between the new proteasome inhibitors for multiple myeloma
- Summarize patient selection approaches for each new proteasome inhibitor
- Outline practical considerations for utilizing proteasome inhibitors in practice

These are the learning objectives for today's presentation: Identify and differentiate between some of the new proteasome inhibitors for the treatment of myeloma; summarize patient's selection approaches for each agent; and then outline some practical considerations for utilizing these new proteasome inhibitors in practice.

Patient Case: MB

- 64-year-old woman with newly diagnosed IgG multiple myeloma
  - IgG 4.3 g/dL serum monoclonal protein
  - Hemoglobin 10 g/dL, CrCL 60 mL/min, calcium normal
  - Medical history and home medications
    - Type 2 diabetes controlled on metformin
    - Hypertension stable on metoprolol
    - Hypercholesterolemia stable on simvastatin
- Treatment options are being considered

So, this is a patient case. This is a woman seen here at Emory with newly diagnosed IgG myeloma. Her IgG paraprotein was 4.3 g/dL at diagnosis. Her hemoglobin is listed here. Creatinine clearance is reasonable for a woman of her age, and her calcium is normal. Her medical history and home medications include metformin for type 2 diabetes. She does have some hypertension which is stabilized and some hypercholesterolemia. So overall, we are thinking about treatment options for this woman for induction therapy for her myeloma.



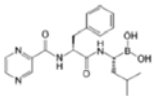
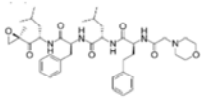
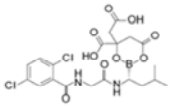
When you think about initial therapy for anyone at this age or anyone with newly diagnosed disease, you have to take into account three major issues. One is age, and that really dictates a little bit more performance status, but consideration of autologous transplant as a therapeutic option for patients is often indicated by age or maybe dictated by other comorbidities as well. In this patient, she is 64 and so would be a reasonable candidate based on age alone for autologous stem cell transplant. Given her comorbidities, specifically diabetes, we have to consider if she has any preexisting neuropathy which may complicate therapy with proteasome inhibitors and other agents. Does she have any renal dysfunction? If yes, then if we are going to consider lenalidomide, we may need to consider the dose of induction lenalidomide for her, and then again finally performance status. In her, she has got quite a good performance status. She seems to be a reasonable candidate for autologous stem cell transplant. Therefore, we need to avoid agents that are toxic to the stem cell compartment, agents like melphalan as well as prolonged lenalidomide therapy.

Treatment Considerations and Adverse Events

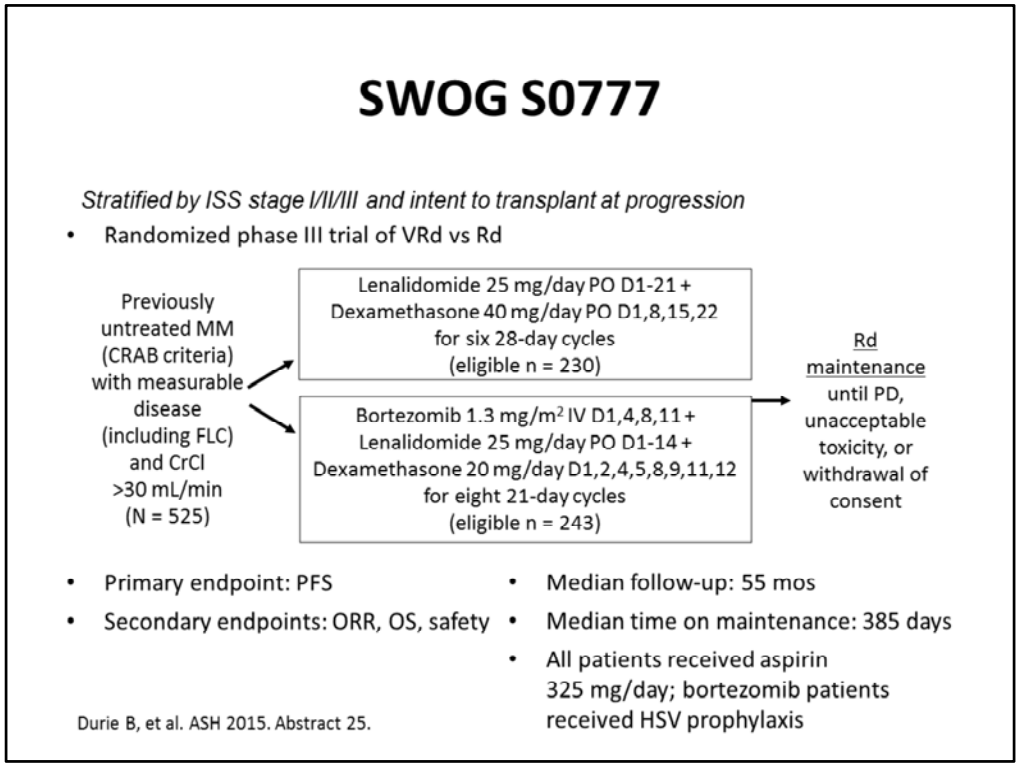
Agent	Adverse Event	Management
Thalidomide, lenalidomide, pomalidomide	VTE	Anticoagulation prophylaxis when combined with corticosteroids
Lenalidomide	Renal dysfunction (needs dose adjustment)	Adjust dose
Bortezomib	Peripheral neuropathy	Administer weekly, SQ preferred over IV
Bortezomib, carfilzomib, ixazomib	Herpes zoster reactivation	Acyclovir or valacyclovir prophylaxis
Carfilzomib	Cardiac complications	Patient selection
Corticosteroids	Hyperglycemia	Weekly corticosteroids preferred; sliding scale insulin and close monitoring in diabetic patients

So looking at some treatment considerations and adverse events with each class of drugs. Thinking first about the IMiDs, one clear adverse event profile for these agents is venous thromboembolic disease, and so prophylaxis with a variety of agents should be considered, and generally aspirin is a reasonable option, but patients who have other risk factors for thromboembolic disease need to be perhaps treated with more aggressive agents like enoxaparin and others. Specifically, with lenalidomide, it is renally cleared so dose adjustment needs to occur in renal dysfunction. The classic adverse event with bortezomib is neuropathy. It is certainly better when given subcutaneously than given intravenously, and then, proteasome inhibitors as a class have a concern of herpes zoster reactivation. So therefore, acyclovir or valacyclovir are needed regardless of the agent. Carfilzomib does have some concerns with cardiac complications and so patient selection is important there, and then finally, corticosteroids while still very important in the management of myeloma do have adverse events profile specifically. In this patient, we need to consider hyperglycemia. And so, understanding that she may need to have more aggressive glucose measurements and perhaps have additional agents added as needed, for example insulin, may be necessary around the time of her corticosteroid dosing.

Differentiating the Proteasome Inhibitors

Drug	Mechanism	PI Class	Administration	Incidence of Severe PN	Chemical Structure
Bortezomib	Reversible inhibition of 26S proteasome	Boronate	IV, SC	Moderate	
Carfilzomib	Irreversible inhibition of 20S proteasome	Epoxyketone	IV	Low	
Ixazomib	Reversible inhibition of 20S proteasome	Boronate	PO	Low	

Thinking about the proteasome inhibitors as a class, the three that we have on the market today, bortezomib, carfilzomib, and ixazomib, have some slightly different profiles in terms of structure and inhibition of proteasome subunits. Bortezomib is a reversible inhibitor. It is a boronic acid derivative that can be given IV or subcutaneously, and again the incidence of peripheral neuropathy and the severity is dependent upon the route of administration, with subcutaneous administration being preferred. Carfilzomib is an irreversible inhibitor. It is an epoxyketone. It is given intravenously and overall has a relatively low adverse event profile as it pertains to neuropathy. Finally, ixazomib the first oral proteasome inhibitor. It is also reversible. It is also a boronic acid derivative and has a relatively low incidence of severe peripheral neuropathy.



Thinking about induction therapy and whether or not to include proteasome inhibitors, there has been a recent trial that was presented at ASH last year that compared lenalidomide with dexamethasone at standard dosing to the combination of bortezomib, lenalidomide, and dexamethasone, and these were patients it is important to note that were relatively ill, meaning that many of them had creatinine clearances that were fairly low, many of them had performance status of 2, and certainly these were all patients that would be candidates though for induction treatment with two or three drugs. And so patients again were randomized to either two-drug induction or three-drug induction, it is important to note that in this trial when it was initiated, IV bortezomib was the standard route of administration and it was given, again, in standard dosage with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone. Patients were continued on treatment, were given about 6 months of treatment with either agent (six 28-day cycles of Rd and eight 21-day cycles of VRd) and then were continued on maintenance, or they withdrew consent. So, the median followup was 55 months with time of maintenance of a little over a year. Everybody received aspirin prophylaxis and those patients who were on bortezomib also received prophylaxis for HSV.

SWOG S0777: Outcomes

Survival, Months	VRd (n = 242)	Rd (n = 229)	HR	*P* Value
Median PFS	43	30	0.712 (0.560 - 0.906)	.0018
Median OS	75	64	0.709 (0.516 - 0.973)	.025

Adverse Event,* %	VRd (n = 241)	Rd (n = 226)	*P* Value
Grade ≥3 AE			
Neurologic	33	11	< .0001
Pain	12	4	.0002
Sensory	23	3	.004
Gastrointestinal	22	8	NR
Secondary primary malignancies	4	4	

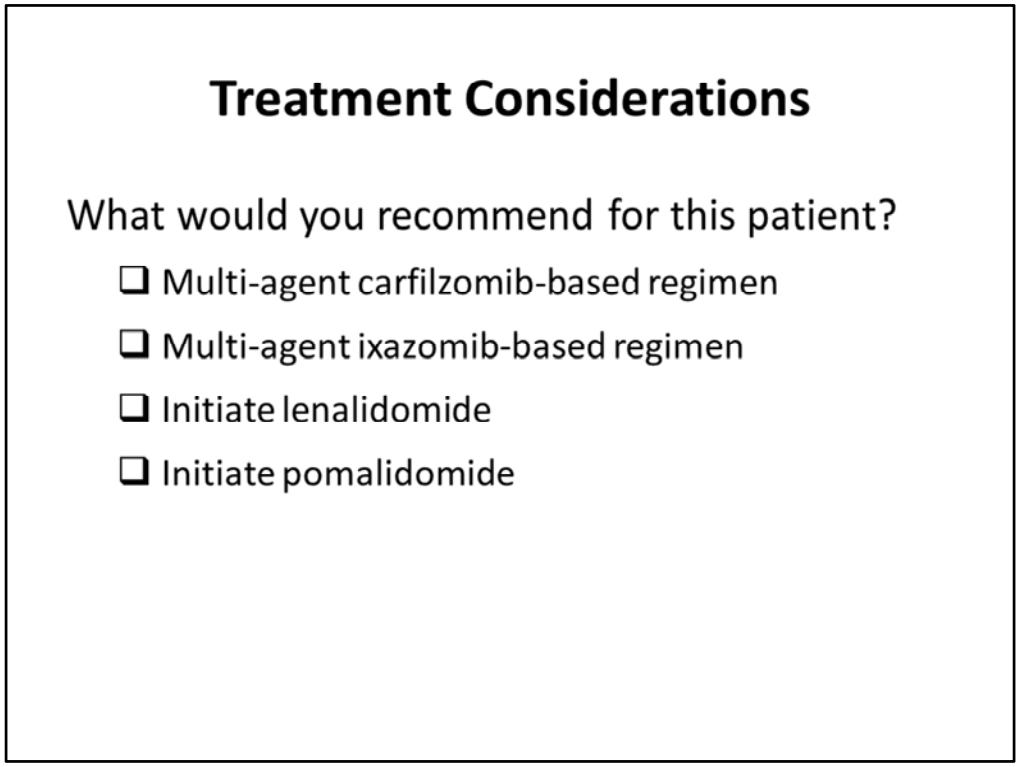
*Hematologic and other toxicities were similar for the 2 arms
Durie B, et al. ASH 2015. Abstract 25.

These are the outcomes and I think this is an important slide in terms of practice changing data, the combination of bortezomib with lenalidomide and dexamethasone improved not only progression-free survival but overall survival as well, and again these were hazard ratios that were statistically different between the two arms. Adverse events are listed here as well and things you might expect again with the IV administration of bortezomib. There were about a third of patients who had grade 3 or higher adverse events as it related to neurologic complications. Similarly, pain and sensory adverse events were higher, as were gastrointestinal adverse events. Again, it is expected that the subcutaneous route would drop these rates and severity of adverse events that were seen with the IV administration of bortezomib. And again those were statistically different in terms of adverse events between the two arms, but again, the primary takeaway here is that the combination of three drugs for induction including a proteasome inhibitor is important and is certainly superior to two drugs of lenalidomide and dexamethasone alone.

Patient Case: JP

- 72-year-old male with relapsed MM
- Diagnosed in 2014
  - IgG kappa; FISH demonstrated t(4;14)
  - Has been on cyclophosphamide, bortezomib, and dexamethasone (completed 8 cycles)
  - Persistent grade 2 peripheral neuropathy with pain (pregabalin)
- Medical history and home medications
  - CHF (EF: 30%): furosemide, potassium chloride
  - CAD with NSTEMI in 2009 requiring 4-vessel CABG
    - Metoprolol, aspirin, rosuvastatin
- He has demonstrated an M-spike increase consistent with progressive disease

So, let's takes a second case. JP is a 72-year-old gentleman with relapsed disease. He was diagnosed in 2014 with an IgG kappa with 4;14 translocation noted on FISH. He was induced with cyclophosphamide, bortezomib, and dexamethasone, and he completed 8 cycles. He had persistent grade 2 peripheral neuropathy after completion of that, and that was noted to be with pain, and he has been on pregabalin to manage that pain over a period of time. His medical history is listed here. He has congestive heart failure with an EF of around 30% which is managed right now by diuretics and potassium. He has coronary artery disease with NSTEMI in 2009 and received the four-vessel CABG for which he is medically managed after that as well. He also has now demonstrated unfortunately an M-spike with progressive disease consistent with the need for additional therapy.



So in this patient, there are a variety of considerations to take into account. You might consider the options that are out there now in terms of agents that are approved in the space, a multi-agent carfilzomib-based regimen is something that would be considered. A multi-agent ixazomib could be considered. You might consider lenalidomide since he has not had that to date, or pomalidomide is also an opportunity in this space as well.

Ixazomib

- **Mechanism**: Reversible and selective inhibition of β5 subunit on the 20S proteasome resulting in accumulation of polyubiquinated substrates, cell cycle disruption, and apoptosis

Recommended Starting Dose

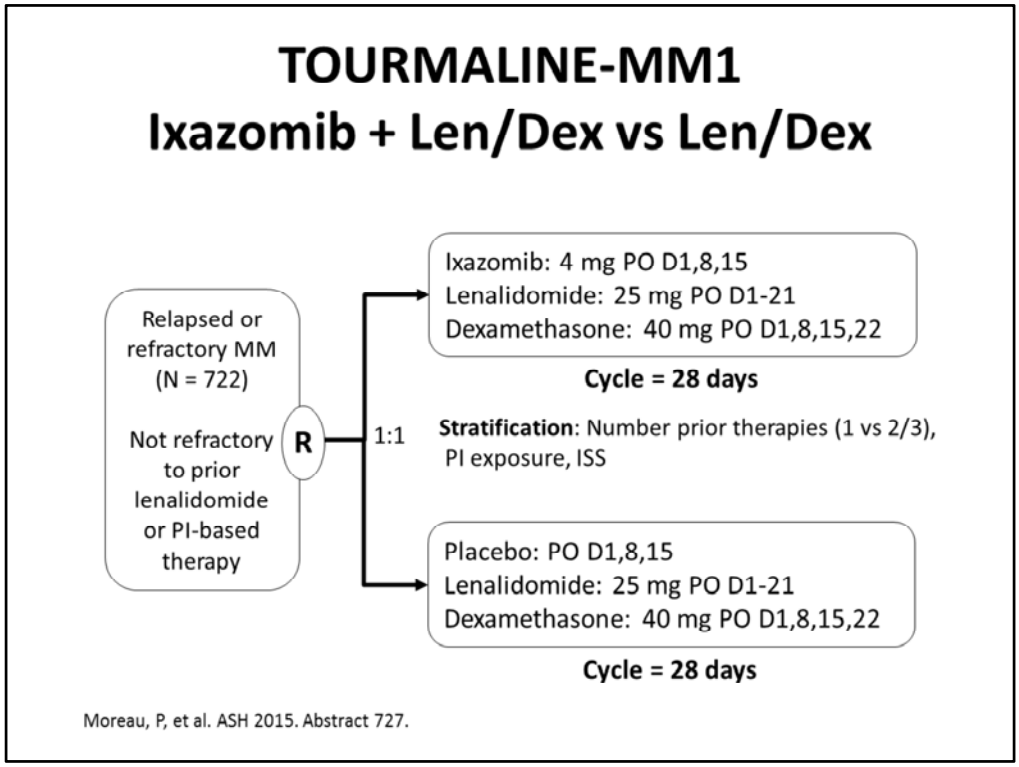
Ixazomib 4 mg PO D1,8,15
Lenalidomide 25 mg PO D1-21
Dexamethasone 40 mg PO D1,8,15,22
Cycle = 28 days

Phase 1/2 Response by Treatment Cycle in Untreated MM

Phase 2	PR, %	VGPR, %	CR, %
Cycle 3	48	33	4
Cycle 6	42	25	23
Cycle 9	32	33	25
Cycle 12	28	35	27

Kumar SK, et al. *Lancet Oncol.* 2014;15:1503-1512.; NINLARO® Prescribing Information.

So, let's talk first about ixazomib. Again, this is the first oral proteosome inhibitor we have available to us for the treatment of myeloma in the relapsed setting, reversible, and selective inhibitor of the beta 5 subunit of the 20 S proteasome. And so what it does, much like the other proteasome inhibitor, is that it really impairs the cell's ability to get rid of proteins and so it is a little bit like not allowing the cell to get rid of the trash, and so it targets the cell, therefore, for apoptotic death. The recommended starting dose has got a quite a long half-life. It is a prodrug. Ixazomib is converted immediately upon absorption to an active component. It is given weekly on days 1, 8, and 15, and the starting dose is part of the trial that we will talk about was with lenalidomide 25 mg orally for 3 weeks and with weekly dexamethasone as well on 28-day cycles. There was early encouraging data in response for combination ixazomib, lenalidomide, and dexamethasone, and you can see here over time patients have responded relatively early. The CR rates do go up over time and this is based on the data presented by Dr. Kumar and colleagues and published in *Lancet Oncology* in 2014.



This is the trial that lead to the approval of ixazomib in combination with lenalidomide and dexamethasone. Over 700 patients were randomized. These were patients that were not refractory to prior lenalidomide or proteasome inhibitor-based therapy and they were randomized to this three-drug treatment with ixazomib and standard len/dex or len/dex with a placebo. They were stratified by the number of prior regimens and prior proteasome inhibitor exposure and staging. Again, these were 28-day cycles.

TOURMALINE-MM1: Efficacy

	Ixazomib + Len/Dex (n = 360)	Placebo + Len/Dex (n = 362)	HR/OR; *P*
Median PFS, mo	20.6	14.7	HR 0.742; 012
Confirmed ORR, %	78.3	71.5	OR 1.44; .035
CR, %	11.7	6.6	OR 1.87; .019
≥ VGPR, %	48.1	38.9	OR 1.45; .014
Median OS,* mo	NR	NR	
Median TTFR, mo	1.1	1.9	
Median DOR (≥ PR)	20.5	15.0	

FDA approved November 20, 2015 in combination with lenalidomide and dexamethasone for patients who have received ≥1 prior therapy

*Pre-specified interim OS analysis occurred at a median follow up of ~23 mos.

Moreau, P, et al. ASH 2015. Abstract 727.

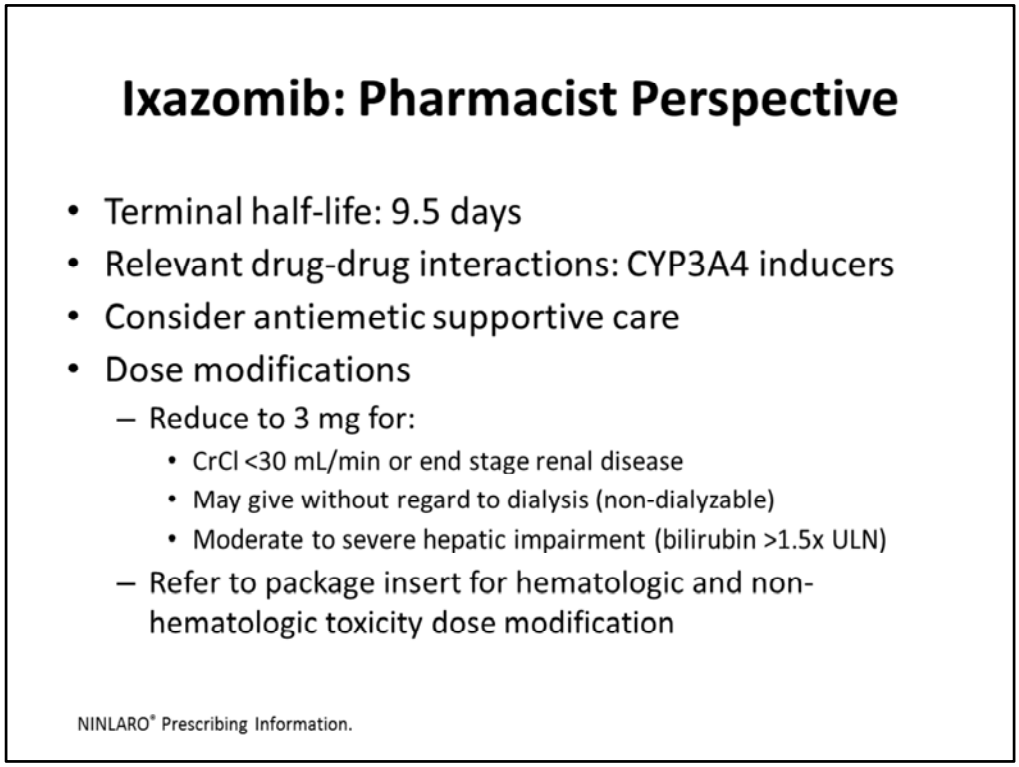
So looking at the efficacy for each arm here, you can see that progression-free survival was statistically improved in patients with the combination of ixazomib, lenalidomide, and dexamethasone, and up and down the line, there were improvements in terms of depth of response as well as overall response. Overall survival had not been reached at the point of presentation of this trial, but overall, each category favored the combination of three drugs as opposed to two drugs with lenalidomide and dexamethasone alone.

TOURMALINE-MM1: Toxicity

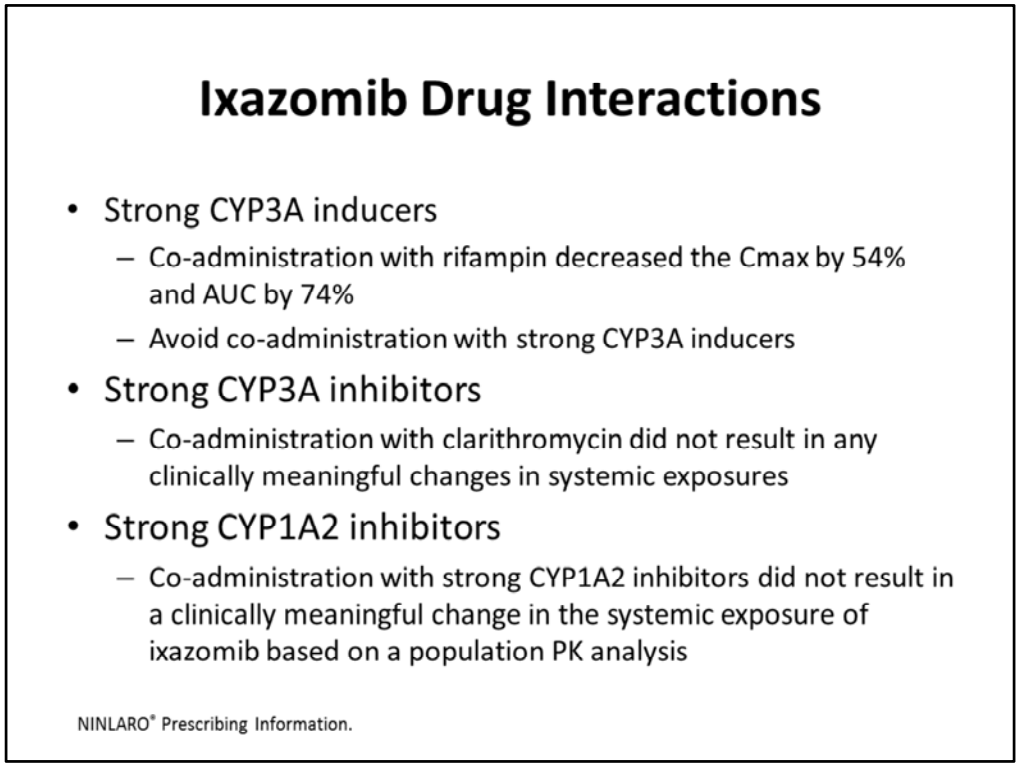
	Ixazomib + Len/Dex (n = 361)		Placebo + Len/Dex (n = 356)	
Toxicity	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Diarrhea	45%	6%	39%	3%
Nausea	29%	2%	22%	0%
Vomiting	23%	1%	12%	<1%
Rash	36%	5%	23%	2%
Peripheral Neuropathy	27%	2%	22%	2%
Neutropenia	33%	23%	31%	24%
Anemia	--	9%	--	13%
Thrombocytopenia	31%	19%	16%	9%
Pneumonia	--	6%	--	8%

Moreau, P, et al. ASH 2015. Abstract 727.

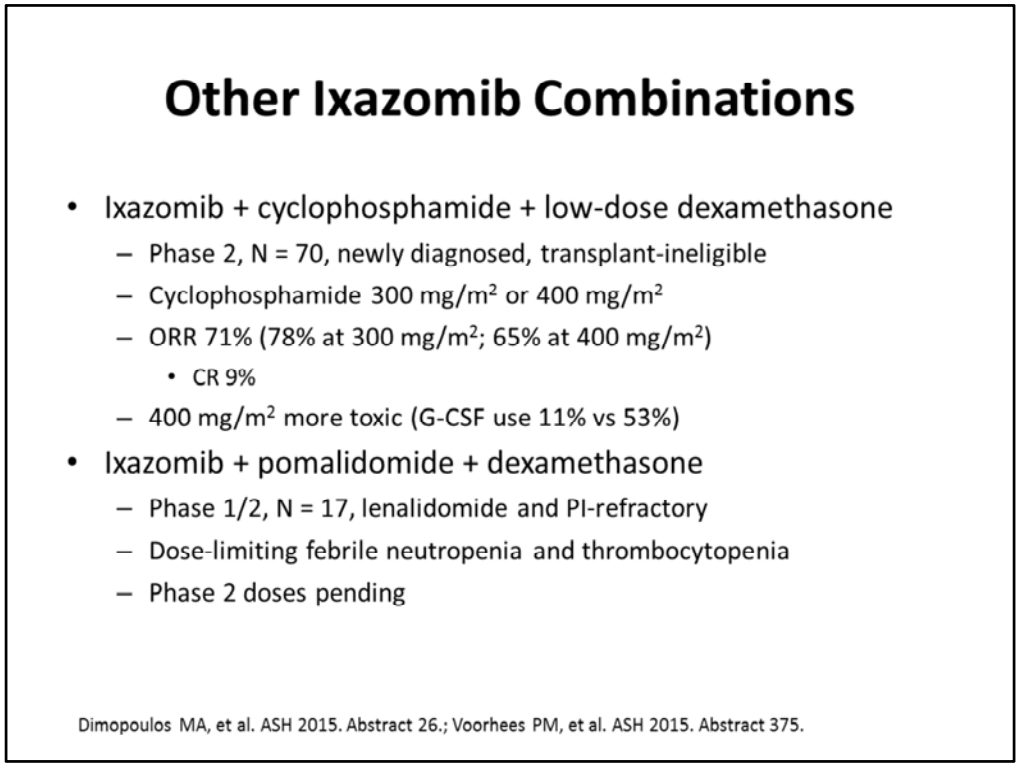
There were some differences in adverse events, and so, ixazomib is different from bortezomib and carfilzomib in terms of adverse event ratings. When three drugs were given together, there were slightly higher rates of nausea and vomiting associated with the oral proteasome inhibitor route. Similarly, the rates of rash were a little bit higher with the three drugs. We will talk about adverse events a little bit with the three drugs and how to manage them. However, an important note was that peripheral neuropathy was actually not that different, suggesting the ixazomib has a superior peripheral neuropathy adverse event profile, but it does have rashes as side effect associated with it independently of lenalidomide, and similarly there are some GI adverse events.



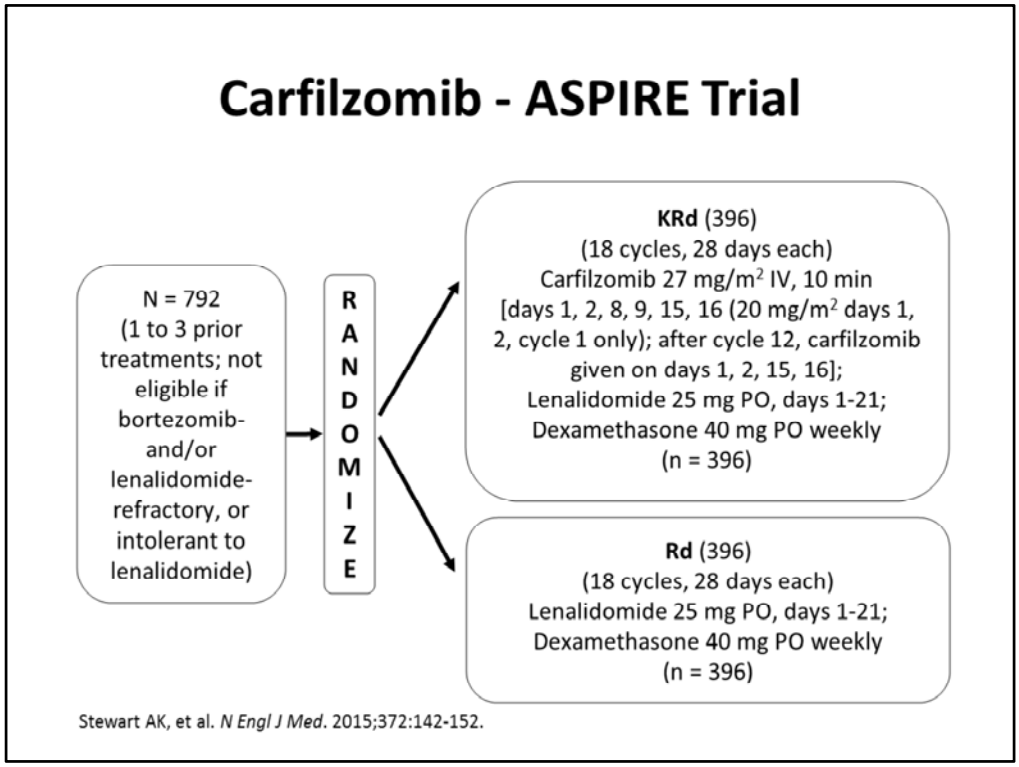
So from a pharmacist's perspective with ixazomib, there are a few things to take into consideration. It does have quite a long half life, just under 10 days so therefore that supports weekly dosing. There are some drugs interactions to be mindful of, although they are not often clinically significant, and that is in patients that are receiving agents like rifampin and antiepileptic agents that may induce cytochrome P450 3A4. You might want to consider anti-emetic supportive care in addition to the dexamethasone that is given with ixazomib. Patients may need an as-needed or even a scheduled dose of something like a 5-HT3 antagonist. Oral ondansetron, for example, may be necessary in many patients to try to prevent some of the nausea and vomiting that was seen in the three-drug combination. Patients do need dose modifications. We have evaluated the use of ixazomib in renal insufficiency. In patients with creatinine clearances below 30, the dose of ixazomib should be reduced from 4 mg to 3 mg. Similarly, in patients with severe hepatic impairment, the dose should also be reduced. It is a relatively rare event but certainly patients with myeloma may have renal insufficiency as part of their disease. Otherwise, there are some modifications that need to be performed with the combination of ixazomib, lenalidomide, and dexamethasone for hematologic and non-hematologic adverse events.



So again, there are some inducers and inhibitors in terms of drug interactions that need to be considered. Overall, it is a CYP1A2 substrate, but there is not a clinically meaningful change in exposure of ixazomib in patients on strong CYP1A2 inhibitors, and so overall, the only class of agents that need to be considered are those that induce CYP3A ,and so patients optimally need to avoid ixazomib in combination of drugs like rifampin.



There are other ixazomib combinations that are being considered for movement into the next phase of treatment combining with cyclophosphamide and low-dose dexamethasone. There was a phase 2 study really looking at the question of the right cyclophosphamide dose in combination with ixazomib and overall the dose of 300 mg/m^2 was superior not only for response rate but also for adverse events. Similarly, combining ixazomib with pomalidomide and dexamethasone has been done in an early phase trial. These were patients that were refractory to lenalidomide and refractory to prior proteasome inhibitors, and the phase 2 doses are pending coming out of the ASH meeting. So, there is still a little bit more work to be done with ixazomib combinations, but we look forward to additional opportunities.



Moving now to carfilzomib, so the second IV proteasome inhibitor, the ASPIRE trial presented by Keith Stewart and colleagues and published in *The New England Journal of Medicine* last year also looked at over 700 almost 800 patients who were randomized and had either between one and three prior regimens. They were not eligible if they were bortezomib or lenalidomide refractory or intolerant to lenalidomide. So, these were patients who really would be expected to be sensitive to lenalidomide therapy. The patients were randomized again to either two-drug therapy with lenalidomide and dexamethasone on a standard ,again 28-day regimens, or doses of carfilzomib 27 mg/m^2 IV given over 10 minutes with a standard schedule and then that was split out after 12 cycles to every other week carfilzomib given 2 days per week.

ASPIRE Trial - Efficacy

	KRd	Rd
PFS, mo (overall)	**26.3**	**17.6***
High-risk	23.1	13.9
Standard risk	29.6	19.5
Median OS mo, %	**NR**	**NR**
ORR, %	**87.1**	**66.7***
≥CR (sCR), %	31.8 (14.1)	9.3 (4.3)*
≥VGPR, %	69.9	40.4*
Mean TTR, mo	**1.6**	**2.3**
Median DOR, mo	**28.6**	**21.2**

*$P < .001$
Stewart AK, et al. *N Engl J Med*. 2015;372:142-152.

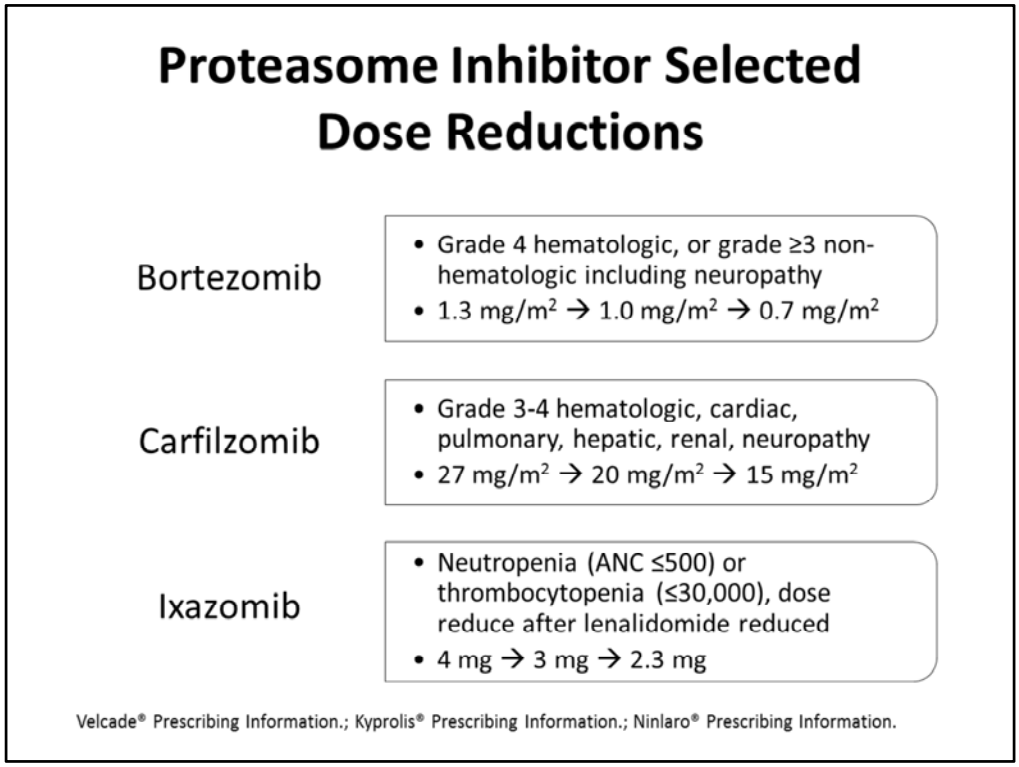
The efficacy listed here again statistically improved activity with the three-drug combination combining carfilzomib with lenalidomide and dexamethasone for progression-free survival, that was statistically different. The overall response rate was also statistically different, and the duration of response was also improved with three drugs compared to two. So, carfilzomib put itself into the space as well with three drugs showing superiority to two drugs, and so really this begs the question, “Is there anyone who outside of adverse event concerns who should be getting two-drug therapy with lenalidomide and dexamethasone alone either in the induction or the relapsed/refractory setting” And if patients can tolerate three drugs, then certainly from a disease perspective they should get three drugs combining with proteasome inhibition.

ASPIRE Trial – Adverse Events

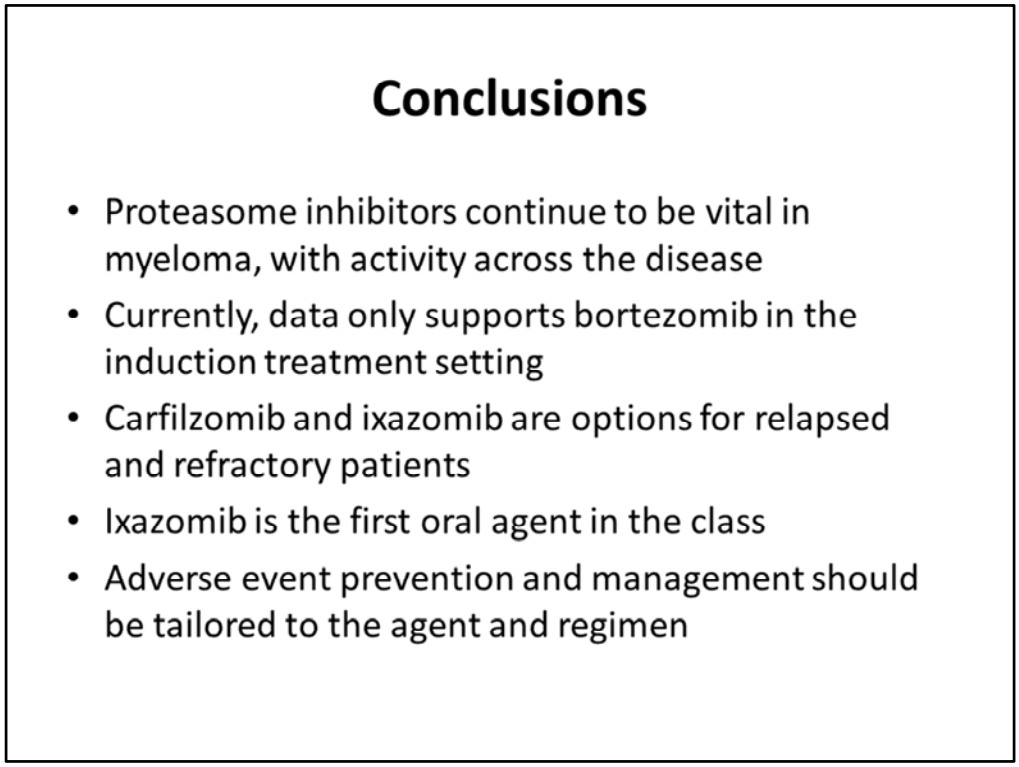
	KRd	Rd
Diarrhea, %	3.8	4.1
Fatigue, %	7.7	6.4
Pyrexia, %	1.8	0.5
URI, %	1.8	1.0
Hypokalemia, %	9.4	4.9
Muscle spasms, %	1.0	0.8
Dyspnea, %	2.8	1.8
Hypertension, %	4.3	1.8
Acute renal failure, %	3.3	3.1
Cardiac failure, %	3.8	1.8
Ischemic heart disease, %	3.3	2.1

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

Adverse events are listed here. There were some adverse events that were more common with the three-drug regimen including hypokalemia, but otherwise there weren't many that were statistically concerning. Hypertension and cardiac failure things that we know with carfilzomib are items to be considered, particularly with patient selection, but also in those who have the disease after going to use carfilzomib, monitoring cardiovascular complications is important. So, thinking about hydration of patients, if patients have heart failure, you are going to choose carfilzomib and then thinking about the extent of hydration, and similarly, patient selection with low ejection fraction heart failure patients, you might want to consider alternative therapies.



So, the proteasome inhibitors as a class do have some standard dose reductions. With bortezomib, again, there is a question of IV versus subcutaneous administration. If you have to dose reduce patients receiving bortezomib, receiving it either through IV or subcutaneous routes, the dose reductions are from 1.3 to 1.0 to 0.7 mg/m^2. Similarly, you may be able to go to just weekly dosing rather than days 1 and 4 in patients who need to have a dose reduction of bortezomib overall. Carfilzomib, there are a variety of doses that have been studied with carfilzomib, and per the product information, the dosing down goes from 27 to 20 to 15 mg/m^2 when needed. With ixazomib, it is a little bit of an unusual dose reduction but 4 mg to 3 mg weekly, and then the next dose step is 2.3 mg. So, that was all noted in early phase trials of dose. So, these are some of the things that you would reduce proteasome inhibitors for, thinking about specifically ixazomib. With rash, in general, one would consider lenalidomide dose reductions first, but there are cytopenia, specifically neutropenia and thrombocytopenia, adverse events that need to be considered, but because of the shorter half-life of lenalidomide, it is often easier to titrate it compared to ixazomib. Thus, the recommendation that lenalidomide be the first agent to be dose reduced.



So, in conclusion with proteasome inhibitors, they continue to be an incredibly important group of compounds in the treatment of myeloma and they do have activity across the disease spectrum. All three of them are very different in terms of activity as well as adverse event profiles. Carfilzomib and ixazomib are options for relapsed/refractory patients, and so far really only bortezomib is supported in the induction treatment setting. There was actually some data released recently that suggested that carfilzomib was not as good as bortezomib in the induction setting. Ixazomib is the first oral proteasome inhibitor in the class. There are likely to be additional agents to come forward with the oral route as an option in myeloma patients. And then finally, adverse events and prevention and management need to be tailored to the agent and to the regimen. For example, again the combination of the ixazomib and lenalidomide, both agents may cause rash, and so one needs to be cognizant of that. Similarly, adverse events of cytopenias, neutropenia, and thrombocytopenia need to be considered in patients receiving two and three drugs.

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