

## **Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents**

# **Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents**

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Welcome to *Managing Myeloma*. My name is Adam Cohen, and I am the Director of Myeloma Immunotherapy and an Assistant Professor in the Hematology/Oncology Division at Abramson Cancer Center of the University of Pennsylvania in Philadelphia. Today, I will be discussing, “Relapsed/refractory multiple myeloma: Standard of care among emerging agents.”

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Definitions

- Relapsed
  - Meeting PD criteria
- Relapsed and refractory
  - PD on or within 60 days of salvage therapy, with at least MR to one prior therapy
- Primary refractory
  - No MR to prior therapy

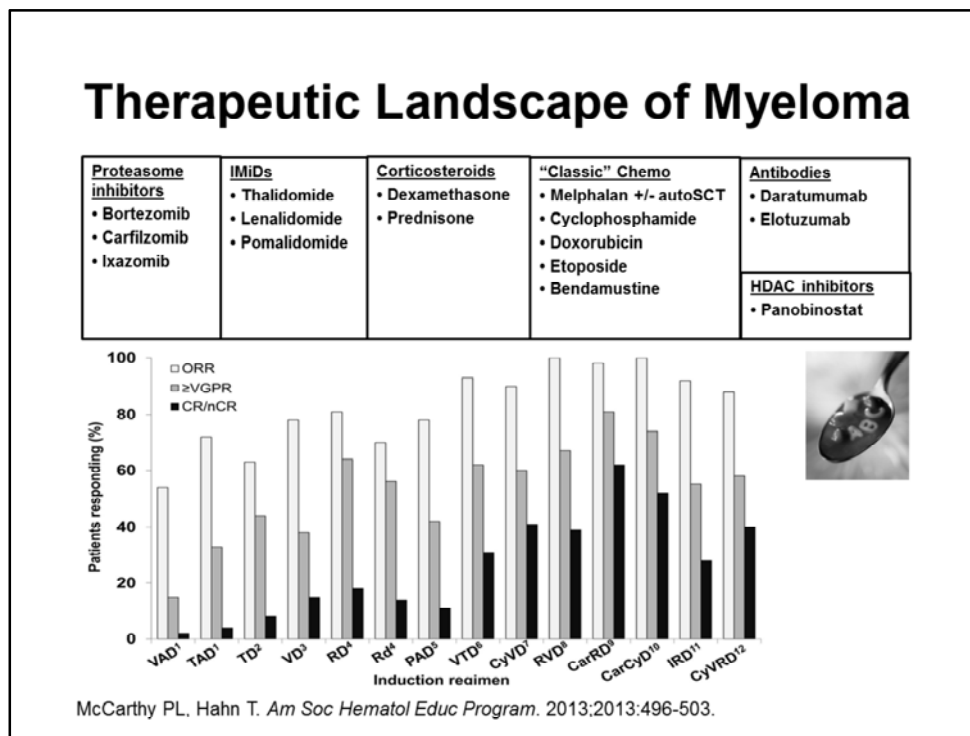
**IMWG Criteria for PD**

- $\geq 25\%$  increase in serum or urine paraprotein from nadir (absolute increase  $\geq 0.5$  g/dL and  $\geq 200$  mg/24 hrs, respectively), or
- $\geq 25\%$  increase in involved-to-uninvolved serum FLC difference (absolute increase  $\geq 100$  mg/L), or
- $\geq 10\%$  increase in bone marrow plasma cells, or
- New bone or soft tissue lesions, or
- Increasing size of existing bone or soft-tissue lesions, or
- Serum calcium  $> 11.5$  mg/dL

PD=progressive disease; MR=minimal response; FLC=free-light chain  
Laubach J, et al. *Leukemia*. 2016;30(5):1005-1017.

So, before we get into some of the new regimens for multiple myeloma, it is important to go over some basic definitions. The IMWG has set distinct criteria for defining progressive disease and this can be based either on biochemical progression with changes in the paraprotein, either in serum or urine or occasionally the involved free-light chains, or progression based on clinical parameters such as increasing size of bone or soft tissue lesions, new renal failure, hypercalcemia, or worsening anemia. For patients who just meet the progressive disease criteria, this is called relapsed disease. For those who are progressing on or within 60 days of their most recent salvage therapy, this would be called relapsed and refractory myeloma, and this is in distinction from primary refractory myeloma which describes patients who have never achieved any significant response to prior therapy and represents a very poor prognostic group.

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Now in terms of looking at the therapeutic landscape of myeloma, we have come a long way from our original available drugs, namely corticosteroids and classic cytotoxic chemotherapeutics as listed here. The first new classes of drugs that really dramatically changed the way we treat myeloma were the proteasome inhibitors, and bortezomib was the first in class, and now, we have carfilzomib and ixazomib, as well as the immunomodulatory drugs, initially thalidomide and now lenalidomide and pomalidomide, and most recently, we have had two new classes of drugs being approved, namely the monoclonal antibodies with daratumumab and elotuzumab, and histone deacetylase inhibitors panobinostat. And by combining these drugs in two- and three- and now even four-drug combinations in initial therapy, we have been able to achieve response rates now routinely above 90% and increasing depth of response as well, but it has become very confusing also as we have a number of different regimens. It can be difficult to help decide which regimen is appropriate for which patient.

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### General Considerations for RRMM

#### Disease-specific

- Biology
  - Cytogenetics
  - ISS stage
  - LDH
- Behavior
  - Clinical manifestations
  - Pace/disease burden
  - Prior response depth and duration
  - Extramedullary disease
  - Cytopenias

#### Patient-specific

- Comorbidities/frailty
- Prior therapies
  - Stem cells available?
- Prior toxicities
- Preferences/goals of care

Now when it comes to relapsed/refractory disease, it is important to take into consideration a few general issues with each patient, and these can be both disease specific as well as patient specific. So first looking at disease-specific considerations, you want to be aware of the underlying biology of the disease for each patient. What were their cytogenetics, LDH which can be a representation sometimes of the aggressiveness of the disease and especially how has the disease manifested itself previously? Did the patient have renal failure when they first presented with myeloma? They would be at higher risk for that at the time of relapse. What is the pace of relapse, the degree of symptom burden, what kind of response did the patient have previously, and the duration of that response, and is the patient now developing extramedullary disease or even circulating disease? And finally is the patient having exhausted marrow with cytopenia as this may affect the choice of therapy going forward. In addition, there are patient-specific factors that should be taken into consideration. Most importantly the comorbidities and/or frailty of the patient, what prior therapies has the patient had and how do they tolerate those therapies in terms of toxicity, and of course what are the preferences and goals of care for the patient given that this is likely an incurable situation.

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### General Considerations

- Slow biochemical relapse without symptoms may be observed initially
- Need to individualize therapy
  - No universal algorithm
  - Can reuse prior regimen if deep and/or durable response
- Treat until progression
  - Can attenuate dose/schedule as maintenance
- Rapidly changing landscape

In addition, it is important to remember that patients who have only slow biochemical relapse without any evidence of worsening symptoms can sometimes be observed initially to get a sense of the pace of the disease and so you do not have to jump into therapy right away in certain situations. The other thing to keep in mind is that there really is a need to individualize therapy for each patient. We are going to go through a lot of data from the various clinical trials, but there is really no universal algorithm that states you must use this regimen in line 2 and this regimen in line 3. I think it really has to depend on the patient in front of you, and you can reuse a prior regimen if there was a deep or durable response obtained. Other things to keep in mind, generally once the disease is relapsed it is going to continue to relapse and so it is important to consider treating until progression. You can attenuate the dose and schedule as sort of maintenance after an initial response is achieved, but in general, continuous therapy is probably most beneficial in this setting. And finally keep in mind this is a very rapidly changing landscape. It seems every few months there is another large randomized phase 3 trial that adds additional regimens to our armamentarium, and so it is important to keep abreast of these changes.

# Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

Regimens for RRMM	
MYELOMA THERAPY <sup>1,4,9</sup>	
Therapy for Previously Treated Multiple Myeloma	
Preferred Regimens	
<ul style="list-style-type: none"> <li>• Repeat primary induction therapy (if relapse at &gt;6 mo)</li> <li>• Bortezomib (category 1)</li> <li>• Bortezomib/dexamethasone</li> <li>• Bortezomib/cyclophosphamide/dexamethasone</li> <li>• Bortezomib/lenalidomide/dexamethasone</li> <li>• Bortezomib/liposomal doxorubicin (category 1)</li> <li>• Bortezomib/thalidomide/dexamethasone</li> <li>• Carfilzomib</li> <li>• Carfilzomib/dexamethasone</li> <li>• Carfilzomib/lenalidomide/dexamethasone (category 1)</li> <li>• Cyclophosphamide/lenalidomide/dexamethasone</li> <li>• Daratumumab<sup>10</sup></li> <li>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)</li> <li>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)</li> <li>• Elotuzumab<sup>11</sup>/lenalidomide/dexamethasone (category 1)</li> <li>• Ixazomib<sup>12</sup></li> <li>• Ixazomib<sup>12</sup>/dexamethasone</li> <li>• Ixazomib<sup>12</sup>/lenalidomide/dexamethasone (category 1)</li> <li>• High-dose cyclophosphamide</li> <li>• Lenalidomide/dexamethasone<sup>13</sup> (category 1)</li> <li>• Panobinostat/bortezomib/dexamethasone<sup>14</sup> (category 1)</li> <li>• Pomalidomide<sup>15</sup>/dexamethasone<sup>13</sup> (category 1)</li> <li>• Thalidomide/dexamethasone<sup>13</sup></li> </ul>
Other Regimens	
<ul style="list-style-type: none"> <li>• Bendamustine</li> <li>• Bortezomib/vorinostat</li> </ul>	<ul style="list-style-type: none"> <li>• Lenalidomide/bendamustine/dexamethasone</li> <li>• Panobinostat<sup>14</sup>/carfilzomib</li> </ul>
<p><sup>1</sup>Selected, but not inclusive of all regimens.</p> <p><sup>2</sup>Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.</p> <p><sup>3</sup>Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.</p> <p><sup>4</sup>Myeloid-specific anti-coagulation recommended for patients receiving immunomodulator-based therapy.</p> <p><sup>5</sup>Consideration for appropriate regimen is based on the context of clinical relapse.</p> <p><sup>6</sup>Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.</p> <p><sup>7</sup>Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.</p> <p><sup>8</sup>Indicated for the treatment of patients who have received at least one prior therapy.</p> <p><sup>9</sup>Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.</p> <p><sup>10</sup>Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.</p> <p><sup>11</sup>Indicated for the treatment of patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.</p> <p><sup>12</sup>Indicated for the treatment of patients who have received at least one prior therapy.</p> <p><sup>13</sup>Indicated for the treatment of patients who have received at least one prior therapy.</p> <p><sup>14</sup>Indicated for the treatment of patients who have received at least one prior therapy.</p> <p><sup>15</sup>Indicated for the treatment of patients who have received at least one prior therapy.</p> <p>All recommendations are category 2A unless otherwise indicated.</p> <p>Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.</p> <p>Version 2.2016. NCCN © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. The NCCN Evidence-Based™ NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN.</p>	
NCCN Multiple Myeloma Guidelines 2016.	

Now, this is from the current NCCN Guidelines listing a number of the available regimens for relapsed/refractory multiple myeloma. This is just to give an overview of a number of regimens that are out there, and we will not have time to go through all of them, but I will be focusing on some of the ones that are either most commonly used or have recent phase 3 data to support their use, but this is a good resource to refer to.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

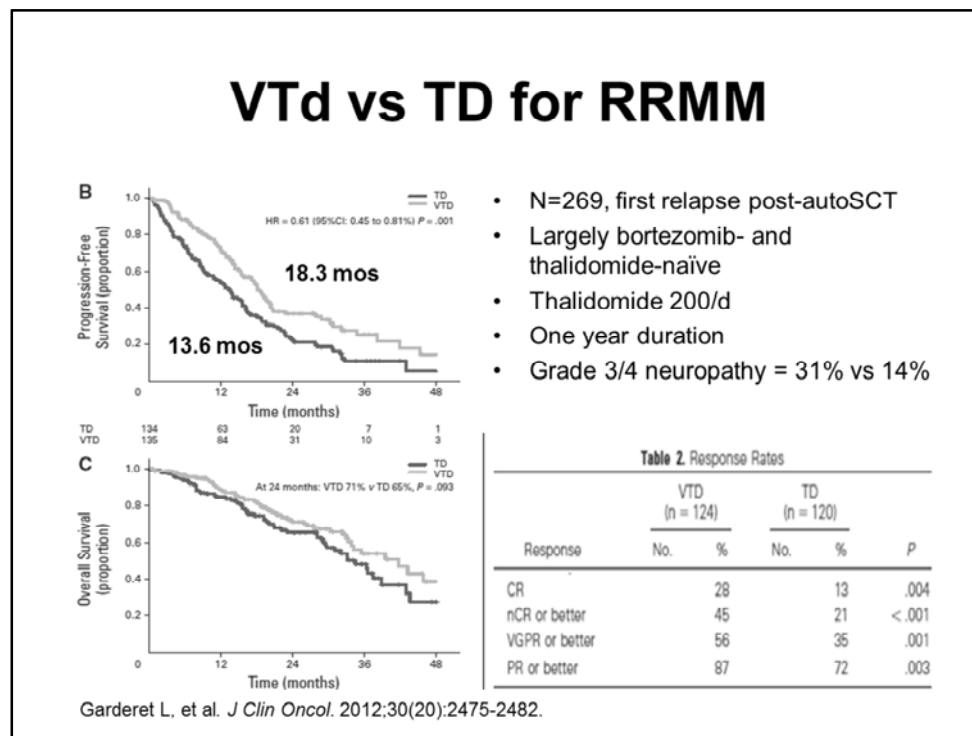
### “Early/Sensitive” Relapsed MM

- 1-3 priors, bortezomib- and/or lenalidomide-sensitive

Selected/commonly-used regimens for early/sensitive relapsed MM	
<u>Phase II/Older Phase III Trials</u>	
VTd	Bortezomib, thalidomide, dexamethasone
VRd	Bortezomib, lenalidomide, dexamethasone
CyBord/CyBorP	Cyclophosphamide, bortezomib, dexamethasone, and prednisone
Vdox	Bortezomib, liposomal doxorubicin
<u>Recent Phase III Trials</u>	
Erd	Elotuzumab, lenalidomide, dexamethasone
KRd	Carfilzomib, lenalidomide, dexamethasone
Ird	Ixazomib, lenalidomide, dexamethasone
Kd	High-dose carfilzomib, dexamethasone
DVd	Daratumumab, bortezomib, dexamethasone

So when going through treatment choices for relapsed/refractory myeloma, I have divided patients up into those who have relatively sensitive disease. These are patients who had only 1 to 3 prior lines of therapy and generally are not refractory to bortezomib and lenalidomide. In this space, we have a number of potential options here and I have listed a few for you, some of which are based on phase 2 or older phase 3 trials listed above, and then, we will go through some of the more recent phase 3 data, including some of the very recently approved drugs just in the past year.

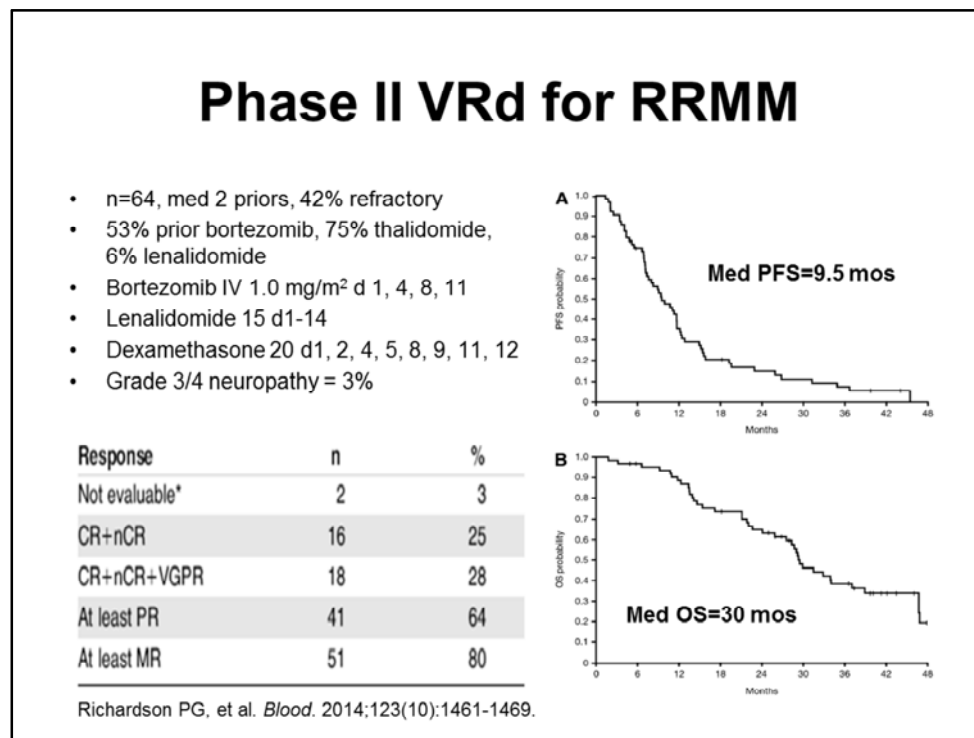
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And so, the first study actually to demonstrate the value of a triplet including a proteasome inhibitor and an IMiD over a doublet in relapsed/refractory disease was this European study published in the JCO about 4 years ago. This was a very defined patient population. They all were in their first relapse after an autologous stem cell transplant, and they were largely naïve to bortezomib and thalidomide having received classic chemotherapy like inductions. This was a high-dose of thalidomide used at 200 per day and it was a fixed duration of therapy. Not surprisingly, there was a large amount of significant neuropathy with the combination of bortezomib and thalidomide. Nonetheless, this trial demonstrated that a triplet can induce a deeper and greater response rate, as seen on the bottom right, and actually met its primary endpoint of increased progression-free survival as well with a hazard ratio of 0.61. There was a trend toward improved overall survival that was not statistically significant.



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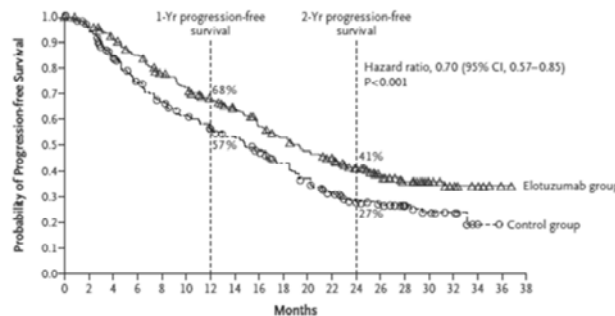


Now in the United States, we often use lenalidomide rather than thalidomide due to its decreased neuropathic effects as well as perhaps more potency, and the data supporting the use of bortezomib-lenalidomide-dexamethasone, the VRD regimen in relapsed/refractory myeloma, largely comes from this phase 2 study led by Dr. Paul Richardson and colleagues at Dana-Farber. Now, this was a more heavily pretreated group than the prior study I just showed, median two prior therapies including the majority of patients having been exposed to bortezomib and thalidomide. It also used what we would likely consider suboptimal dosing of bortezomib and lenalidomide based on their initial phase 1 experience. Nonetheless, they found a 64% response rate in relapsed/refractory multiple myeloma with this combination, with a median PFS of 9½ months and overall survival of 30 months. And so, while VRD is now being used upfront much more commonly, there are still patients who have retained sensitivity to proteasome inhibitors and IMiDs where this could be an option for you in the early relapsed setting as well.

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### ERd vs Rd for RRMM

- Elotuzumab: anti-SLAMF7 (CS1) mAb
  - No single-agent responses
- Elotuzumab/lenalidomide/dexamethasone improved ORR (79% vs 66%) and PFS (med 19.4 vs 14.9 mos) over lenalidomide/dexamethasone in RRMM (1-3 priors)
  - At 3-year f/u, OS 43.7 vs 39.6 mos (HR 0.77,  $P=0.026$ )
- Little added toxicity (lymphopenia, infusion rxn (10%))



Lonial S, et al. *N Engl J Med*. 2015;373:621-631.; Dimopoulos MA, et al. *Blood*. 2015;126:28.

Now, the first of the really new drugs that I will discuss is elotuzumab, and this was studied in the ELOQUENT trial which compared elotuzumab-lenalidomide-dexamethasone to lenalidomide-dexamethasone for relapsed/refractory myeloma patients who had 1 to 3 prior lines of therapy. Elotuzumab is an anti-SLAMF7 monoclonal antibody, SLAMF7 is a molecule expressed highly on plasma cells, including malignant plasma cells, and also expressed to a lower degree on other immune cell such as natural killer cells. Interestingly, there were no single-agent responses with elotuzumab in a relapsed/refractory study, but there was significant synergy seen in combination with lenalidomide both pre-clinically and in a phase 1/2 study. And so in this randomized phase 3 trial, elotuzumab was added to lenalidomide and dexamethasone and was shown to improve both the overall response rate as well as progression-free survival with a hazard ratio of 0.7 as seen here. Further follow-up shows that this PFS advantages retained at 3 years, and there is now an emerging overall survival advantage with a hazard ratio of 0.77. And importantly, elotuzumab did not seem to add a lot of significant new toxicity. There is some lymphopenia, there is about a 10% risk of infusion reactions, but overall, this triplet combination was well tolerated and seemed to improve outcomes compared with lenalidomide-dexamethasone alone, making it a reasonable choice in this population.

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### Carfilzomib

- Novel, irreversible proteasome inhibitor
- Approved for RRMM
- Less neuropathy
- Multiple doses/schedules (28d cycle)
  - 20/27 mg/m<sup>2</sup> (2-10 min infusion) d1, 2, 8, 9, 15, 16
  - 20/36, 20/45, 20/56 (30 min) d1, 2, 8, 9, 15, 16
  - 20/70 mg/m<sup>2</sup> (30 min) d1, 8, 15

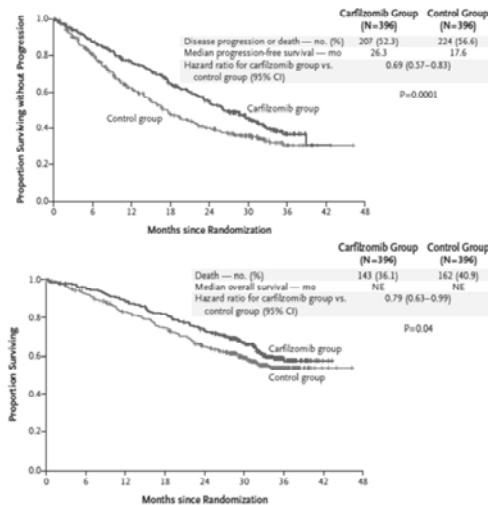
The next novel drug we will talk about is carfilzomib. This differs from bortezomib, in that it is an irreversible proteasome inhibitor. It has to be given intravenously and certainly has less neuropathy than bortezomib, which is one of its advantages. It is important to be aware that there are a number of different doses and schedules of carfilzomib that are out there. The original approval as a single agent was at 27 mg/m<sup>2</sup> given as a 2 to 10 minute infusion, and it is important to remember that for the first two doses, you should always start at 20 mg/m<sup>2</sup> to minimize first dose reactions and tumor lysis. Subsequent studies, however, have shown that if you extend the infusion duration to 30 minutes or more, you can get in higher dosage of the drug, even as high as 56 mg/m<sup>2</sup> when given on the classic day 1, 2, 8, 9, 15, and 16 schedule. And finally, there have now been a couple of studies looking at weekly carfilzomib and demonstrating you can actually push the dose up to 70 mg/m<sup>2</sup>. So, it is really key and important to keep in mind which dosing schedule of carfilzomib your regimen is using when you select one for the patient and make sure you try to match what was actually used in the clinical study.

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### KRd vs Rd for RRMM

- n=792, med 2 priors
- 66% bortezomib, 19% lenalidomide
- Carfilzomib 20/27, max 18 cycles
- Lenalidomide 25 until PD
- Dexamethasone 40 until PD

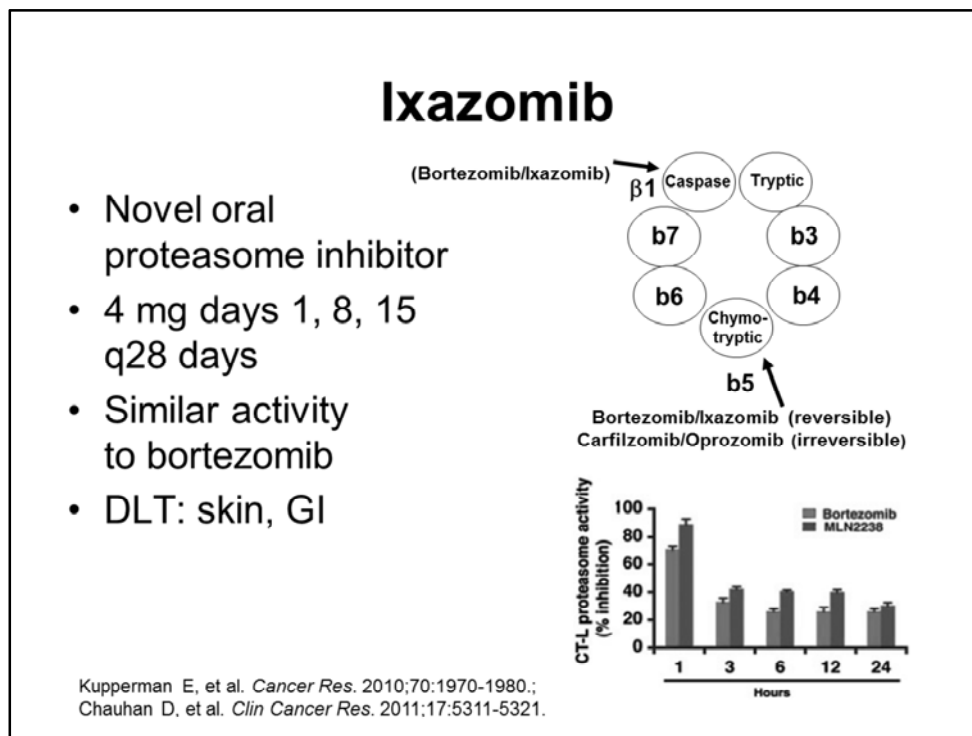
	KRd	Rd
ORR	87%	67%
≥VGPR	70%	40%
CR	32%	9%



Stewart AK, et al. *N Engl J Med*. 2015;372(2):142-152.

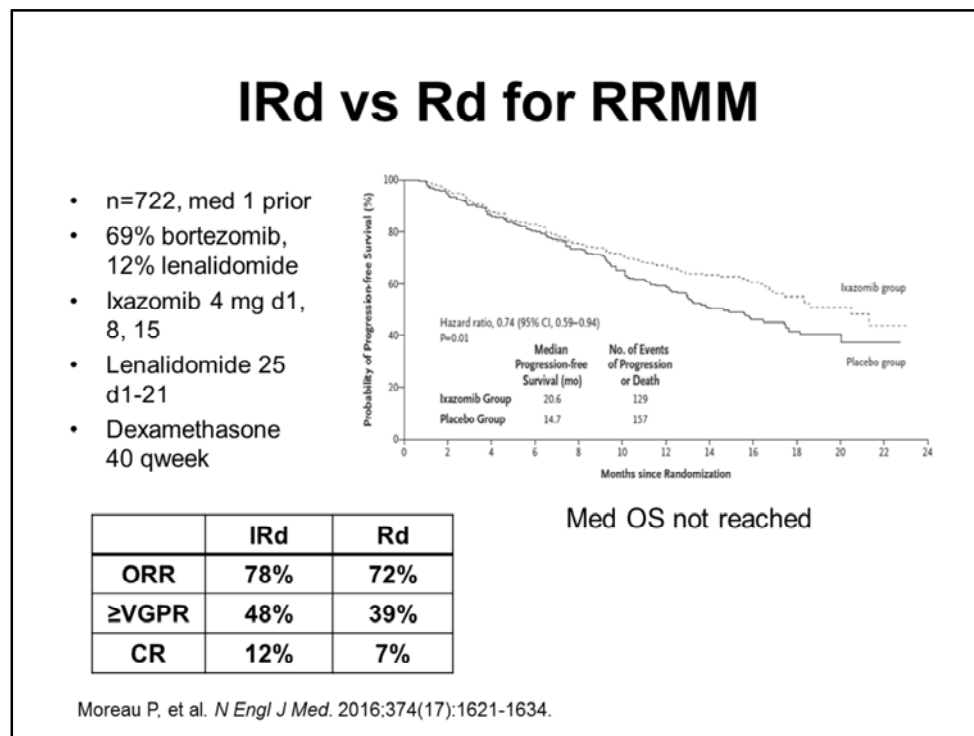
Now in terms of looking in the 1 to 3 prior line space, this is the ASPIRE trial which compared carfilzomib-lenalidomide-dexamethasone to lenalidomide-dexamethasone for relapsed/refractory myeloma. This was almost 800 patients with a median of 2 prior lines. Most have been exposed to bortezomib. Only 19% had seen lenalidomide, and they could not be bortezomib refractory. The carfilzomib was given at the 20/27 mg/m<sup>2</sup> dosing up to a total of 18 cycles. Lenalidomide and dexamethasone were given on the standard dosing of dexamethasone 40 mg once a week. And the study did demonstrate an improved overall response rate including deeper responses with more VGPRs and impressively 32% complete remission rate with the KRd arm compared to RD. It also met the primary endpoint of improving progression-free survival with a median PFS of 26.3 months versus 17.6 months for lenalidomide-dexamethasone with hazard ratio of 0.69. There also was a trend toward improved overall survival, although the followup was short and this did not meet a pre-specified statistical endpoint.

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Now, the other new proteasome inhibitor is ixazomib. This is the only oral proteasome inhibitor currently approved by the FDA. This is very similar structurally to bortezomib. It has a similar backbone and had similar preclinical activity and pharmacokinetics. However, it is given as an oral drug at 4 mg once a week for three weeks on and one week off. The toxicities are a little different in bortezomib. There is much less neuropathy. There is however a risk of rash or other skin toxicity and there is a bit more GI toxicity with some nausea, vomiting, and sometimes diarrhea.

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Ixazomib did have single-agent activity in the relapsed/refractory setting, but there was clear synergy and activity in combination with lenalidomide and therefore this randomized phase 3 trial called TOURMALINE-MM1 was performed comparing ixazomib-lenalidomide-dexamethasone to lenalidomide-dexamethasone for relapsed/refractory myeloma. This had a median of one prior line of therapy. Most patients were bortezomib exposed. Most were lenalidomide naïve. Again, they could not be refractory to either agent to get on study. The study did demonstrate slight improved overall response rate as well as improved depth of response with the triplet combination and did meet its primary endpoint for improving progression-free survival with a median of 20.6 months for the ixazomib, lenalidomide, and dexamethasone compared to its 14.7 for the lenalidomide-dexamethasone group. Overall survival was not reached for either group and was not statistically different at the time of analysis.

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### Lenalidomide-based Triplets for Early RRMM

All lenalidomide-naïve or sensitive  
1-3 prior lines

OS data immature

	ASPIRE		TOURMALINE		ELOQUENT1	
	KRd (n=396)	Rd (n=396)	IRd (n=360)	Rd (n=362)	EloRd (n=321)	Rd (n=325)
AEs of note	HTN, dyspnea, cardiac		GI tox, rash		Lymphopenia, infusion rxn	
ORR %	87	67	78	72	79	66
CR%	32	9	12	7	4	7
Med PFS	26.3	17.6	20.6	14.7	19.4	14.9
PFS HR (95% CI)	0.69 (0.57-0.83)		0.74 (0.59-0.94)		0.70 (0.57-0.85)	
Med OS	NR	NR	NR	NR	63.7	59.6
OS HR (95% CI)	0.79 (0.63-0.99)		Not available		0.77 (0.61-0.97)	

d=dexamethasone; Elo=elotuzumab; I=ixazomib; K=carfilzomib; R=lenalidomide

So, how do we put all these data into perspective? This is a table comparing these different lenalidomide-based triplets in the early relapsed/refractory setting. These are all patients who had 1 to 3 prior lines of therapy and were lenalidomide naïve and sensitive, and what I have listed here are just a few key take-home points from each study. Number one that the toxicity or side effects are a bit different for each of these agents, the unique side effects I should say. In the carfilzomib-based studies, it is important to know that carfilzomib does have a low but real incidence of cardiopulmonary dysfunction. This can include hypertension, dyspnea, pulmonary hypertension, and even frank cardiac failure with an incidence of around 5%. This is largely reversible with holding of the drug and some patients can be re-challenged at a lower dose. As I mentioned, the ixazomib can add GI toxicity and a rash. The elotuzumab has a risk of lymphopenia and a low risk of infusion reactions. You can see there also were differences in the complete remission (CR) rates between the three groups, with the highest CR rate being seen with the carfilzomib-based regimen. It is important to know, however, that elotuzumab is an IgG kappa antibody. It can interfere with the SPEP and immunofixation by showing a band that is actually picking up the elotuzumab not the myeloma, making it difficult to assess for CR. So, I think the CR rate of 4% is probably an underestimation. Finally, it is important to note that despite these differences in CR rates, the hazard ratio in terms of improving progression-free survival over the control arm was pretty similar across all three studies, suggesting a fairly similar magnitude of benefit. You will notice that in the ASPIRE trial the control arm had the longest PFS compared to the other two studies, suggesting perhaps that the patient populations were a little bit different. And finally that the overall survival has really not been statistically different in either of the studies, although there are some early trends that are emerging and further followup is needed. So, I think really any of these are very reasonable approaches for the patient with 1

to 3 prior lines who is still sensitive or naïve to lenalidomide.

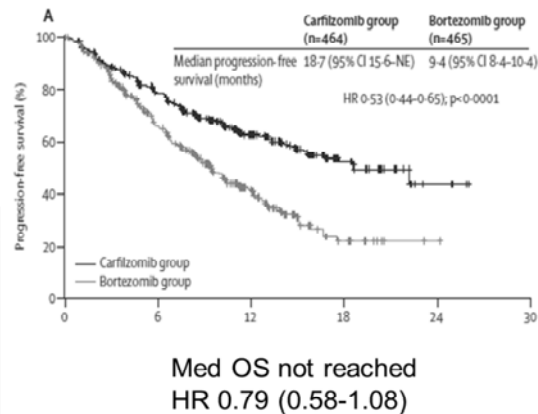


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### ENDEAVOR: Kd vs Vd

- n=929, med 2 priors
- 54% bortezomib, 38% lenalidomide
- Bortezomib: 1.3 mg/m<sup>2</sup>
- Carfilzomib 20/56 mg/m<sup>2</sup> (30 min)

	Kd	Vd
ORR	77%	63%
≥VGPR	54%	29%
CR	13%	6%
Toxicity		
Neuropathy	19%	52%
HTN	25%	9%
CHF	8%	3%



Dimopoulos MA, et al. *Lancet Oncol.* 2016;17(1):27-38.

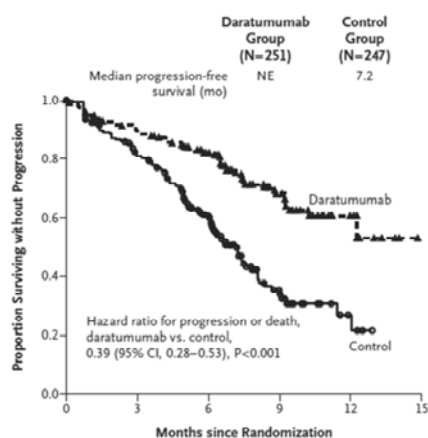
Now the other approach in relapsed/refractory disease is a proteasome inhibitor-based backbone, and so the ENDEAVOR study was actually a phase 3 trial comparing a bortezomib and dexamethasone control arm to high-dose carfilzomib and dexamethasone. So interestingly still a doublet but increasing the carfilzomib dose up to 56 mg/m<sup>2</sup> given as that 30 minute infusion as mentioned earlier, and this was treated until progression. The bortezomib was given on the day 1, 4, 8, and 11 schedule and could be given intravenously or subcutaneously, and the carfilzomib arm actually had an increased overall response rate including increased depth of response with greater VGPR and CRs. As expected, there was less neuropathy with the KD arm compared to the VD arm. There was a higher rate, however, of hypertension and congestive heart failure as shown here in the table. The study did meet its primary endpoint in terms of increasing progression-free survival, with an impressive hazard ratio of 0.53, almost a doubling of PFS. Median overall survival was not reached, and the hazard ratio was 0.79 favoring the carfilzomib arm, but this was not statistically significant.

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### DaraVd vs Vd (CASTOR)

- Daratumumab=anti-CD38 mAb
- n=498, med 2 priors
- 66% PI, 76% IMiD
- Daratumumab 16 mg/kg until PD
- Bortezomib 1.3 mg/m<sup>2</sup> x 8 cycles
- Dexamethasone 20 x 8 cycles

	DVd	Vd
ORR	83%	63%
≥VGPR	59%	29%
CR	19%	9%
Gr 3/4 tox		
Plts	45%	33%
ANC	13%	4%
Infections	21%	19%

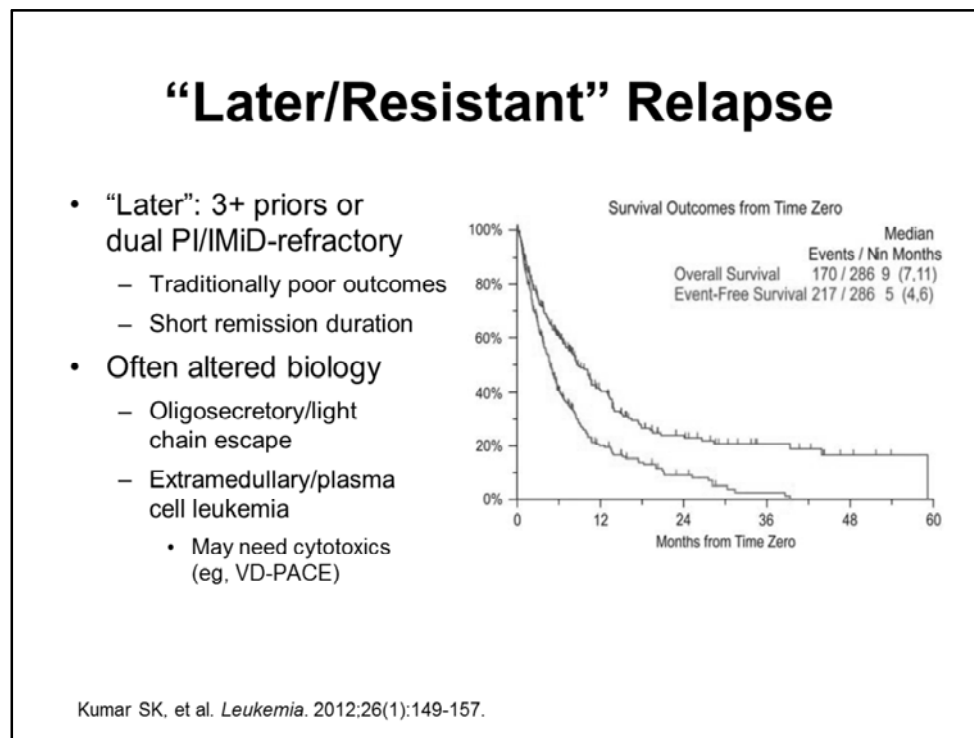


Greatest PFS benefit seen with 1 prior  
- ?should be used earlier?

Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.

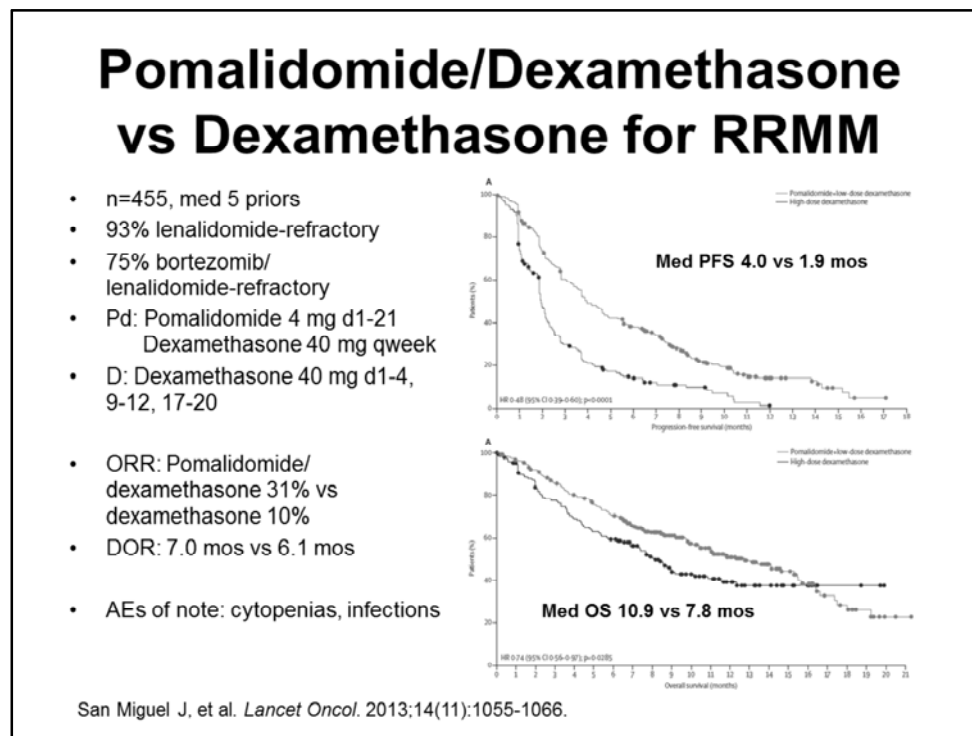
The other recent phase 3 study that builds on a bortezomib-dexamethasone backbone that has been published just in the last few weeks in *The New England Journal of Medicine* was this CASTOR study which added the monoclonal antibody daratumumab, an anti-CD38 antibody, to bortezomib and dexamethasone, and this also was for patients with at least one prior therapy. The median was two priors. Most have been exposed to a proteasome inhibitor and an IMiD. They could not, however, be bortezomib refractory in order to get on the study. The bortezomib and dexamethasone were given at the standard dosing schedule for a total of 8 cycles. The daratumumab arm was given at the standard 16 mg/kg dose; however, this continued until progression in the daratumumab-bortezomib-dexamethasone arm. And what you can see in the table was that there was an improvement in response rate including a near doubling of the VGPR or better rate as well as the CR rate with the DVD arm. There was some increase in myelosuppression with grade 3, 4 thrombocytopenia and neutropenia higher with the DVD arm, but total rates of infections were not different between the two arms. The study did meet its primary endpoint of increasing progression-free survival. You can see on the curves on the right that the DVD arm had a median PFS that was not reached compared to 7.2 months in the control arm for hazard ratio of 0.39. And when they did a subgroup analysis, it seems like the greatest PFS benefit was seen in patients who had only had one prior therapy with an even greater hazard ratio on magnitude of benefit. And this raises the question of whether we should be using daratumumab a little earlier in treatment. I will be speaking in a few slides about the single-agent daratumumab studies that led to the FDA approval of daratumumab, which currently is only approved for patients who have 3 or more prior lines of therapy or dual proteasome inhibitor IMiD refractory, and so right now, the FDA has not approved the use of daratumumab in earlier lines of therapy, but I think we will have to see after these data are submitted if something changes.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents



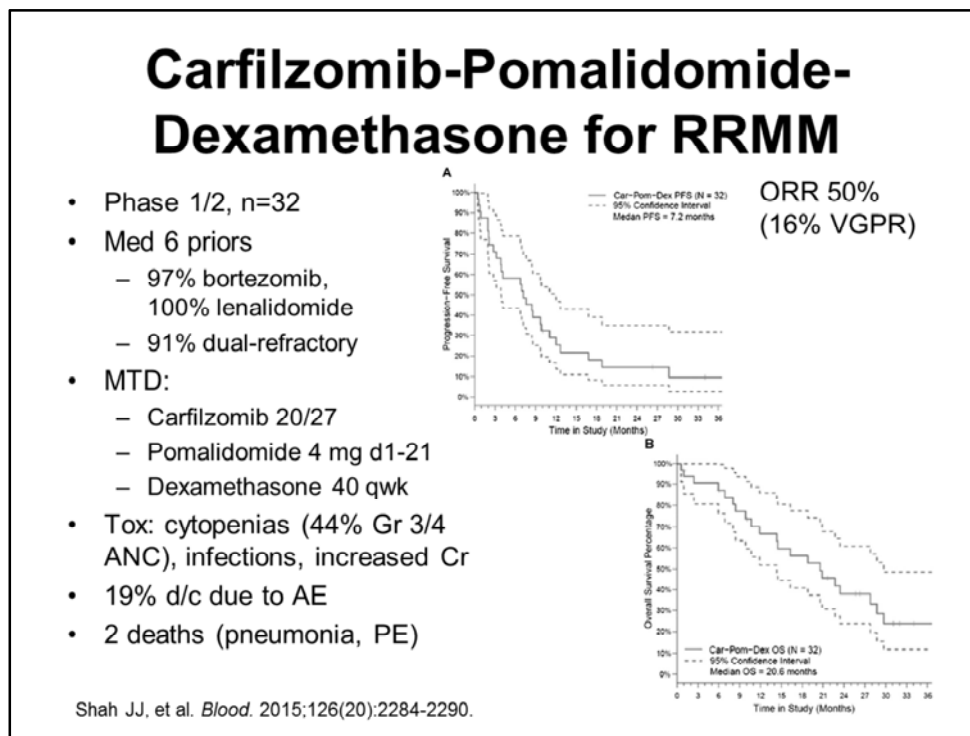
Moving on now to somewhat more resistant patients, we know that once patients have had 3 or more prior lines of therapy and particularly have become resistant to both a proteasome inhibitor and an IMiD that their prognosis traditionally has been poor. This is the off-cited study from Kumar and colleagues published in *Leukemia* 4 years ago showing a median event-free and overall survival of only 5 and 9 months respectively once this happens, and unfortunately, patients tend to either respond or have stable disease for short periods of time and then progress, and this is likely due to altered biology of the disease with clonal evolution. Patients can become oligosecretory or have light-chain escape. They can also start to develop extramedullary disease or plasma cell leukemia which can be a very difficult problem, and I will just mention that in some of these cases once the disease gets out of the marrow, you may need classic cytotoxic agents. VD-PACE, infusional cyclophosphamide, and some of the older drugs can sometimes get these under control for a short period of time and provide a bridge to other therapies.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents



So what is available in this more heavily pretreated resistant relapsed space? I will first talk about the MM-003 trial which was a randomized phase 3 study of pomalidomide and dexamethasone versus dexamethasone. Pomalidomide is a third-generation IMiD that has been approved based on these data. This was a more heavily pretreated population, median 5 prior lines of therapy, almost all refractory to lenalidomide, and three-quarters dual bortezomib lenalidomide refractory, so a very tough population to treat. Pomalidomide was given at 4 mg for 3 out of 4 weeks and dexamethasone was given 40 mg a week in the pomalidomide-dexamethasone arm. The dexamethasone control arm was the old-fashioned pulsed dexamethasone of 4 days on and 4 days off, and the study demonstrated an improved response rate of pomalidomide-dexamethasone of 31% with improved duration of response and met its primary endpoint of improving progression-free survival. There also actually was an overall survival advantage for the pomalidomide-dexamethasone arm as well. Pomalidomide like lenalidomide can cause myelosuppression and cytopenias, and there was an increased rate of cytopenias in the pomalidomide-dexamethasone arm as well as a slight increased risk of infections as well, that is something to keep in mind.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

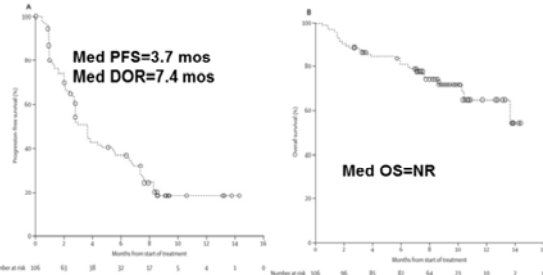
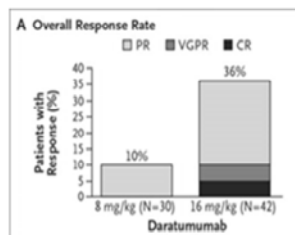


Now, I have mentioned that carfilzomib was previously approved for relapsed/refractory myeloma and pomalidomide-dexamethasone as I just showed you has a response rate of about 30%. Given the known synergy between proteasome inhibitors and IMiDs, this phase 1/2 study was started, a multi-institutional study of carfilzomib-pomalidomide-dexamethasone to relapsed/refractory myeloma. Again, a very heavily pretreated population, median 6 priors, almost all dual refractory to bortezomib and lenalidomide, and in this case, the maximum tolerated dose in this setting was carfilzomib at 20/27 mg/m<sup>2</sup> with pomalidomide at 4 mg and dexamethasone 40 mg a week. Toxicities were significant including cytopenias in a significant proportion of patients, and about 19% discontinued due to an adverse event, there were two deaths on the study that were possibly treatment related. However, the response rate was about 50% including 16% VGPRs which compares favorably to the response rates of either single-agent carfilzomib or pomalidomide-dexamethasone, suggesting there might be some synergy between this triplet. And the median progression-free survival of 7 months and overall survival of 20 months was much better than would be expected for this heavily pretreated group, and so even though this lacks phase 3 data, I think this is an option for your patients, particularly those that have become refractory to bortezomib and lenalidomide, or you can regain a response by using these drugs together, just watch for increased cytopenias and toxicity.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Daratumumab (Anti-CD38 mAb)

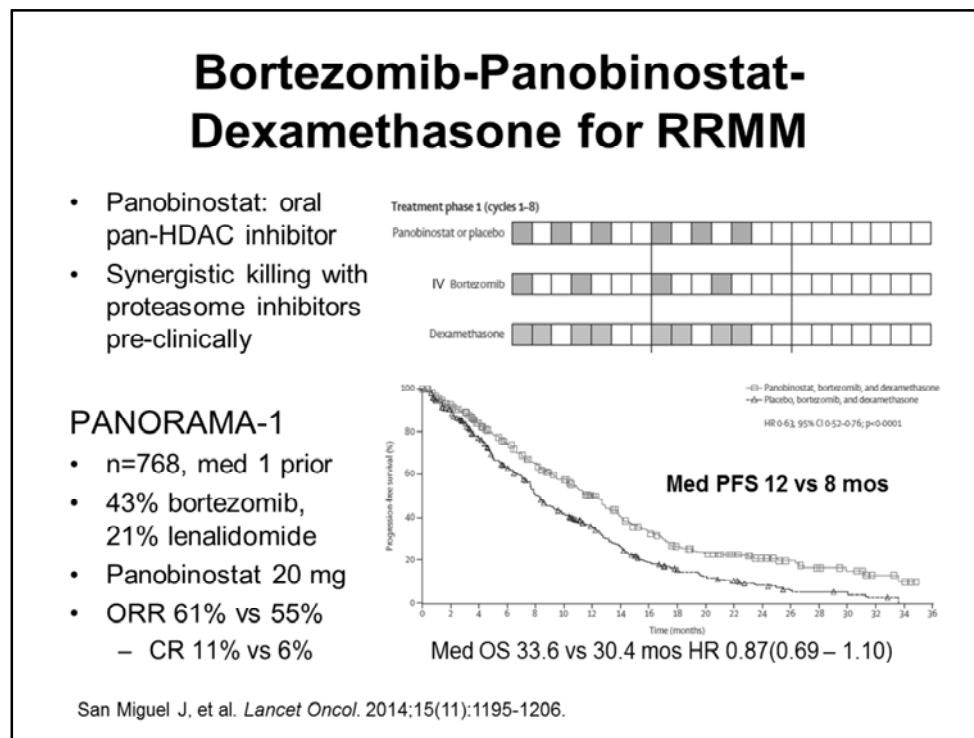
- Phase 1 (n=104) and 2 (n=106 at 16 mg/kg)
- Weekly x 8, then q2wks x 8, then q4wks
  - Long infusions (7-8 hrs wk 1, then 3-4 hrs)
- Phase 2: med 5 priors, 95% dual-refractory, 31% quad-refr
- Toxicities:
  - Grade 3/4 Hgb (24%), plts (19%), ANC (12%)
  - Infusion reactions in 42% (grade 3 in 5%)
  - No d/c due to tx-related AE, 2 deaths due to infection
  - Interference with blood typing, no hemolysis



Lokhorst HM, et al. *N Engl J Med.* 2015;373(13):1207-1219.;  
Lonial S, et al. *Lancet Oncol.* 2016;387(10027):1551-1560.

Next, I will talk a little bit more about daratumumab in the more heavily pretreated setting. There were actually two studies of daratumumab. First a phase 1/2 looking at identifying the optimal dose, and then a second study that initially compared 8 mg/kg to 16 mg/kg and found 16 mg/kg to be superior and then had an expansion at 16 mg/kg. You will recall the daratumumab is given initially weekly for 8 weeks then every 2 weeks for 8 doses and then goes to monthly for maintenance. There is a long infusion with daratumumab. Due to risk of infusion reactions, it can take 7 to 8 hours with the first infusion but then can be given somewhat more rapidly thereafter. For very heavily pretreated patients, median 5 priors 95% refractory to a proteasome inhibitor and an IMiD and 31% refractory to actually bortezomib, carfilzomib, lenalidomide, and pomalidomide. The main toxicities were fairly modest cytopenias. Infusion reactions were seen in 40-50% of patients but were largely grade 1 and 2 and can be mitigated by appropriate pre-medications. There were no discontinuations due to treatment-related toxicities. There were two deaths due to infection. It is important to keep in mind that daratumumab, because CD38 is found on red cells, can interfere with blood typing. So, it is important to let your blood bank know that your patient is on daratumumab if you are trying to type and screen them and you should get it typed and screened prior to treatment in order to identify any preexisting antibodies. The bottom line though was that this single antibody had a 30-36% response rate in the two studies, the median PFS was 3.7 months, and the median duration of response was 7½ months with overall survival not reached. So, fairly impressive activity in a very refractory population for a single-agent with good tolerability.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

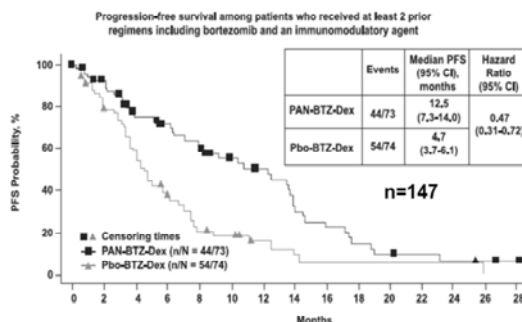


The last new drug we will discuss is panobinostat. Panobinostat is an oral pan-histone deacetylase inhibitor. It demonstrated to be significant synergy in combination with proteasome inhibitors preclinically based on nice work done out of Ken Anderson's lab in Dana-Farber, now led first to a phase 2 study, and then this randomized phase 3 study called PANORAMA-1 which compared bortezomib-panobinostat-dexamethasone to bortezomib and dexamethasone for relapsed/refractory myeloma patients who had 1 to 3 prior lines of therapy. The panobinostat dosing was 20 mg given on Monday, Wednesday, and Friday for 2 weeks in a row and then a week off. Bortezomib was given intravenously on the day 1, 4, 8, 11 schedule, and the dexamethasone was given the day of and day after each bortezomib. After the first 6 months, patients could go on to an attenuated schedule for another 24 weeks. There is a median of 1 prior line of therapy. Most patients actually were bortezomib naïve, and they could not be bortezomib refractory to go on study, and the bottom line was that there was a slight increase in overall response rate including an increasing complete response rate, and the trial did meet its primary endpoint of increasing progression-free survival which you can see increased from 8 months for the bortezomib-dexamethasone to 12 months for the bortezomib-panobinostat-dexamethasone arm. No significant difference in overall survival.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Bortezomib-Panobinostat- Dexamethasone for RRMM

AE	V-pano-d	Vd
	All (Gr 3/4)	All (Gr 3/4)
Diarrhea	68% (25%)	42% (8%)
Asthenia	57% (24%)	41% (13%)
Anorexia	28% (3%)	12% (1%)
Plts	98% (68%)	84% (31%)
ANC	75% (35%)	36% (11%)
d/c for AE	36%	20%
Death on tx	8%	5%



- Approved for  $\geq 2$  priors, including PI and IMiD
- Alternative dosing/scheduling, combo with carfilzomib ongoing

Richardson PG, et al. *Blood*. 2016;127(6):713-721.

However, there was a significant amount of toxicity with this regimen. You can see this on the left. The panobinostat arm had significant increase in diarrhea including grade 3/4 diarrhea as well as asthenia, anorexia, thrombocytopenia, and neutropenia, and there were significantly more patients who discontinued due to side effects, and there were more deaths on study in the panobinostat arm. And so, because of this increased toxicity profile, there was a subsequent analysis that was performed just in patients who had 2 prior lines of therapy and had a proteasome inhibitor and an IMiD as part of their previous treatment. And in this subset analysis of 147 patients, the magnitude of the PFS benefit was much greater, and that is shown in the slide here with a median PFS of 12½ months compared to 4.7 months for the control arm. And so, the FDA decided to approve the drug in this combination just for this subset of patients, 2 or more prior lines including a proteasome inhibitor and IMiD, because of the best risk/benefit ratio and largest magnitude of benefit. I will say that there are alternative dosing and scheduling that are being explored for panobinostat. I think some of the toxicity here certainly could have been attributed also to using intravenous twice-weekly bortezomib which is not often used anymore, and with weekly subcutaneous dosing and also with carfilzomib, there may be a better way to use this drug, and so, we are awaiting those follow-up studies to improve the safety profile.



## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Stem Cell Transplant

- Autologous
  - Can attempt recollection if no stem cells remaining
  - Consider if >18 mos remission after first ASCT
  - Expect roughly half of prior remission duration
  - Helpful for disease/drug-related cytopenias
- Allogeneic
  - Limited use outside clinical trials
    - Still high TRM, GVHD risk
  - Consider for young, high-risk, short remission duration post-autoSCT
    - Early (eg, first or second relapse)

Laubach J, et al. *Leukemia*. 2016;30(5):1005-1017.

Moving on in terms of just other options, it is important not to forget about stem cell transplant as an alternative salvage option for relapsed/refractory patients. This I think is being done a little bit later on now that we have so many other drugs, but certainly if patients had a deep and durable remission after their first transplant, usually at least 18 months if they were not on maintenance and at least 2 to 3 years if they were on maintenance, you might want to consider a second transplant to consolidate their response. You would expect about half the prior remission duration. This also can be helpful for patients who have really exhausted marrows and drug-related cytopenias that limits your ability to give salvage therapy. If you give additional high-dose melphalan and fresh stem cells, sometimes they get reconstituted hematopoiesis and then they can tolerate more therapies or go on a trial. Allogeneic transplant I think still has very limited use, but for selected patients perhaps who have achieved a second remission, are young with very high-risk disease, you could consider it ideally on a clinical trial.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Pembrolizumab for RRMM

- Pre-clinical rationale for PD-1/PD-L1 blockade in MM
- Single-agent nivolumab with no responses
  - 67% stable disease
- Pembrolizumab activity in combo with lenalidomide or pomalidomide (ORR 50%)
  - Including lenalidomide-refractory
  - irAEs: thyroiditis, pneumonitis
- Multiple PD1/PD-L1 inhibitor trials underway in MM

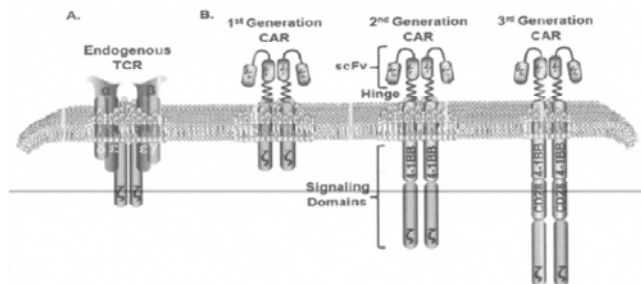
Lesokhin AM, et al. *J Clin Oncol*. 2016;34(23):2698-2704.; Badros AZ, et al. *Blood*. 2015;126:506.; Mateos M-V, et al. *J Clin Oncol*. 2016;34:(suppl; abstr 8010).

Finally, just to finish up with immunotherapy, I think the PD-1 and PD-L1 inhibitors have been lagging a little bit behind in myeloma compared to some of the other cancers, but there are now a few studies that are demonstrating perhaps some activity. The single-agent nivolumab study in myeloma in 27 patients did not have any true partial responses, but a number of patients did have stable disease, and based on preclinical synergy with IMiDs, there have been two phase 2 studies looking at pembrolizumab and alternative anti-PD1 antibody in combination with either lenalidomide or pomalidomide with an overall response rate of 50% including in patients truly refractory to lenalidomide, suggesting that there may really be some synergy here. You do have to look out for immune-related adverse events, although these are largely manageable with discontinuation of the drug and steroids, and based on this promising data, there are now a number of PD1 or PD-L1 inhibitor trials that are underway both in the relapsed/refractory setting, largely in combination with IMiDs or monoclonal antibodies, and also a few upfront trials that are getting underway as well. So, I think in another couple of years we will know a lot more about the role of checkpoint blockade in multiple myeloma and whether this is going to be a valid addition to our armamentarium, but this is something I think you could consider using now if necessary and exhausting other options.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Chimeric Antigen Receptors (CAR)

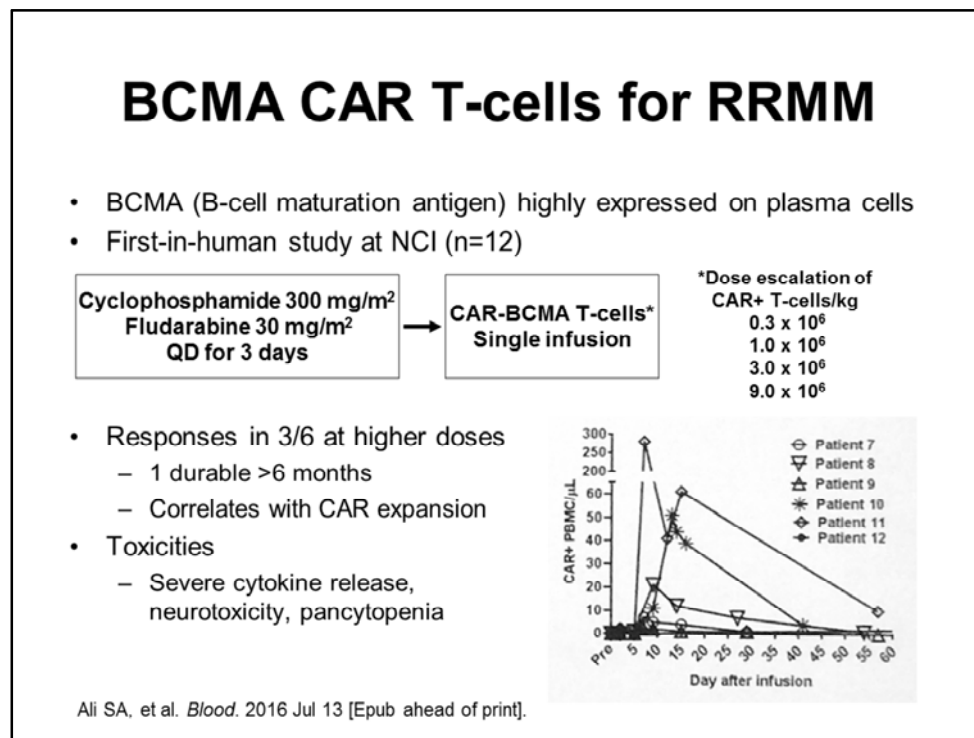
- Recognition domain of antibody with signaling domain of T-cell
- Uses gene transfer to stably express CAR on T-cells → confers novel antigen specificity
- Addition of co-stimulatory domains (CD28, 4-1BB) augments proliferation and survival
- CART19 cells active in B-ALL, CLL, and NHL



Garfall AL, et al. *Discov Med*. 2014;17(91):37-46.

Finally, just a quick word about what hopefully is coming down the pike in terms of the T-cell mediated immunotherapy. Chimeric antigen receptors are a novel type of immune therapy where patients' autologous T-cells are reengineered to express a unique receptor with a signaling domain of a T-cell but with the recognition domain of an antibody so that they can then recognize surface antigens, and the most success to date with CAR T-cells have been in B-cell malignancies, particularly targeting CD19 with very high response rates in B-ALL as well as in CLL and non-Hodgkin lymphoma.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents



The first data looking at CAR T-cells in relapsed/refractory myeloma have been published recently by the group at the NCI. These CAR T-cells target a molecule called BCMA which is expressed highly on plasma cells including malignant plasma cells. This was a pilot first in human study. Patients got lympho-depleting conditioning with cyclophosphamide and fludarabine and then a single infusion of their CAR BCMA T-cells looking at escalating doses. Once they got to the two highest dose levels, they actually saw responses in three out of six patients. These were fairly refractory patients, one of which is still durable 6 months or more after the single infusion, and this correlated with expansion of the T-cells. Now there are significant toxicities with CAR T-cells including severe cytokine release syndrome as well as neurotoxicity and pancytopenia, and so, this continues to be refined, but a number of additional CAR studies in multiple myeloma are now underway, and so we are waiting further data about the efficacy and safety of this approach.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Conclusions

- Growing list of options for RRMM
- Individualize treatment based on disease and patient characteristics
  - No proven “best” regimen
- Triplet regimens superior in early relapse
- Continuous therapy prolongs remissions
- Maintain quality of life

So, to conclude we are fortunate now to have a growing list of options for relapsed/refractory myeloma and patients continue to do better and better. I think it is important to continue to individualize treatment based on the underlying disease and patient characteristics. There is still no proven “best regimen,” and many times, it is somewhat of an empiric choice based on their prior therapies and their toxicities and you may be going from one regimen to the next. It does seem now from several randomized phase 3 trials that triplet regimens adding a new drug to a backbone of lenalidomide, bortezomib, and dexamethasone is superior to the doublet regimens, and these are generally now recommended in terms of deeper responses and more durable responses in PFS. Think about continuous therapy, not just for upfront patients, but in the relapsed setting as well. This does seem to prolong remissions, and always remember it is important to maintain quality of life. This is an incurable disease, and so, dose reductions are key if patients are having significant toxicity. It is better to keep a patient on the drugs longer than have them come off early on due to some severe toxicity.

## Relapsed/Refractory Multiple Myeloma: Standard of Care Among Emerging Agents

### Future Questions/Challenges

- Optimal sequencing
- Role of 4-drug regimens
  - Antibody-PI-IMiD-steroid
- Role of MRD testing
  - Response-adapted therapy?
- Earlier use of immunotherapy
- Cost

I think there are still a number of questions and challenges of course the optimal sequencing of how we use these drugs, and is there are any particular biomarkers that may be predictive of response to one drug or one class of drugs than the other and a lot of that research is ongoing. I think we are going to be re-exploring the role of four-drug regimens. I think prior attempts to add classic cytotoxics to a proteasome inhibitor-IMiD-steroid triplet did not seem to add additional efficacy and just added toxicity, but now that we have antibodies with non-overlapping toxicities, we are going to see a lot more antibody-PI-IMiD-steroid combos, and some of those trials are now underway. I think the role of minimal residual disease testing which really was not an issue in the relapsed setting because we were not getting very deep responses is now something we might want to reconsider as we are starting to get complete remissions even in relapsed patients and could we eventually move to some type of response-adapted therapy where the intensity of the treatment is adjusted based on the depth of response. I mentioned the role of immunotherapy which is really just starting to get tested in myeloma and whether this will be moved up earlier. Finally, always an issue as we start to combine all these new drugs together is the role of cost and cost to both the patient and the health care system in general, and so, these are all I think future challenges, but overall, the future is bright and we have a lot of more options than we used to, which is really great for our patients.

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