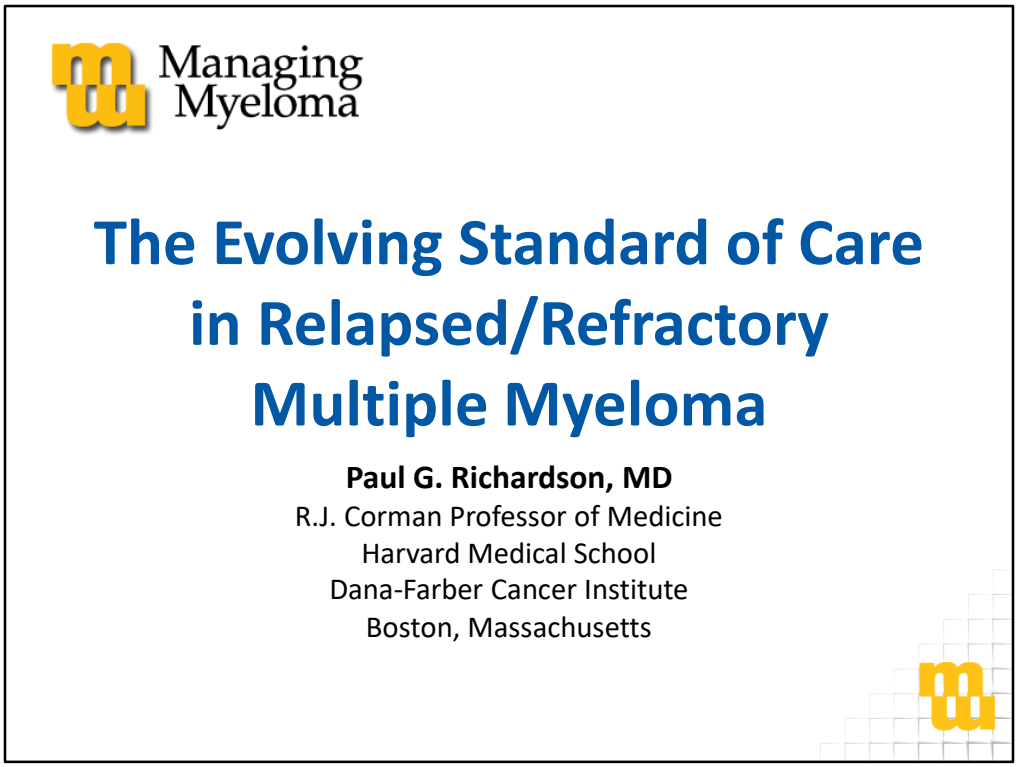
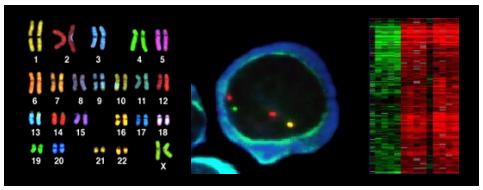
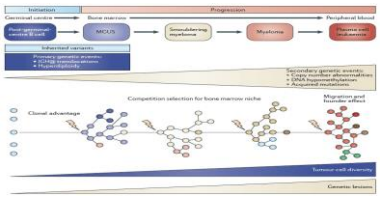
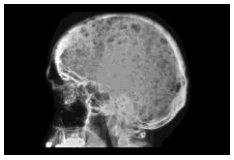
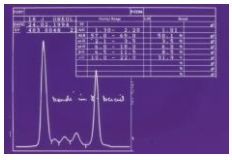
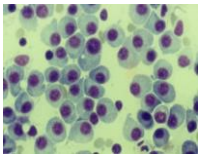


Welcome to *Managing Myeloma*, my name is Dr. Paul Richardson. In today's presentation, I will review the evolving standards of care in relapsed and refractory multiple myeloma (RRMM) over the period of 2016 through 2017. During the course of this presentation, I will provide you with the information and tools we hope you will find helpful and necessary to help you develop drug selection strategies to effectively individualize therapy in patients with RRMM. I will try to do this by discussing current treatment paradigms in this setting, as well as explaining various new drug regimens that are now being used as the standard of care in clinical practice. We fully recognize the field is evolving (fortunately) very rapidly, and some of these changes therefore are very dynamic. In that context, we are going to discuss the potential therapies under investigation that have the promise to impact the future standard of care in RRMM, and hopefully provide you with a framework not only for treating patients now, but in the future as well. Let us begin.

Multiple Myeloma (MM)
…Not Just One Disease!

- Risk stratification, recognition of clonal heterogeneity
- Individualization of treatment, advent of novel therapies

3 decades

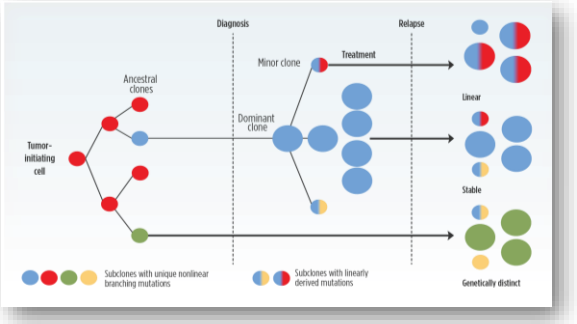






Drach J, ASH 2012.; Morgan GJ, et al. *Nat Rev Cancer.* 2012;12:335-348.

As you know, multiple myeloma is not just one disease. It is a highly heterogenous disease that varies between patients and within patients, and the individualization of treatment, therefore, has become very important. This is fortunately being made possible with the advent of novel treatments.

Multiple Genetically Distinct Subclones Can Occur in MM

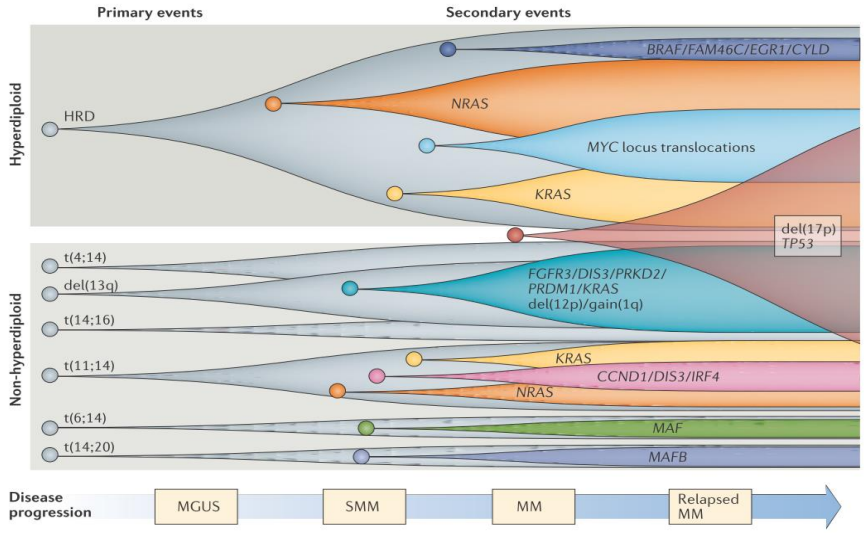
- Multiple genetically distinct subclones are present at diagnosis [1-4]
  - These evolve over time due to selective pressures from treatment and factors in the microenvironment[1,4]
  - This clonal evolution can result in disease progression and treatment resistance[5]



[1]Bahlis N, et al. *Blood*. 2012;120:927-928. [2]Keats JJ, et al. *Blood.* 2012;120:1067-1076. [3]Bianchi G, Ghobrial IM. *Curr Cancer Ther Rev.* 2014;10:70-79. [4]Bolli N, et al. *Nat Commun.* 2014;5:2997. [5]Brioli A, et al. *Br J Haematol.* 2014;165:441-454.

In that context, it is very important to recognize the entity of multiple, genetically distinct subclones that are present both at diagnoses in a patient, and which evolve over time. These clones evolve over time due to selective pressures from treatment and factors in the tumor microenvironment, as well as intrinsic to the disease itself. Most importantly, clonal evolution can result in disease progression and treatment resistance.

Co-occurrence of Genomic Events and Clonal Evolution During Progression in MM



Manier S, et al. *Nat Rev Clin Oncol*. 2017;14:100-113.

This next slide shows you very nicely the co-occurrence of genomic events and clonal evolution during progression in myeloma. It is adapted from a very nice paper recently published by Dr. Manier and colleagues. In the context of primary events, secondary events follow, and by the time we reach relapsed myeloma, patients have disease that is highly genetically unstable and full of mutations, leading to real challenges in trying to overcome resistance in this setting.

Key Targets in MM 2017

Genomic Abnormalities:

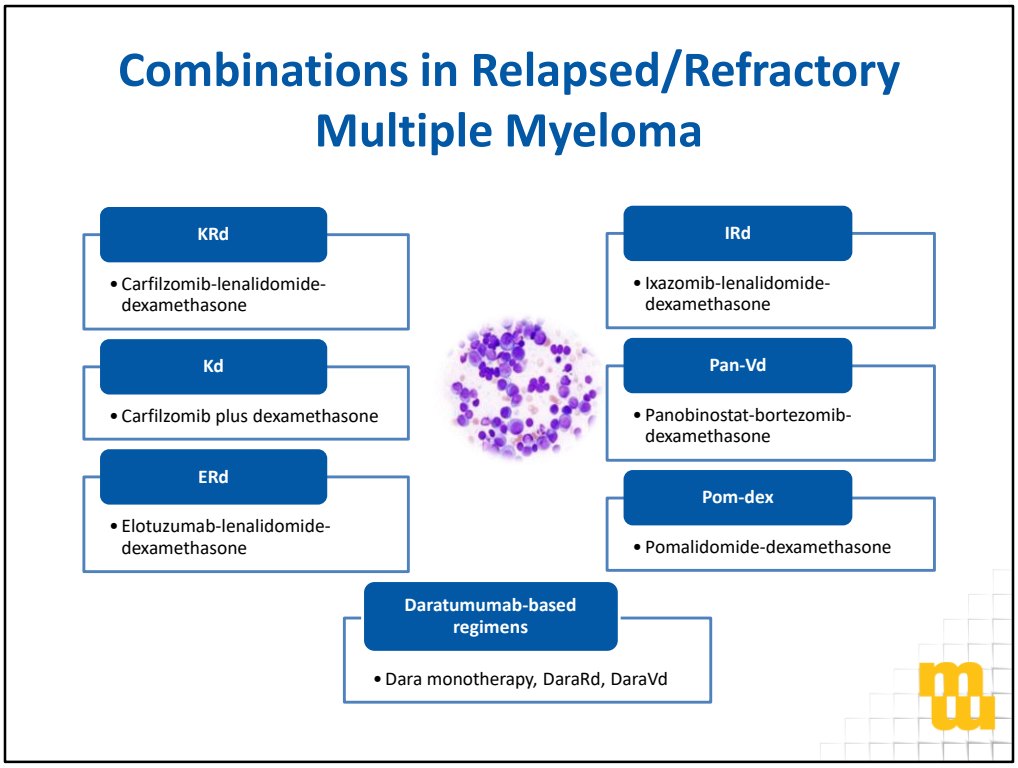
- Precision medicine
- Combination therapy
- Minimize genotoxic stress
- Overcome mutational thrust

Immune Suppression:

- Restore anti-MM immunity

The next slide shows very nicely that there are key targets this year in terms of what we need to go after for the disease. These include genomic abnormalities, and the ways to target these include precision medicine and most importantly, combination therapy. I also suggest that we need to use treatments that minimize genotoxic stress in and of themselves, and therefore overcome mutational thrust. A recognition that immune suppression is absolutely critical in this disease is vital to appreciate, because not only does that mean this is an important therapeutic target, but it means also that by restoring anti-myeloma immunity, we may improve patient outcome.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma



As we think about combinations in RRMM that are FDA-approved, it is worth summarizing this, and show the variety of combinations that are currently approved. These include carfilzomib-based therapies, elotuzumab in combination with lenalidomide and dexamethasone, with some very compelling recent data for the combination with bortezomib. There is very exciting data around the use of ixazomib combined with lenalidomide and dex. Moreover, the first-in-class HDAC to be approved in this setting, panobinostat, has been approved in combination with bortezomib and dexamethasone, and of course pomalidomide and dexamethasone in combination has been approved as a platform in RRMM. A major breakthrough that we will spend some time on is the integration of daratumumab-based therapies into the therapeutic paradigm. These include daratumumab monotherapy; daratumumab combined with lenalidomide; daratumumab combined with bortezomib; and most recently, the use of daratumumab in combination with pomalidomide.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

Complex Environment for Treatment Decisions

Multiple Factors to Be Considered When Determining a MM Patient's Next Therapy[1,2]

Patient-Related Factors	Disease-/Treatment-Related Factors
Age	Prior treatment received and response duration
Comorbidities, eg, cardiac dysfunction	Refractory status (progression on prior therapy)
Renal impairment	Toxicities from prior therapies
VTE risk	Tumor burden: Biochemical vs aggressive relapse; presence of EMD or PCL
Performance status	Poor-risk cytogenetics; advanced R-ISS stage
Geography (drug availability in country/ region; access to clinic)	Pre-existing peripheral neuropathy
Lifestyle/quality of life	
Prior history of malignancy	

EMD=extramedullary disease; PCL=plasma cell leukemia; VTE=venous thromboembolism
[1]Dimopoulos MA, et al. *Nat Rev Clin Oncol.* 2015;12(1):42-54. [2]Baz R, et al. *Support Care Cancer.* 2015;23(9):2789-2797.

This results in a complex environment for treatment decisions, and multiple factors need to be considered when determining a myeloma patient's best next therapy. I have sought to summarize this in this slide by describing age-related factors and disease- or treatment-related factors.

Consensus Guidelines for Salvage ASCT in RRMM (ASBMT, EBMT, BMT CTN, and IMWG)

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard
2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of >18 months
3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT

Giralt S, et al. *Biol Blood Marrow Transplant*. 2015;21(12):2039-2051.

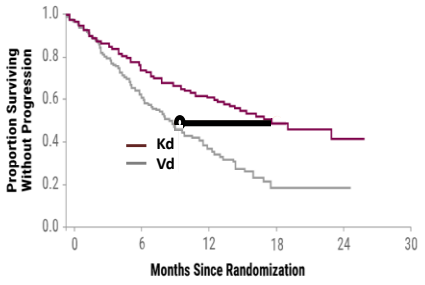
When we also look at other opportunities in the setting of RRMM, it is important not to forget that in transplant-eligible patients, there may be a role for autologous transplant This will be critically dependent on how long a patient enjoyed disease control from their first transplant if they've already had one, and if they haven't already had one or had cells collected, this might be an ideal opportunity in which to exploit this approach. Finally, in highly selective patients in a protocol-directed setting, there may be a role for autologous transplant as a bridging strategy to allogeneic transplant, recognizing – as I have mentioned – that should really only be performed in the setting of protocols in the clinical trial.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

ENDEAVOR: Bortezomib-Dexamethasone (Vd) vs Carfilzomib-Dexamethasone (Kd)

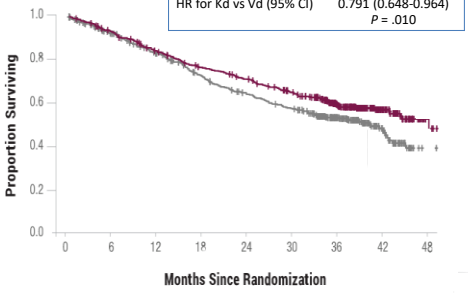
Primary Endpoint: PFS

	Kd	Vd
Events, n	171	243
Median PFS, mo	18.7	9.4
HR (95% CI)	0.53 (0.44-0.65) *P* <. 0001	



Secondary Endpoint: OS

	Kd n = 464	Vd N = 465
Death, n (%)	189 (40.7)	209 (44.9)
Median OS, mo	47.6	40.0
HR for Kd vs Vd (95% CI)	0.791 (0.648-0.964) *P* = .010	

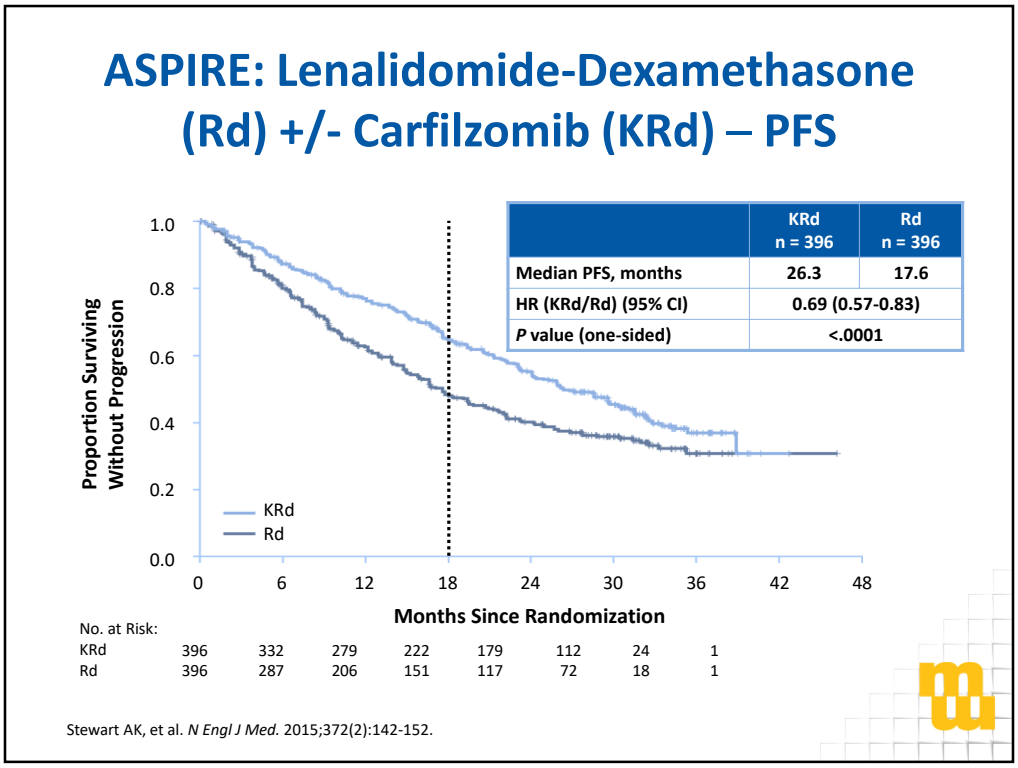


Orr (Kd vs Vd): 77% vs 63%. ≥CR: 13% vs 6%.
Median DOR (Kd vs Vd): 21.3 months vs 10.4 months.

Dimopoulos MA, et al. *Lancet Oncol.* 2016;17(1):27-38.; Dimopoulos MA, et al. Presented at: 16th International Myeloma Workshop; March 1-4, 2017; New Delhi, India. Abstract PS-254.

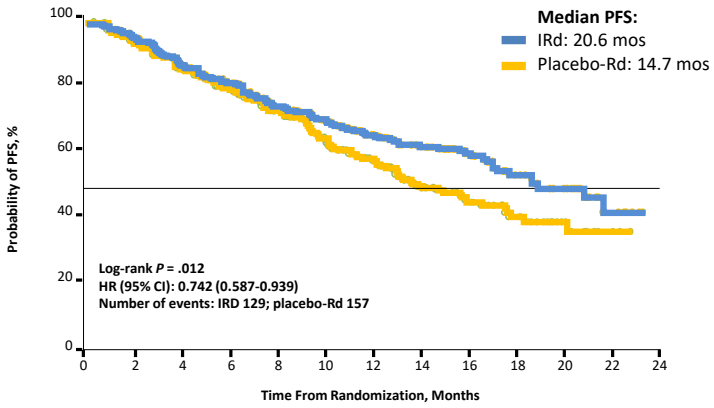
What do have in terms of primary data to support decisions in this setting? First and foremost, I want to show you the comparison of bortezomib and dexamethasone (Vd) versus carfilzomib and dexamethasone (Kd) in the relapsed setting. These are two doublets being employed in this particular randomized trial, after patients could have had prior bortezomib (although they could not be refractory to it) or prior immunomodulatory-based therapy, and patients were, of course, carfilzomib-naïve. In this setting, response rate advantages were seen in favor of carfilzomib, and duration of response was also superior for the carfilzomib-based approach. This has further resulted in a progression-free survival (PFS) advantage and now, most recently, an overall survival (OS) advantage as well.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma



When one combines carfilzomib with lenalidomide and dexamethasone (KRd) the results are particularly striking. In the landmark ASPIRE study illustrated here, we show a striking difference in favor of the combination of KRd compared to lenalidomide and dexamethasone (Rd) as its control. The PFS advantage here is impressive and this, too, has most recently resulted in survival gain. It is important to note that with carfilzomib use in the relapsed/refractory setting, we are now increasingly using it in combination with pomalidomide, and I will come to that in a moment.

TOURMALINE-MM1: Rd +/- Ixazomib (IRd) – PFS



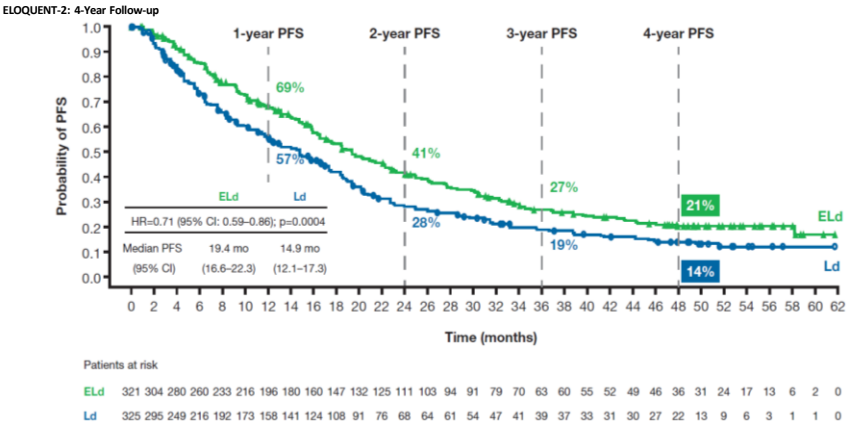
- PFS benefit with ixazomib seen in all prespecified subgroups, including cytogenetic high risk, and PI and IMiD exposed

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

Finally, in the context of the next-generation proteasome inhibitors, very exciting data has emerged with ixazomib. This is the first boronic peptide of the oral route that can be used, has been exhaustively tested in phase 1 and 2 testing, and now has moved in phase 3 with the results of the TOURMALINE-MM1 study, led by my colleague Philippe Moreau, which was recently published. In this context, a PFS advantage is being seen for ixazomib combined with lenalidomide and dexamethasone (IRd), compared to the control arm. This has been a solid six months. What's particularly important about ixazomib is that it is very convenient: once-a-week dosing of this oral agent is part of an all-oral regimen. It is also very important that it is very well-tolerated. Interestingly in this particular study, PFS benefit did not become apparent until somewhat later in the treatment course. There may be a number of factors that explain this including: placebo control, disease characteristics of patients in this trial, and also the fact that the effect of once-weekly dosing of ixazomib may take some time to see in terms of clinical benefit. That being said, this was a clearly positive study and we await further data from this trial with interest. We will also touch a little bit more on it in a moment.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

ELOQUENT-2: Elotuzumab-Lenalidomide-Dexamethasone (ERd) vs Rd – PFS



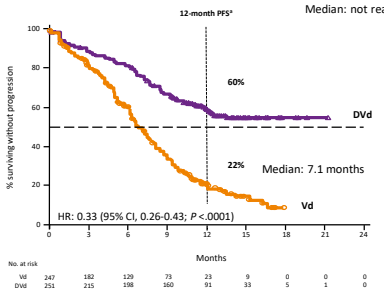
A 29% reduction in the risk of progression or death and a relative improvement of 50% in the PFS rate (21% vs 14%) were observed with ERd vs Rd

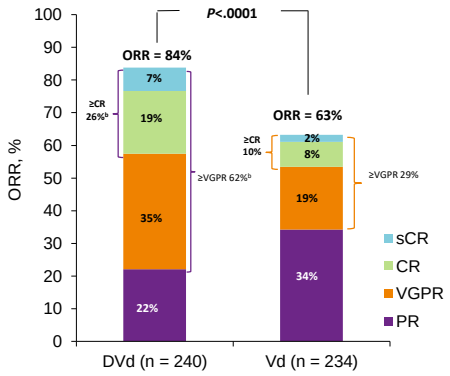
Lonial S, et al. *N Engl J Med.* 2015;373(7):621-631.; Lonial S, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8028.

Now on the context of other studies, I want to emphasize the first-in-class elotuzumab monoclonal antibody that has been developed for targeting SLAMF7. This was validated in the ELOQUENT-2 study led by my colleague Sagar Lonial, in which the combination of elotuzumab, lenalidomide, and dexamethasone (ERd) was shown to be superior to the control, Rd. The PFS advantage was not only impressive and positive at one, two, and three years, but has been sustained with longer follow-up. Very importantly, we have data from this trial now showing survival benefit with a median gain of eight months for the three drugs compared to the two. This is a very well-tolerated antibody that enhances lenalidomide effects, and vice versa, through the activation of natural killer cells targeted against myeloma. It constitutes a very important advance.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

CASTOR: Daratumumab-Bortezomib-Dexamethasone (Vd) vs Vd – Updated Efficacy





Median (range) follow-up: 13.0 (0-21.3) months

An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

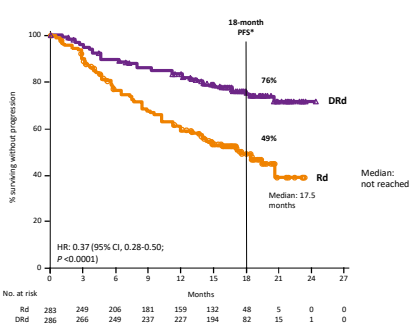
- DaraVd-treated patients had a 67% reduction in the risk of disease progression or death in comparison with Vd
- Responses continue to deepen in the DVd group with longer follow-up

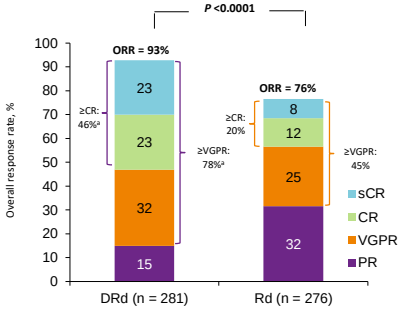
Mateos M, et al. *Blood.* 2016;128: Abstract 1150.; Lentzsch S, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8036.

However, far and away, the most positive data for antibody-based therapy lies with CD38 targeting. In this regard, daratumumab-based data has been really remarkable and breakthrough in its nature. These data from the CASTOR study, led by Antonio Palumbo and presented by co-investigators Marivi Mateos and Suzanne Lentzsch, show really striking information in terms of clinical benefit for the combination of daratumumab, bortezomib and dexamethasone (DVd), compared to the bortezomib and dexamethasone (Vd) control. As you can see on the left-hand side of the slide, the triplet far outperforms the doublet in terms of PFS advantage, with the median not reached. This is also reflected by striking differences in terms of overall response rate in favor of the triplet, including high quality of responses.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

POLLUX: Daratumumab-Lenalidomide-Dexamethasone (DRd) vs Rd – Updated Efficacy





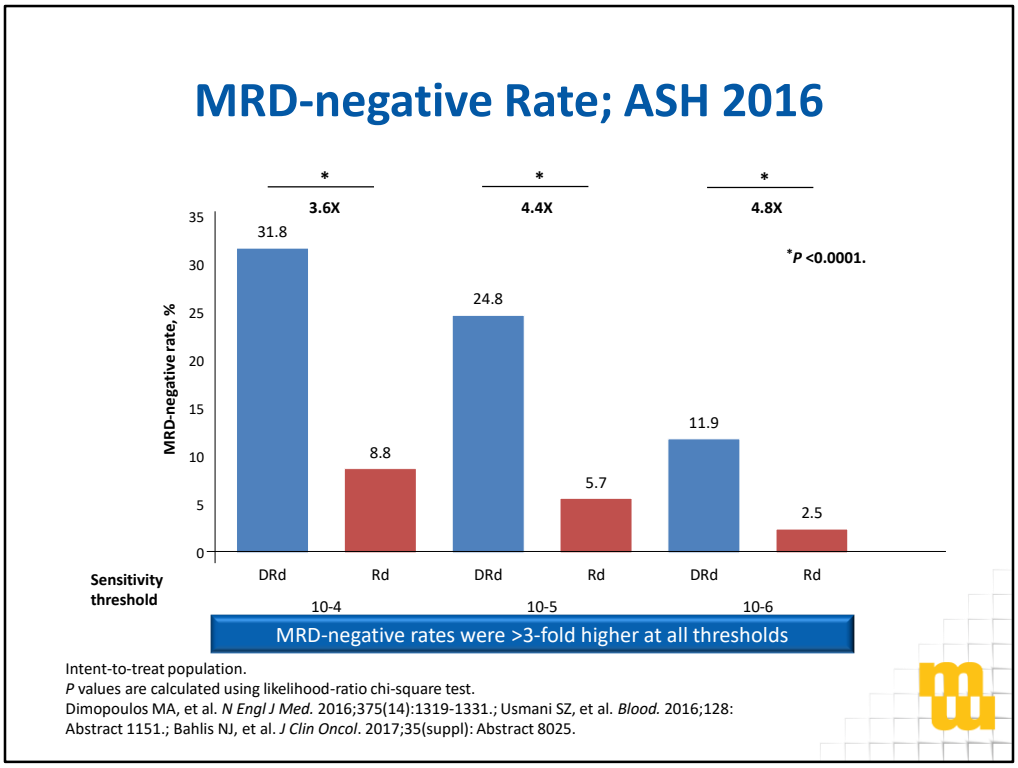
Median follow-up: 17.3 (range, 0-24.5) months

- DRd-treated patients had a 63% reduction in the risk of disease progression or death in comparison with Rd
- Responses continue to deepen in the DRd group with longer follow-up

Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.; Usmani SZ, et al. *Blood.* 2016;128: Abstract 1151.; Bahlis NJ, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8025.

When one moves into the space of daratumumab combined with lenalidomide in this setting, the POLLUX trial, the data are even more striking. This study compared daratumumab, lenalidomide and dexamethasone (DRd) to Rd in a randomized prospective large phase 3 setting. You can see here a striking PFS benefit with the impressive plateau effect seen for the triplet over the doublet, and this is also reflected by high quality of response differences in favor of the three drugs versus the two.

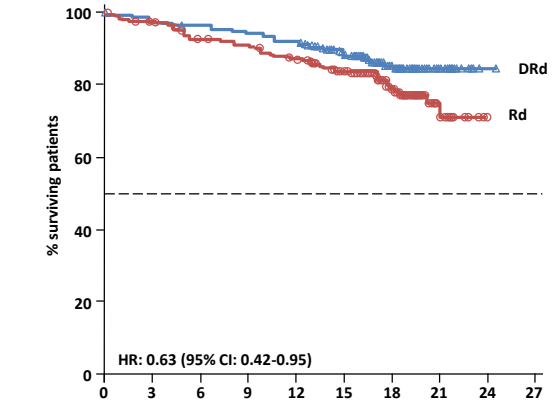
The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma



What is particularly interesting in this trial in my view is the MRD negative rate, which is strikingly in favor of the three drugs versus the two at various levels of sensitivity, which I think is particularly impressive, given this is in the relapsed/refractory setting

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

OS; ASH 2016



No. at risk

Rd	283	272	255	249	236	215	94	18	0	0
DRd	286	277	271	266	260	232	102	21	1	0

- OS events
  - 40 (14%) in DRd
  - 56 (20%) in Rd

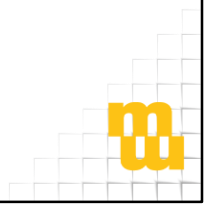
Curves are beginning to separate, but OS data are immature

Intent-to-treat population.
Median OS was not reached; results did not cross the prespecified stopping boundary.
Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.; Usmani SZ, et al. *Blood.* 2016;128: Abstract 1151.; Bahlis NJ, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8025.

Already we are starting to see evidence of an OS benefit emerging.

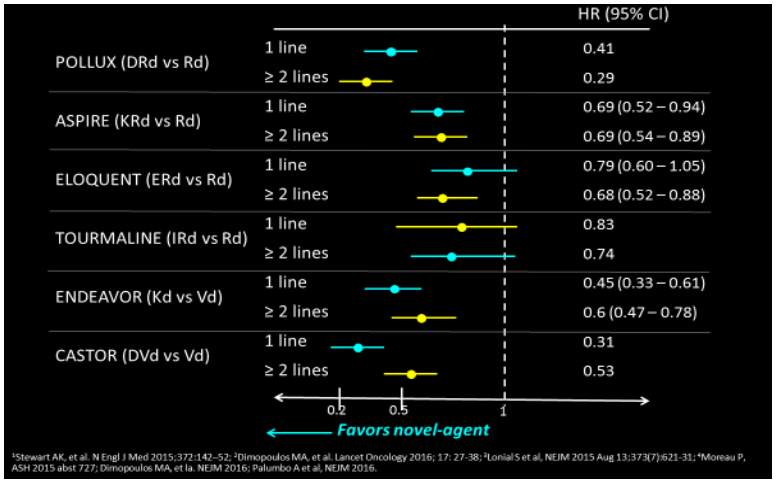
What Would Your Preferred Regimen Be at Relapse?

- **According to previous lines of therapy**
- If the patient has refractoriness to PIs or IMiDs?
- If the patient has high-risk cytogenetics?
- If the patient is elderly?



With these very impressive data, how would we think about which would be the preferred regimen to use when patients relapse? There are a number of factors to think about, and we will start with the first, which I would suggest to you, according to the patient's previous lines of therapy. It is very important to remember in myeloma that – unlike epithelial cancers where, if a class of drug fails a patient, revisiting that particular class is unlikely to be beneficial – the opposite is true in myeloma. Different classes of drugs can be revisited even if the patients have been exposed to them previously. The important point is that we have different agents within these respective classes that can be rationally used. Most importantly, we can also rationally develop combinations that can overcome resistance and restore response that is durable, particularly if continuous therapy is employed.

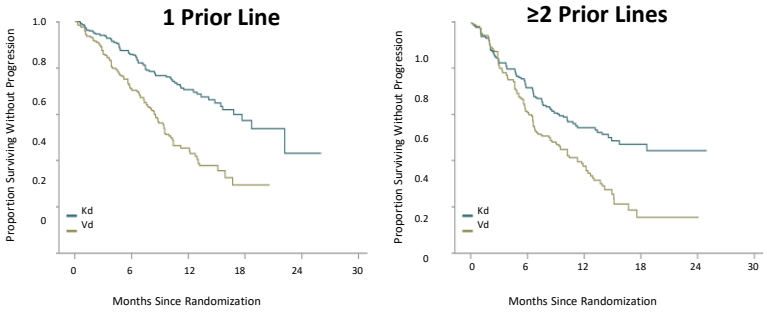
Prior Lines of Therapy



Courtesy of Prof J San Miguel.

With that in mind, let us think about this in the context of the trials I have just shown you. If you look at prior lines of therapy, you can see that for the POLLUX study, ASPIRE, ELOQUENT, TOURMALINE, ENDEAVOR and indeed CASTOR, all of these studies favored novel agent combinations in the triplet setting compared to the doublet, regardless of the number of lines of therapy. Particularly striking are the data from the POLLUX trial, and also in the CASTOR study. Although I will say for the CASTOR study, it is striking that the triplet was far superior in first relapse compared to second relapse, but a function of this may also reflect the designs of the study and the fact that the Vd control arm was given for a relatively fixed duration. That being said, in all of these studies, clinical benefit is seen regardless of number of prior lines. But it is fair to say, in general, that using these agents in earlier relapse did appear to confer greater benefit than in later relapse, as illustrated by these Forest plots.

ENDEAVOR: PFS by Prior Lines of Therapy Intent-to-Treat Population (N = 929)

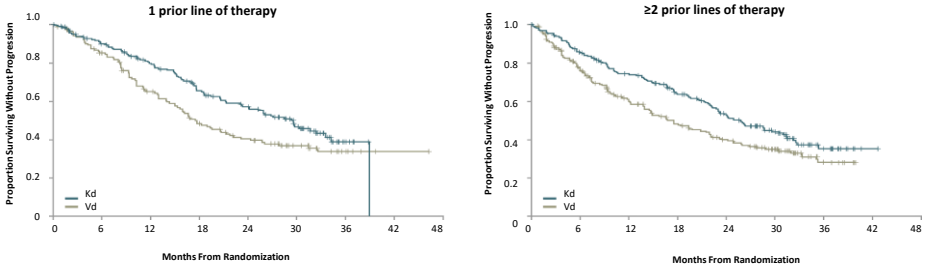


	Kd n = 232	Vd n = 232		Kd n = 232	Vd n = 233
Median PFS, months	22.2	10.1	Median PFS, months	14.9	8.4
Hazard ratio (95% CI)	0.447 (0.330–0.606)		Hazard ratio (95% CI)	0.604 (0.466–0.783)	
P value (1-sided)	<.0001		*P* value (1-sided)	<.0001	

Moreau P, et al. *Leukemia.* 2017;3(1)1:115-122.

If one looks at the ENDEAVOR study, PFS by prior lines of therapy with intent to treat, again you can see differences in favor of the doublet of Kd over Vd, both for one and two prior lines. The median PFS is impressive in both settings, but it has to be said: in first relapse, the differences again appear to be more potent, with a better hazard ratio for one prior versus two. That being said, I think it is always important to remember that these are guidelines as opposed to hard and fast rules, and the important point is that we have choices as we select these particular regimens. Two of the most important aspects of selection are tolerability and toxicity; so that is worth emphasizing.

ASPIRE: PFS by Prior Lines of Therapy



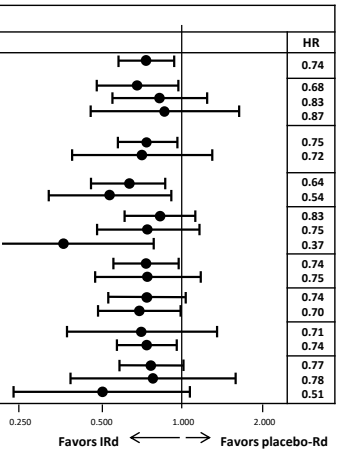
	KRd n = 184	Rd n = 157		KRd n = 212	Rd n = 239
PFS, median months	29.6	17.6	PFS, median months	25.8	16.7
Hazard ratio (95% CI)	0.69 (0.52–0.94)		Hazard ratio (95% CI)	0.69 (0.54–0.89)	
P value (one-sided)	.008		*P* value (one-sided)	.002	

Dimopoulos MA, et al. *Blood Cancer J.* 2017;7(4):e554.

Suffice to say when one looks at carfilzomib in the form of the ASPIRE study combined with lenalidomide and dexamethasone, the same basic principle appears to apply, with impressive PFS advantages seen in both settings.

TOURMALINE MM1: IRd vs Rd PFS in Different Patient Subgroups

			N	Median PFS, Months			
Variable	Subgroup	Placebo-Rd	IRd	Placebo-Rd	IRd		HR
All patients	ALL	362	360	14.7	20.6		0.74
Age (yrs)	≤65	176	168	14.1	20.6		0.68
	>65-75	125	145	17.6	17.5		0.83
	>75	61	47	13.1	18.5		0.87
ISS stage (stratification factor)	I or II	318	314	15.7	21.4		0.75
	III	44	46	10.1	18.4		0.72
Cytogenetic risk	Standard-risk	216	199	15.6	20.6		0.64
	High-risk	62	75	9.7	21.4		0.54
Number of prior therapies	1	217	224	15.9	20.6		0.83
	2	111	97	14.1	17.5		0.75
	3	34	39	10.2	NE		0.37
Proteasome inhibitor	Exposed	253	250	13.6	18.4		0.74
	Naive	109	110	15.7	NE		0.75
Prior IMiD therapy	Exposed	204	193	17.5	NE		0.74
	Naïve	158	167	13.6	20.6		0.70
Refractory to last prior therapy	Yes	55	59	NE	NE		0.71
	No	307	301	14.1	20.6		0.74
Relapsed or refractory	Relapsed	280	276	15.6	18.7		0.77
	Refractory	40	42	13.0	NE		0.78
	Ref & rel	42	41	13.1	NE		0.51

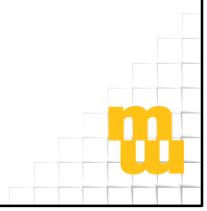


Moreau P, et al. *N Engl J Med.* 2016;374(17):1621-1634.

Interestingly enough, we see the same positive with the TOURMALINE studies in favor of IRd versus Rd, which again is impressive.

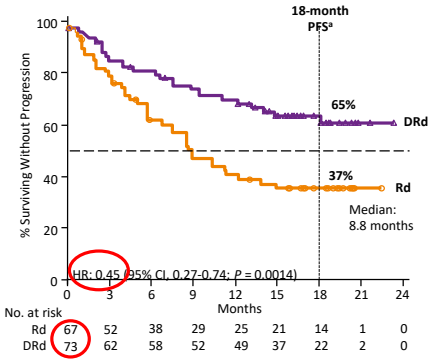
What Would Your Preferred Regimen Be at Relapse?

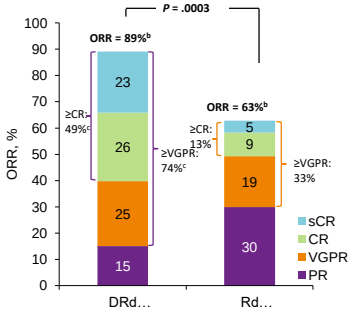
- According to previous lines of therapy
- **If the patient has refractoriness to PIs or IMiDs?**
- If the patient has high-risk cytogenetics?
- If the patient is elderly?



What preferred regimen would be used at relapse in the context of not just previous lines of therapy, but refractoriness to prior exposure to proteasome inhibitors or IMiDs?

POLLUX: Refractory to Last Line of Therapy 1 to 3 Prior Lines



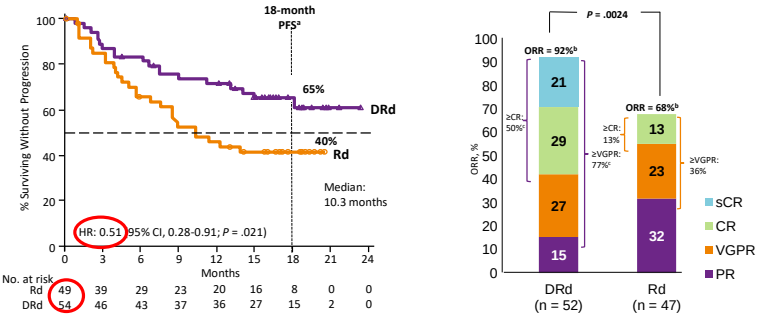


DRd treatment benefit observed in patients refractory to last line of therapy

[a]Kaplan-Meier estimate
[b]Response-evaluable population
[c]*P*<.0001 for DRd vs Rd
Moreau P, et al. *Blood.* 2016;128: Abstract 489.

If we look at the POLLUX study, which is the combination of DRd compared to Rd control, you can see here that DRd treatment benefit was clearly observed in patients refractory to their last line of therapy. That it is an important observation and quite striking.

POLLUX: Bortezomib-Refractory in 1 to 3 Prior Lines

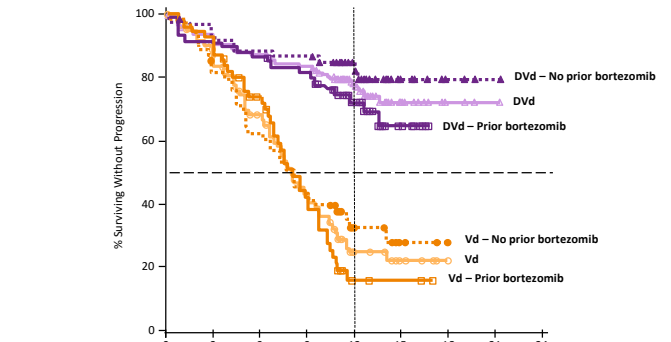


DRd significantly improves outcomes irrespective of bortezomib refractoriness

[a]Kaplan-Meier estimate
[b]Response-evaluable population
[c]*P*<.0001 for DRd vs Rd
Moreau P, et al. *Blood.* 2016;128: Abstract 489.

What is also very interesting is that DRd significantly improved outcome, irrespective of bortezomib refractoriness. In the nature of this study you could not be IMiD refractory for obvious reasons, because the Rd control arm would have to have to have equipoise compared to the triplet, but in this setting clearly if you are bortezomib refractory, this particular platform is particularly compelling.

CASTOR: PFS by Prior Bortezomib Exposure (1-Prior-Line Population)



No. at risk

Vd	113	91	69	43	11	5	0	0	0
DVd	122	109	104	99	59	19	3	1	0
Vd – No prior bortezomib	56	43	33	23	8	3	0	0	0
DVd – No prior bortezomib	60	54	52	51	30	10	3	1	0
Vd – Prior bortezomib	57	48	36	20	3	2	0	0	0
DVd – Prior bortezomib	62	55	52	48	29	9	0	0	0

Mateos M, et al. *Blood.* 2016;128: Abstract 1150.

If you look at the CASTOR study which compared Vd to DVd and looked at prior bortezomib exposure which was permitted (although refractoriness was not), you can see again striking clinical benefit. What is particularly important is in those patients who had no prior bortezomib, or if they had prior bortezomib there was a slight dip, but again, in terms of clinical benefit, the differences were very strikingly in favor of the triplet.

Three-Drug Regimens for RRMM After 1-3 Prior Lines

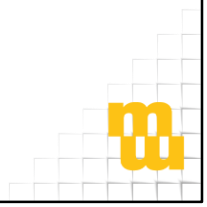
Based on previous exposure or refractoriness to bortezomib or lenalidomide (according to inclusion/exclusion criteria of respective studies)

		KRD	KD	Elo-RD	IRD	DRd	DVd	Pano-VD
Bortezomib	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	-	+	-	+	-	-
Lenalidomide	Exposure	+	+	+	+	+	+	+
	Refractoriness	-	+	-	-	-	+	+

When one looks across the trials more broadly and looks at the three-drug regimens for RRMM across one to three prior lines, and looks at this in the context of previous exposure or refractoriness to either bortezomib or lenalidomide according to the inclusion and exclusion criteria of the respective studies, some interesting points emerge. ERd and DRd (combined antibody approaches in patients refractory to bortezomib) are compelling. Conversely, those who were lenalidomide refractory were enriched in the carfilzomib studies: in particular, ENDEAVOR, and similarly enriched in the CASTOR trial. I think we can reasonably see that there are references there that could provide as guideposts to selecting different classes of drugs. Say, for example, you are refractory to bortezomib, an IMiD antibody approach would be very attractive. Conversely, if one is IMiD-refractory, the use of a proteasome inhibitor-based strategy next would make sense. Having said all of that though, it is important to note that if you are proteasome inhibitor resistant in one class, for example bortezomib, salvage with one in a different class like an epoxyketone (specifically carfilzomib) makes good sense.

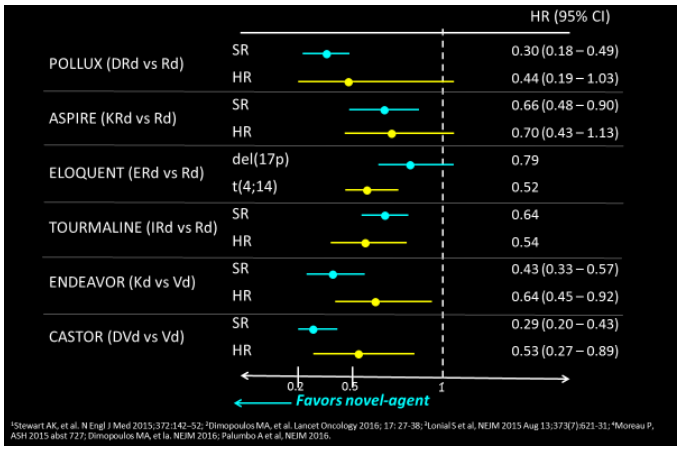
What Would Your Preferred Regimen Be at Relapse?

- According to previous lines of therapy
- If the patient has refractoriness to PIs or IMiDs?
- **If the patient has high-risk cytogenetics?**
- If the patient is elderly?



In that context, when we think about particular choices for patients, let us now focus on high-risk cytogenetics.

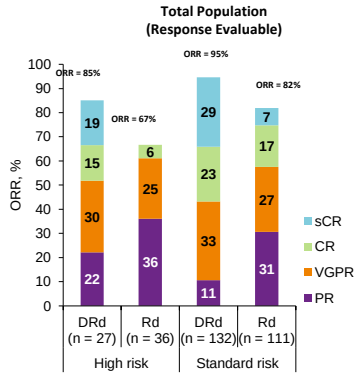
Cytogenetic Abnormalities

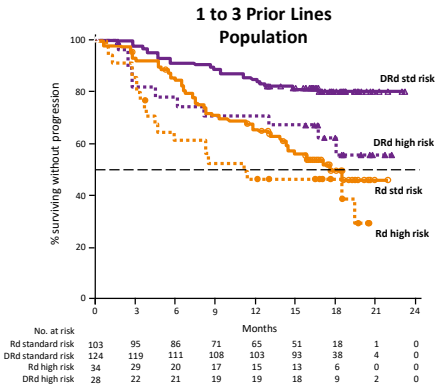


Courtesy of Prof J San Miguel.

Cytogenetic abnormalities are very importantly overcome in all of these triplets in favor of the novel agents, which I think is particularly important to share. If one has various high-risk strategies available, it is critically important to note that in these patients with high-risk disease, all of these triplets appear to have benefit. If one looks down this particular table (I am very grateful to my colleague Professor Jesus San Miguel for this slide), you can see that the triplets all are favorable for higher-risk but the order of magnitude of benefit for higher-risk does appear in a number of studies to be marginally less than it is for standard risk. This would fit with our understanding of the more aggressive and dangerous biology of high-risk disease as defined by deletion 17p, for example, or translocation (4;14).

POLLUX: Responses and PFS by Cytogenetic Status

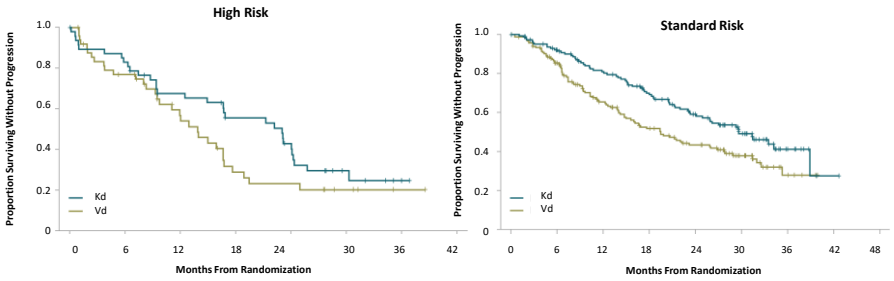




Moreau P, et al. *Blood.* 2016;128: Abstract 489.

But if we drill down in detail, some important lessons emerge. If you look at for example the POLLUX study (DRd vs Rd), you can see that for DRd in high-risk, the clinical benefit is striking, and this is clearly superior to the high-risk populations treated with Rd alone. This is also reflected by differences in response.

ASPIRE: KRd vs Rd
PFS by Cytogenetic Risk Status at Baseline



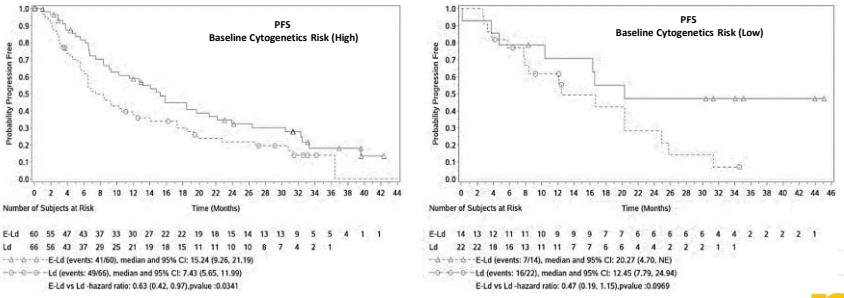
	KRd n = 48	Rd n = 52		KRd n = 147	Rd n = 170
PFS, median months	23.1	13.9	PFS, median months	29.6	19.5
Hazard ratio (95% CI)	0.703 (0.426–1.160)		Hazard ratio (95% CI)	0.656 (0.480–0.897)	
P value (1-sided)	.0829		*P* value (1-sided)	.0039	

Avet-Loiseau H, et al. *Blood.* 2016;128(9):1174–1180.

The same story is essentially true also of the ASPIRE study (KRd vs Rd), where standard-risk patients get substantial benefit, but similarly importantly, substantial benefit is also seen in the high-risk group.

ELOQUENT-2 (ERd vs Rd): PFS in del17p and t(4;14)

del(17p)+	0.70 (0.49–0.99) p=0.042	21.2 (16.6–27.5)	14.9 (10.6–18.5)
del(17p)–	0.73 (0.58–0.92) p=0.007	18.5 (15.8–22.8)	14.8 (11.7–18.4)
t(4;14)+	0.52 (0.29–0.93) p=0.027	15.8 (8.4–18.5)	5.6 (3.1–10.3)
t(4;14)–	0.74 (0.60–0.91) p=0.004	20.3 (17.3–23.3)	15.7 (13.0–18.5)



ERd improves the outcome of patients with high risk CA in comparison with Rd
High risk defined by: t(4;14) or t(14;16) or with del(17p) in ≥1% of PCs

Moreau P, et al. *Blood.* 2015;126: Abstract 727.

This also holds up in the ELOQUENT-2 study where the combination of ERd does impact favorably, particularly in deletion 17p patients and those with (4;14) translocation, where the differences appear to be really quite impressive in favor of the three drugs over the two.

TOURMALINE-MM1: Outcomes by Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, Months		
	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	IRd	Placebo-Rd	HR
All patients	78.3*	71.5	48.1*	39	11.7*	6.6	20.6	14.7	0.742*
Standard-risk patients	80	73	51	44	12	7	20.6	15.6	0.640*
All high-risk patients	79*	60	45*	21	12*	2	21.4	9.7	0.543
Patients with del(17p)†	72	48	39	15	11*	0	21.4	9.7	0.596
Patients with t(4;14) alone	89	76	53	28	14	4	18.5	12.0	0.645

**P*<.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n = 7).

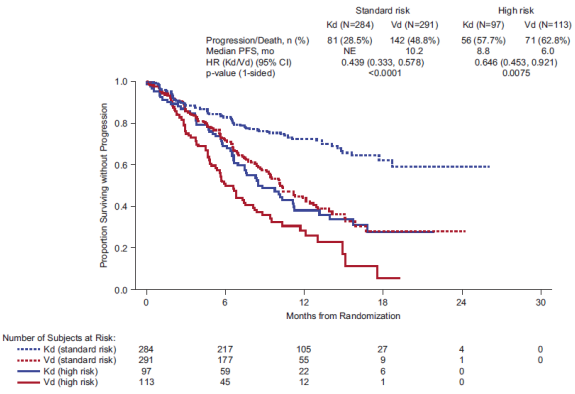
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics
- High risk was defined by t(4;14) or t(14;16) or del17p in ≥5% of PCs

Moreau P, et al. *Blood.* 2015;126: Abstract 727.

The ixazomib experience is worthy of emphasis. As you can see with this study, the use of IRd, particularly in deletion 17p-positive patients, results in almost a 10-month difference in favor of the triplet over the doublet. This is one of the largest orders of magnitude seen, and the hazard ratio reflects it. In this context, the median PFS in high-risk patients was indeed similar to that in the overall population, but high-risk defined as (4;14) (14;16) or deletion 17p in over 5% of plasma cells in the marrow, clearly in the 17p group, the biggest order of magnitude of difference was seen. This may reflect the ability to give ixazomib weekly for prolonged periods because of its favorable tolerability profile.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

Kd vs Vd: PFS by Cytogenetic Risk Status at Baseline (Kd is Not a Good Option for High-risk Cytogenetics)



High risk

High Risk	Kd n = 97	Vd n = 113
PFS, median months (95% CI)	8.8 (6.9–11.3)	6.0 (4.9–8.1)
HR (95% CI)	0.646 (0.453–0.921)	
P value	.0075	

Standard risk

Standard Risk	Kd n = 284	Vd n = 291
PFS, median months (95% CI)	NE (18.7–NE)	10.2 (9.3–12.2)
HR (95% CI)	0.439 (0.333–0.578)	
P value	<.0001	

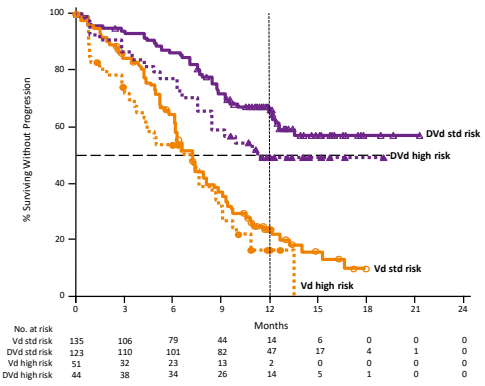
NE=not estimable

Chng WJ, et al. *Leukemia*. 2017;31(6):1368-1374.

I should also emphasize that high-risk cytogenetics were favorably impacted by the use of carfilzomib when compared to bortezomib, although both drugs clearly are active in the high-risk setting.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

CASTOR: PFS by Cytogenetic Risk



High risk[b]	DVd n = 44	Vd n = 51
Median PFS, mo	11.2	7.2
HR (95% CI)	0.49 (0.27-0.89)	
P value	.0167	
	n = 44	n = 47
ORR, %	82	62
P value	.039	

Standard risk	DVd n = 123	Vd n = 135
Median PFS, mo	NR	7.0
HR (95% CI)	0.29 (0.20-0.43)	
P value	<.0001	
	n = 118	n = 131
ORR, %	85	64
P value	.0003	

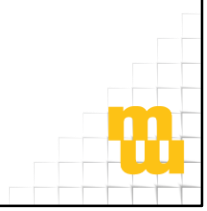
NR=not reached
[a]ITT/Biomarker risk-evaluable analysis set
[b]Central NGS. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities

Mateos M, et al. *Blood.* 2016;128: Abstract 1150.

Finally, in the CASTOR study (DVd vs Vd), the same essential story emerges, that daratumumab further improves high-risk outcome.

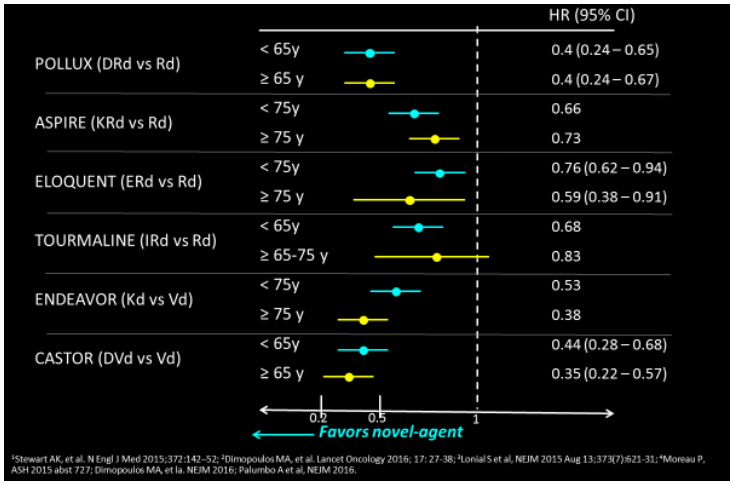
What Would Your Preferred Regimen Be at Relapse?

- According to previous lines of therapy
- If the patient has refractoriness to PIs or IMiDs?
- If the patient has high-risk cytogenetics?
- **If the patient is elderly?**



Let us close this section by discussing the use of these agents in the elderly population. Describing people as elderly is a changing landscape at the moment, given the improvement in the overall health of folks as they get older and "older" becomes a very relative term; but in those patients who may be older or frail, regardless of their biological age, this may be important to consider and let us quickly move through this.

Impact of Age on Treatment Strategy



Courtesy of Prof J San Miguel.

Specifically, if you look at the impact of age on treatment strategy, again it is the same good news; the novel agent combinations clearly perform well in patients under the age of 75 and over the age of 75 (or under the age of 65 or over the age of 65 to 75, depending on the particular criteria used in the various studies).

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

ENDEAVOR: Kd vs Vd by Age

Table. Efficacy outcomes and grade ≥3 adverse events of interest

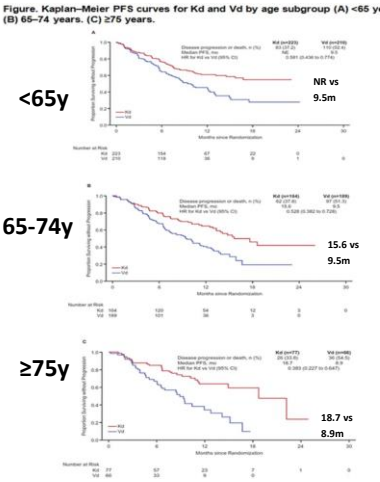
Outcome	<65 years		65–74 years		≥75 years	
	Kd (n=223)	Vd (n=210)	Kd (n=164)	Vd (n=189)	Kd (n=77)	Vd (n=66)
Median PFS, months	NE	9.5	15.6	9.5	18.7	8.9
HR for Kd vs Vd (95% CI)	0.58 (0.44–0.77)		0.53 (0.38–0.73)		0.38 (0.23–0.65)	
Best overall response, n (%)						
Complete response or better	35 (16)	16 (8)	19 (12)	11(6)	4 (5)	2 (3)
Very good partial response or better	118 (53)	64 (30)	88 (54)	54 (29)	46 (60)	15 (23)
ORR, % (95% CI)	74 (68–80)	61 (54–68)	77 (70–84)	66 (58–72)	84 (74–92)	59 (46–71)
Median DOR, months	NE	11.1	NE	10.3	21.3	10.2
Select grade ≥3 AEs of interest, n (%)[a]						
Hypertension[b]	20 (9)	6 (3)	12 (7)	4 (2)	9 (12)	2 (3)
Dyspnea[b]	8 (4)	3 (1)	11 (7)	6 (3)	6 (8)	1 (2)
Cardiac failure[b]	2 (1)	1 (1)	5 (3)	1 (1)	3 (4)	1 (2)
Renal failure[b]	3 (1)	0	3 (2)	2 (1)	1 (1)	0
Treatment discontinuations due to an AE, n (%)[a]	37 (17)	31 (15)	35 (21)	41 (22)	20 (26)	23 (35)

[a]In the <65 year subgroup, 223 (Kd) and 208 (Vd) patients were evaluable for safety; in the 65–74 year subgroup, 163 (Kd) and 183 (Vd) patients were evaluable for safety; in the ≥75 year subgroup, 77 (Kd) and 65 (Vd) patients were evaluable for safety.

[b]Preferred term

AE, adverse event; CI, confidence interval; DOR, duration of response; HR, hazard ratio; Kd, carfilzomib and dexamethasone; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

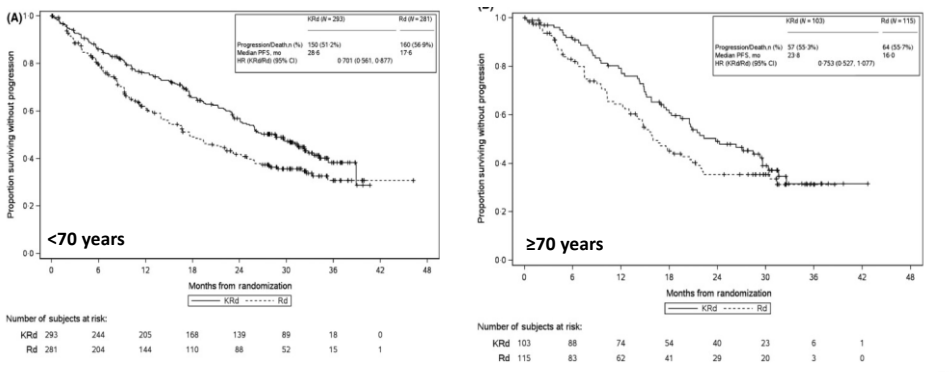
Figure. Kaplan–Meier PFS curves for Kd and Vd by age subgroup (A) <65 years. (B) 65–74 years. (C) ≥75 years.



Ludwig H, et al. *Leuk Lymphoma.* 2017 Mar 17. [Epub ahead of print].

In terms of the ENDEAVOR study, it is important to note clinical benefit was seen in older patients; but one has to be a little careful here because there is a well-recognized cardiovascular toxicity to carfilzomib-based therapy (believed to be based on endothelial toxicity) that has a number of manifestations including hypertension, shortness of breath, cardiac failure, and renal failure. Moreover, there is also a higher risk of thromboembolism. Putting that all together, one has to approach this with some caution in older patients.

ASPIRE: KRd vs Rd by Age



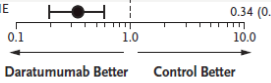
Dimpoulos MA, et al. *Br J Haematol.* 2017;177(3):404-413.

Nonetheless, in those patients deemed fit enough to tolerate carfilzomib-based therapy, clinical benefit is also seen in older patients in the ENDEAVOR trial and also in ASPIRE.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

CASTOR: PFS Subgroup Analysis

Subgroup	Control Group (no. of progression or death events/total no.)	Daratumumab Group (no. of progression or death events/total no.)	Control Group (median progression-free survival (mo))	Daratumumab Group (median progression-free survival (mo))	Hazard Ratio (95% CI)
Age					
<65 yr	59/125	39/132	7.3	10.3	0.44 (0.28–0.68)
≥65 yr	63/122	28/119	6.7	NE	0.35 (0.22–0.57)
≥75 yr*	–	–	**8.1**	**NE**	**0.27 (0.12–0.61)**
Sex					
Male	80/147	38/137	6.3	NE	0.41 (0.27–0.61)
Female	42/100	29/114	7.6	NE	0.38 (0.22–0.64)
ISS disease staging					
I	36/96	15/98	8.4	NE	0.25 (0.13–0.48)
II	55/100	26/94	6.2	NE	0.37 (0.23–0.61)
III	31/51	26/59	5.3	8.6	0.55 (0.31–0.98)
No. of previous lines of therapy					
1	51/113	20/122	7.5	NE	0.31 (0.18–0.52)
2	37/74	22/70	6.5	10.3	0.50 (0.28–0.89)
3	17/32	16/37	6.6	8.8	0.66 (0.31–1.41)
>3	17/28	9/22	5.4	8.4	0.48 (0.20–1.16)
Previous autologous stem-cell transplantation					
Yes	74/149	42/156	6.7	NE	0.38 (0.26–0.57)
No	48/98	25/95	7.2	NE	0.34 (0.19–0.59)



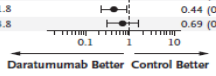
*Mateos MV, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8033.; Palumbo A, et al. *N Engl J Med.* 2016;375(8):754-766.

As we move forward and look at other populations and other studies, we can see that in the CASTOR study the same story holds up.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

POLLUX: PFS Subgroup Analysis

Subgroup	Daratumumab Group no. of progression events or deaths/total no.	Control Group no. of progression events or deaths/total no.	Daratumumab Group median progression-free survival (mo)	Control Group median progression-free survival (mo)	Hazard Ratio (95% CI)
Age					
<65 yr	24/133	55/140	NE	18.4	0.40 (0.24–0.65)
65–74 yr	26/124	43/108	NE	NE	0.40 (0.24–0.67)
≥75 yr	3/29	18/35	NE	11.4	0.11 (0.02–0.51)
ISS disease stage					
I	18/137	40/140	NE	18.4	0.40 (0.23–0.72) *
II	21/93	45/86	NE	11.7	0.29 (0.17–0.50)
III	14/56	31/57	NE	8.8	0.40 (0.21–0.76)
No. of previous lines of therapy					
1	27/149	55/146	NE	18.4	0.41 (0.26–0.66)
2	16/85	39/80	NE	11.9	0.29 (0.16–0.53)
3	7/38	14/38	NE	NE	0.36 (0.13–1.03)
>3	3/14	8/19	NE	NE	0.53 (0.10–2.87)
Previous lenalidomide					
Yes	10/50	20/50	NE	NE	0.42 (0.19–0.90)
No	43/236	96/233	NE	18.4	0.36 (0.25–0.52)
Previous proteasome inhibitor					
Yes	48/245	103/242	NE	18.4	0.37 (0.26–0.52)
No	5/41	13/41	NE	NE	0.35 (0.12–1.00)
Refractory to proteasome inhibitor					
Yes	19/64	28/60	NE	12.2	0.50 (0.27–0.93)
No	29/181	75/182	NE	18.4	0.27 (0.17–0.43)
Refractory to last line of therapy					
Yes	23/80	40/76	NE	10.3	0.47 (0.27–0.80)
No	30/206	76/207	NE	18.4	0.32 (0.20–0.49)
Type of multiple myeloma					
IgG	16/151	50/158	NE	18.4	0.30 (0.17–0.52)
IgA	13/49	26/51	NE	11.8	0.44 (0.22–0.89)
Serum free light chain only	13/39	15/33	NE	13.8	0.69 (0.30–1.57)

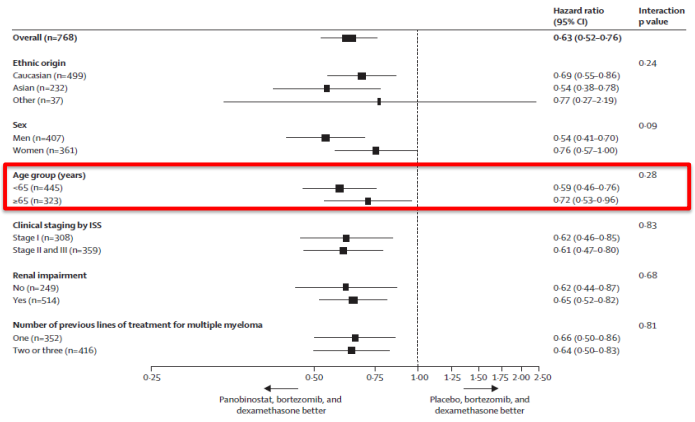


*Data updated at ASCO 2017:
HR 0.19 (0.06-0.55); *P* = .00007

Mateos MV, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8033.
Dimopoulos MA, et al. *N Engl J Med.* 2016;375(14):1319-1331.

The use of these drugs in the older population is also effective similarly in the POLLUX trial .

PANORAMA 1: Panobinostat + Bort + Dex vs Bort + Dex



San-Miguel JF, et al. *Lancet Oncol.* 2014;15(11):1195-1206.

And very interestingly similarly in the panobinostat, bortezomib, and dexamethasone study where we clearly show that this is active in patients over the age of 65 as well as under the age of 65. Now in the context of the panobinostat, bortezomib, and dexamethasone population, it is very important to note that the PFS gain for this particular combination was particularly striking in those patients who had had prior bortezomib and lenalidomide. I would make a point of emphasis here because I think that is critical. In fact, what we saw for the overall population was a PFS gain of approximately 4-1/2 months. When we looked at the bortezomib and IMiD-exposed population, we showed that this PFS benefit improved to 7-1/2 months. Therefore, this is a very important observation from this trial, and as this drug combination continues to be refined and developed to improve tolerability, I do see a clinical benefit from panobinostat in combination being a mainstay of RRMM management; in particular as we move forward with next-generation histone deacetylase inhibitors that have the promise of being more potent and potentially less toxic.

Options for 2nd+ Relapse

Comparison of Pom-Dex Trials (and Combinations)

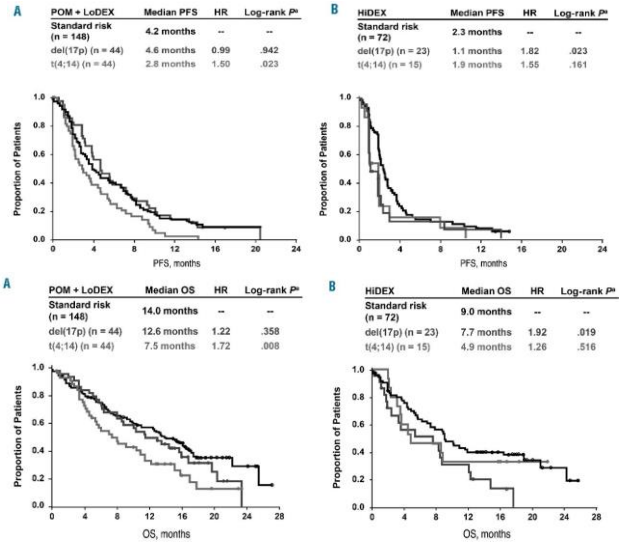
	MM-003[1]	STRATUS (MM-010)[2]	Pom-Dex vs Pom-Cyclo-Dex[3]		Pom-Btz-Dex[4]
Treatment	PD	PD	PD	PCD	PVD
n	302	682	36	34	47
Population	Failed Bort & Len & refr to last line		At least 2 prior lines & Len-refractory		1-4 prior lines & Len-refractory
ORR, %	31	32.6	39	65	85
≥VGPR, %			14	12	45
PFS, months	4.0	4.6	4.4	9.5	10.7
OS, months	13.1[5]	11.9	16.8	NR	94*

*EFS at 12 months

[1]San Miguel J, et al. *Lancet Oncol.* 2013;14(11):1055-1066. [2]Dimopoulos MA, et al. *Blood.* 2016;128(4):497-503. [3]Baz RC, et al. *Blood.* 2016;127(21):2561-2568. [4]Lacy MQ, et al. *Blood.* 2014;124: Abstract 304. [5]Dimopoulos MA, et al. *Haematologica.* 2015;100(10):1327-1333.

Now let us close in the next few minutes in the setting of currently available studies and data derived from them, looking at pomalidomide- and dexamethasone-based combinations. This has been a very important advance. These are options for patients in second relapse and beyond, by virtue of the currently FDA-approved label. As you can see, the data for this are derived from a number of trials; the MM-003 study in Europe and, very importantly, the 002 trial which was actually the study that led to FDA approval in the US. Further validation from the STRATUS study (the so-called MM-010 trial) and then in this particular slide, I also showcase work with pomalidomide, cyclophosphamide and dexamethasone as well as with bortezomib, and dexamethasone, to illustrate the point that these combinations are both well-tolerated and very active with a very consistent signal.

MM-003/Pom-Dex in High-Risk Cytogenetic Patients: PFS and OS



Dimopoulos MA, et al. *Haematologica.* 2015;100(10):1327-1333.

This also applies in the high-risk setting as well, and there is evidence of survival benefit potentially emerging in favor of those patients with high-risk features, such as deletion 17.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

Other Pom/dex Combinations

	POM + Vd[1]	K + POMdex[2]	Ixa + POMdex[3]	Dara + POMdex[4]	Isa+ POMdex[5]	MOR202+ POMdex[6]
Regimen	POM 1–4 mg PO D1–14 + BORT 1 mg/m² IV or 1.3 mg/m² IV or SC C1-8: D1,4,8,11; C9+: D1,8 + LoDex 20 mg (>75 y: 10 mg) C1-8: D1,2,4,5,8,9,11,12; C9+: D1,2,8,9 (n = 34)†	Carfilzomib 20/27/36 mg/m² D1,2,15,16 + POM 3 or 4 mg/day D1–21 + Dex QW 40 mg C1–4 (20 mg C5–8) (n = 46)‡ The same combination but K weekly (n = 57)	Ixazomib 3 or 4 mg D1,8,15 + POM 4 mg/day D1–21 + Dex 40 mg D1,8,15,22 (>75 y: 20 mg) (All, n = 32; Ixa 4 mg, n = 25)	Daratumumab 16 mg/kg C1–2 QW; C3–6 Q2W; C7–13 or until PD Q4W + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 98)	Isatuximab 10 mg/Kg IV C1 QW; Q2W thereafter + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 14)	MOR202 at dose of 4, 8, 16 mg/kg QW + POM 4 mg/day D1–21 + Dex 40 mg (>75 y: 20 mg) (n = 11)
Study phase	I	I/II	I/II	I	I/II	I/II
Prior lines of therapy, n	1–4		1–5 including PI and Len	≥2 (2–13)	4.5 (2-11)	3
Refractory to Len, n (%)	All patients were Len-refractory	40 (87)/41(72)	32 (100); 25 (100)	87 (89)	15(75)	11(100)
Refractory to PI, n (%)	All pts were PI-exposed (but not refractory)	NR	20 (63); 15 (60)*	74 (76)	-	-
ORR, %	65	64/64	44	71	64	56
Median (range) DOR	7.4 (4.4–9.6) months	NR	56 (28-160) months	NR	4 months	-
Median PFS, months	NR	12.9/9.2	NR	6-m rate = 66%	-	-

[1]Richardson P, et al. *Haematologica.* 2016;101(s1): Abstract P653. [2]Rosenbaum CA, et al. *Blood.* 2015;126: Abstract 8007. [3]Krishnan AY, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 8008. [4]Chari A, et al. *Blood.* 2015;126: Abstract 508. [5]Richardson PG, et al. *Blood.* 2016;128: Abstract 2123. [6]Raab M, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 8024.

Pomalidomide and dexamethasone is an excellent dance partner with other drugs. Our own work with pomalidomide and bortezomib and dexamethasone (PVd), in a classical setting in those patients who are very refractory and aggressive in terms of the disease characteristics, is summarized on the left. We saw a very solid 65% response rate, and this has provided the platform for the OPTIMISMM trial which has been recently completed and which will hopefully establish the basis of pomalidomide, bortezomib and dexamethasone in early relapse. Similarly, carfilzomib combined with pomalidomide and dexamethasone, as well as ixazomib combined with pomalidomide and dexamethasone, can be very active in the setting (ixazomib, pomalidomide and dexamethasone is particularly well-tolerated and has promise). And last but not least, the combination of pomalidomide and dexamethasone with either daratumumab or isatuximab (or even a very preliminary fashion with a small number of patients in MOR202 studies, which is another CD38-targeting antibody in development) have shown real promise in the setting. It is important to emphasize that daratumumab plus pomalidomide and dexamethasone is now FDA-approved, and this I think is a particularly powerful and promising combination going forward.

ASCO/ASH 2016 – 2017

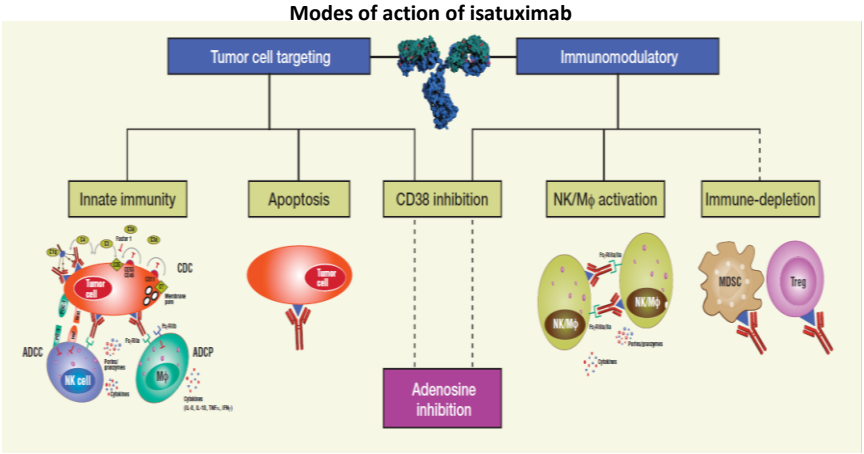
RRMM – Selected Highlights/Targets

- CD38, BCMA
- t(11,14), BCL2
- Others

I want to finish in the last few minutes by giving you some highlights of ASH and ASCO 2016 through into 2017, recognizing that the 2017 ASH meeting December 8-12 will provide very important updates to all the data I have shown you. I want to focus briefly on CD38-targeting, BCMA-targeting, targeting of 11;14 and BCL-2 in particular, as well as other strategies.

ASH 2016 – CD38: Isatuximab-Pomalidomide-Dexamethasone: Introduction

Modes of action of isatuximab



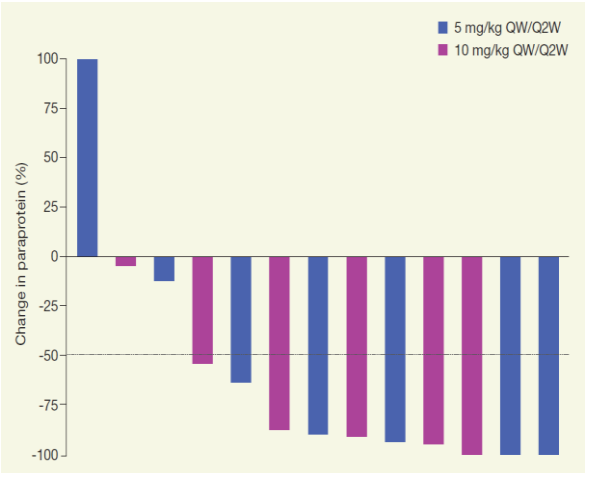
ADCC/CP=antibody-dependent cellular cytotoxicity/phagocytosis; CDC=complement-dependent cytotoxicity; Mϕ=macrophage; MDSC=myeloid-derived suppressor cell; NK=natural killer cell
Richardson PG, et al. ASH 2016.

The development of isatuximab in combination with pomalidomide and dexamethasone is showing promise, particularly as there may be qualitative differences between this antibody in the CD38 space.

Results: Paraprotein Reduction

Reductions in paraprotein levels were recorded in the majority of patients

Waterfall plot of best percentage change in paraprotein levels

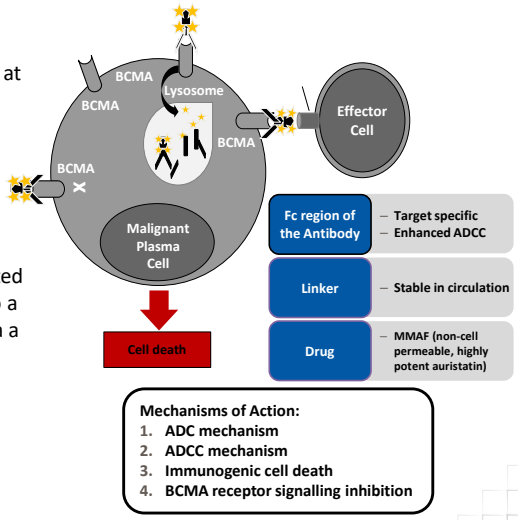


Post-baseline paraprotein data were not available for one patient in the 5 mg/kg cohort
QW=weekly; Q2W=once every 2 weeks
Richardson PG, et al. ASH 2016.

Results with this combination have been very promising and phase 3 studies are now under way to further validate this observation.

Targeting BCMA GSK2857916: Background[1]

- BCMA expression is restricted to B cells at later stages of differentiation and is requisite for the survival of long lived plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- GSK2857916 is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to a microtubule disrupting agent MMAF via a stable, protease resistant maleimidocaproyl linker
  - Preclinical studies demonstrate its selective and potent activity[2]



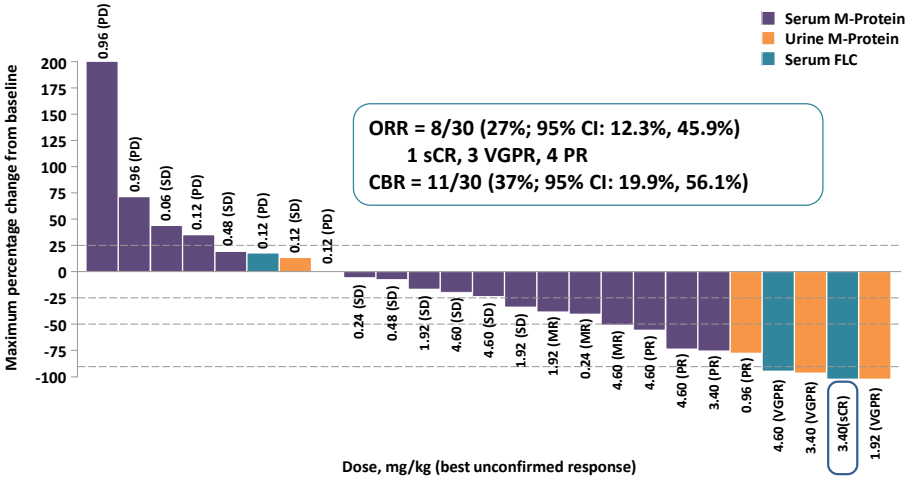
Mechanisms of Action:
1. **ADC mechanism**
2. **ADCC mechanism**
3. **Immunogenic cell death**
4. **BCMA receptor signalling inhibition**

ADC=antibody-drug conjugate; ADCC=antibody-dependent cell-mediated cytotoxicity; BCMA=B-cell maturation antigen; Fc=Fragment crystallizable; IgG=immunoglobulin G; MMAF=monomethyl auristatin-F

[1]Cohen A, et al. ASH 2016 Annual Meeting. Abstract 1148. [2] Tai YT, et al. *Blood*. 2014;123(20):3128-3138.

In the same spirit, the targeting of BCMA has shown great excitement. One representative study, led by my colleague Dr. Adam Cohen, has shown that as a single agent, targeting BCMA has been very promising with an antibody conjugated to a toxin.

Maximum % Change in M-Protein or Free Light Chain



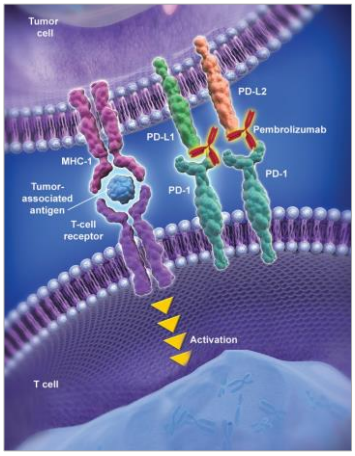
CBR=clinical benefit rate; CI=confidence interval; FLC=free light chain; M-protein=myeloma protein; MR=minimal response; ORR=overall response rate; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response

[1]Cohen A, et al. ASH 2016 Annual Meeting. Abstract 1148.

And single agent activity has been seen at the maximum tolerated dose (MTD) in approximately two-thirds of patients.

Pembrolizumab and the PD-1 Pathway

- The PD-1 pathway is often exploited by tumors to evade immune surveillance[1-3]
- Role of PD-1 inhibitors in MM[1-2]
- Pembrolizumab blocks interaction between PD-1 and PD-L1/PD-L2 [4-6]
- Rationale for the combination of IMiDs and PD-L1 blockade[7]
  - Lenalidomide reduces PD-L1 and PD-1 expression on MM cells and T- and myeloid-derived suppressor cells
  - Lenalidomide enhances checkpoint blockade-induced effector cytokine production in MM bone marrow and induced cytotoxicity against MM cells

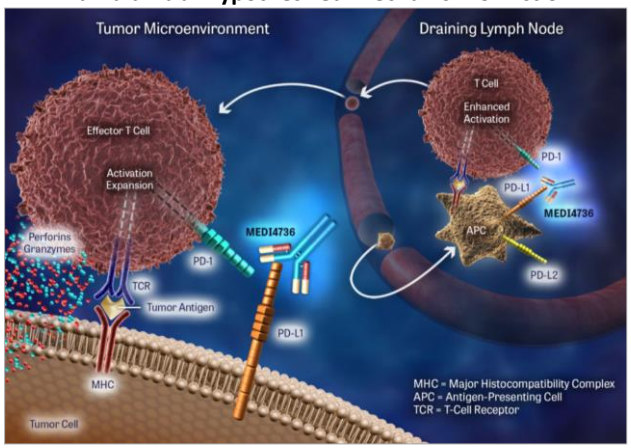


[1]Liu J, et al. *Blood*. 2007;110:296-304. [2]Tamura H, et al. *Leukemia*. 2013;27:464-472. [3]Paiva B, et al. *Leukemia*. 2015;29:2110-21103. [4]Keir ME, et al. *Annu Rev Immunol*. 2008;26:677-704. [5]Hallett WH, et al. *Biol Blood Marrow Transplant*. 2011;17:1133-1145. [6]Homet Moreno B, Ribas A. *Br J Cancer*. 2015;112:1421-1427. [7]Görgün G, et al. *Clin Cancer Res*. 2015;21:4607-4618.

Obviously, there was great excitement around checkpoint inhibition. I think what one has to say is recent toxicity data with a combination of pembrolizumab with immunomodulating therapy has injected a great deal of caution in the field now, recognizing that further safety information is necessary before we can move forward.

ASH 2016: Durvalumab in MM – Combos with DARA, POM, DEX

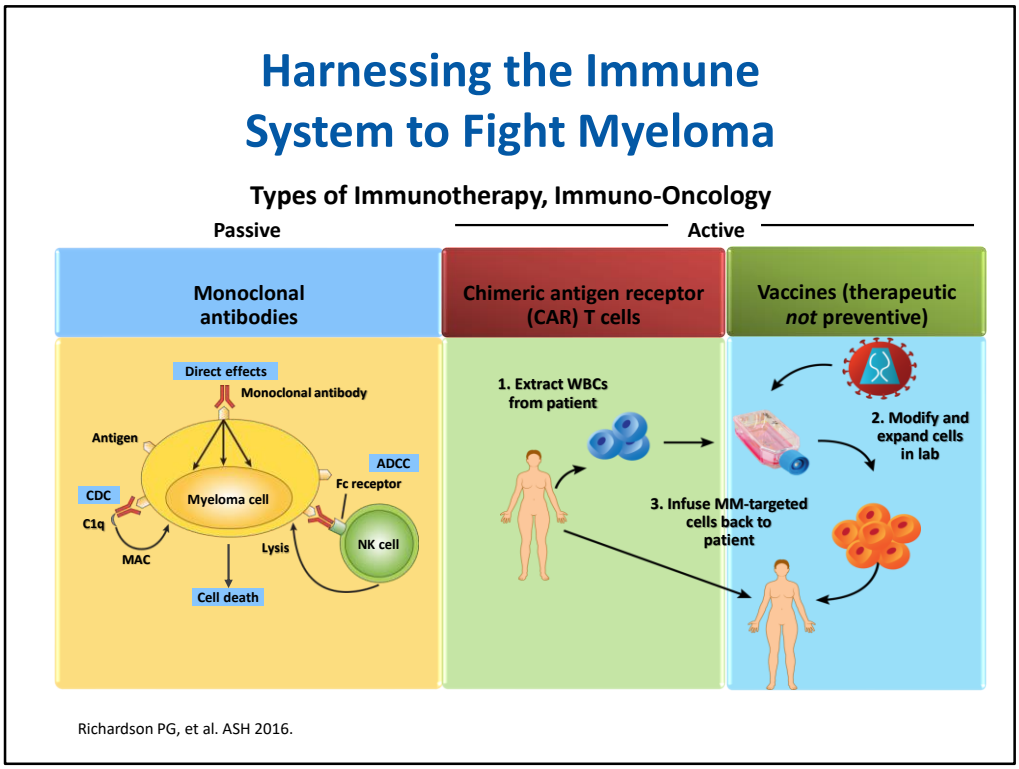
Durvalumab: Hypothesized Mechanism of Action



Reprinted from Ibrahim R et al. Semin Oncol. 2015;42(3):474-483, Copyright 2015.

Siegel DS, et al. *J Clin Oncol*. 2016; Abstract TPS8072.; Richardson PG, et al. ASH 2016, MMRF Symposium.

Having said that, the PD-L1 target as illustrated by work using durvalumab in combination with a variety of other agents has great promise. Hopefully once the safety issues have been properly addressed, the field can continue to advance exploring agents like durvalumab and nivolumab in this setting.



In the last few minutes, I want to conclude by focusing on chimeric antigen receptor T cell (CAR-T) work and also mention briefly the importance of vaccines (although this approach is probably best-suited in earlier disease). Certainly, however, as far as CAR-T cell technologies, these have been very exciting in this setting.

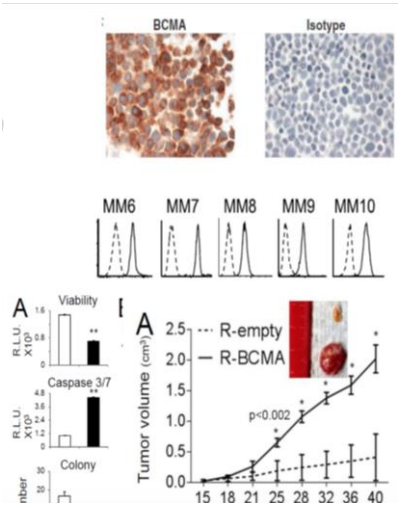
Myeloma CAR-T Cell Therapy
ASH 2016

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA
- Functional CAR-T cells can be generated from MM patients
- CAR-T and NK cells have in vitro and in vivo activity against MM
- Clinical trials underway
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - Optimal co-stimulatory domains
  - Optimal vector
  - Optimal dose and schedule
  - Need for chemotherapy
  - Perhaps 'cocktails' of multiple CARs or CARs + chemotherapy will be required for best outcomes

Based upon what we know so far, the best targets appear to be BCMA, SLAMF7, and CD38, with BCMA work leading the charge. What we've recognized is that functional CAR-T cells can be generated from myeloma patients, that CAR-T and NK cells have in vitro and in vivo activity against myeloma, and now clinical evidence supports that. A number of clinical trials are under way. We now see in the subset of patients prolonged responses. It is fair to say that robust efficacy data is not yet available, but it is certainly true that the efficacy results to date are very promising. Many questions remain about CAR-T design, including optimal costimulatory domains, optimal vectors, dose and schedule, the need for chemotherapy, and perhaps there will be cocktails for the future.

BCMA (TNFRSF17, CD269)

- Receptor for BAFF (Blys) and APRIL
- Expressed on plasma cells, some mature B cell subsets, and plasmacytoid DCs
  - Maintains plasma cell homeostasis
  - Not on other normal tissues
- Expressed consistently on myeloma cells
  - Varying intensity
- Promotes MM pathogenesis



Cohen A, et al. *Blood.* 2016;128: Abstract 1147.

Now one representative example of this is provided by the following study led by Dr. Adam Cohen at the University of Pennsylvania and his colleagues, and this targets BCMA.

Patient Characteristics – Cohort 1 (n=9)

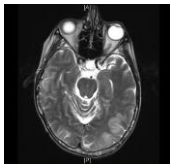
Characteristic	Median (range) or %
Age	57 (44 – 70)
Gender	67% male; 33% female
Isotype	IgG (33%), IgA (44%), LC (22%)
Prior lines of therapy	9 (4-11)
Lenalidomide	100% (refractory: 78%)
Bortezomib	100% (refr: 89%)
Pomalidomide	100% (refr: 89%)
Carfilzomib	100% (refr: 89%)
Autologous SCT	78%
Cyclophosphamide	100% (refr: 67%)
Daratumumab	44% (refr: 44%)
Anti-PD1	33% (refr: 33%)
High-risk genetics -17p or *TP53* mutation	100% 67%
Extramedullary dz	33%

Cohen A, et al. *Blood.* 2016;128: Abstract 1147.

In a small number of patients, nine patients,

Safety (n=9)

- Cytokine release syndrome in 8/9 (89%)
  - Grade 1 (n=1); Grade 2 (n=4); Grade 3 (n=2); Grade 4 (n=1)
  - 4/9 received tocilizumab
  - Median hospital stay = 9 days (range 3-40)
- Dose-limiting toxicity (pt. 03):
  - Grade 4 PRES (posterior reversible encephalopathy syndrome)
    - Recurrent seizures, obtundation
    - MRI brain: diffuse enhancement w/ swelling and sulcal effacement
    - Rapid peripheral CART expansion
    - Solumedrol 1 g/d x 3 → Cytoxan 1.5 g/m^2 day 17
    - Rapid improvement, resolution of MRI changes and neuro deficits



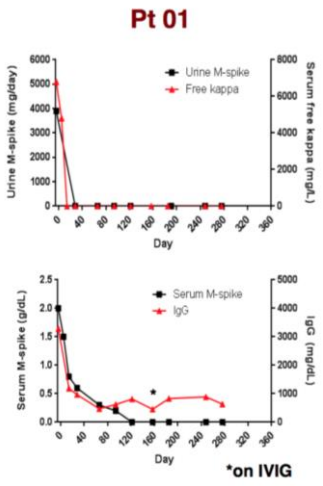
Cohen A, et al. *Blood.* 2016;128: Abstract 1147.

data reported in this highly refractory population showed manageable toxicities although they were significant, as summarized here.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

Clinical Responses

Pt	BM PC %	Cytogenetics	CART dose received (% of planned)	CRS grade	Time to 1st response (days)	Best Heme response	PFS (mos.)
01	70	+11 -17p -16q	2 x 10e8 (40%)	3 (toci)	14	sCR*	12+
02	60	+1q +4p -17p	5 x 10e8 (100%)	1	14	MR	2
03	95	+1q t(4;14) -16q	2 x 10e8 (40%)	3 (toci)	15	VGPR*	5
09	15	t(11;14)-16q -17p	5 x 10e8 (100%)	2	-	SD	2
10	95	+1q t(11;14)	1.8 x 10e8 (100%)	-	-	PD	0.5
11	80	+1q t(4;14) -17p	5 x 10e8 (100%)	2	25	MR	2.5
07	15	+1q, +11, -4, -14, -16	5 x 10e8 (100%)	2	14	uPR**	1.5
08	80	-1p +1q, -4 -17p	5 x 10e8 (100%)	4 (toci)	-	PD	0.5
15	90	+1q, t(11;14)	5 x 10e8 (100%)	2 (toci)	14	VGPR*	2+

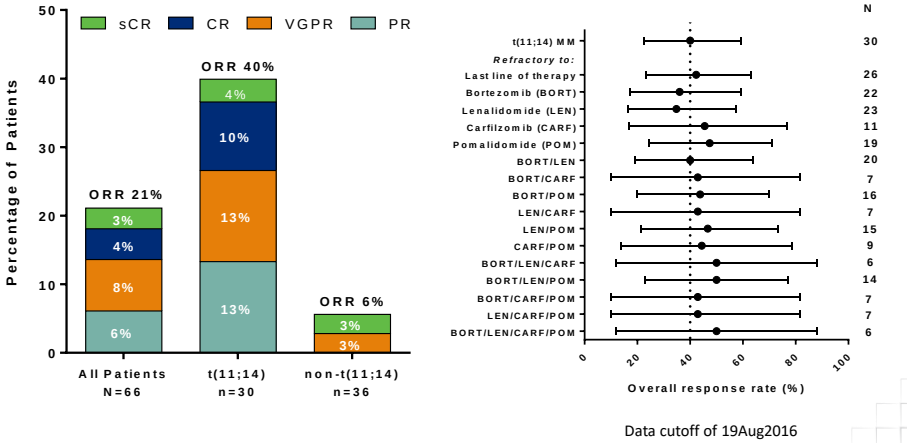


* No MM by flow
**Unconfirmed; 24 hour UPEP not repeated

Cohen A, et al. *Blood.* 2016;128: Abstract 1147.

But in those patients who were able to go through with the program, very encouraging early efficacy data was seen.

Venetoclax Monotherapy: Objective Response Rates in all Patients and by t(11;14) Status

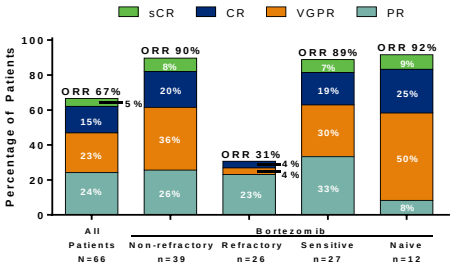


Data cutoff of 19Aug2016

Kumar S, et al. *Blood*. 2016;128: Abstract 488.

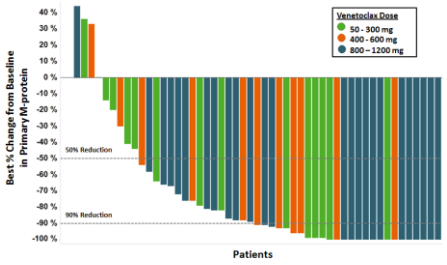
Now in the last couple of seconds, I want to focus on venetoclax very briefly as a very exciting advance in therapy targeting t(11;14) translocation of BCL-2. Work led by Shaji Kumar has shown high objective response rates in this population.

Venetoclax Combined with Bortezomib and Dexamethasone: Objective Responses and Best Percent Change in M-Protein Response by Dose



ORR=PR or better; numbers are based on evaluable patients per subgroups

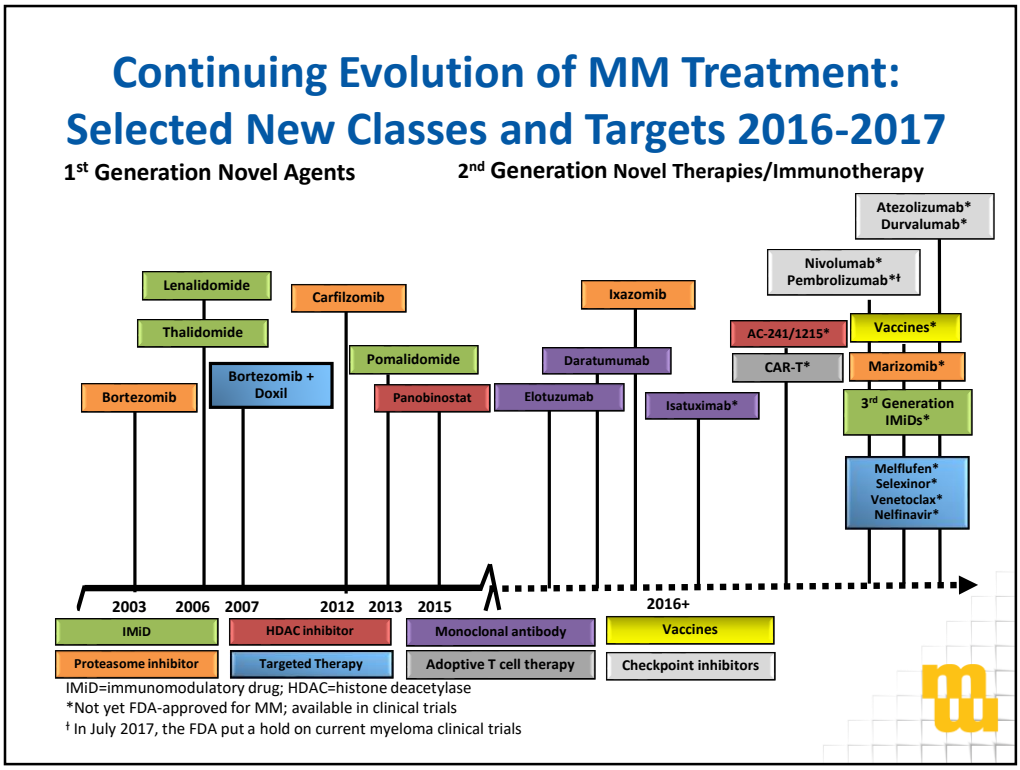
Data cutoff of 19Aug2016



Moreau P, et al. *Blood*. 2016;128: Abstract 975.

And Dr. Moreau and colleagues have shown that when you combine venetoclax with bortezomib, you see better objective responses, which is exciting and very promising. Moreover, the data around safety has been very promising as well.

The Evolving Standard of Care in Relapsed/Refractory Multiple Myeloma

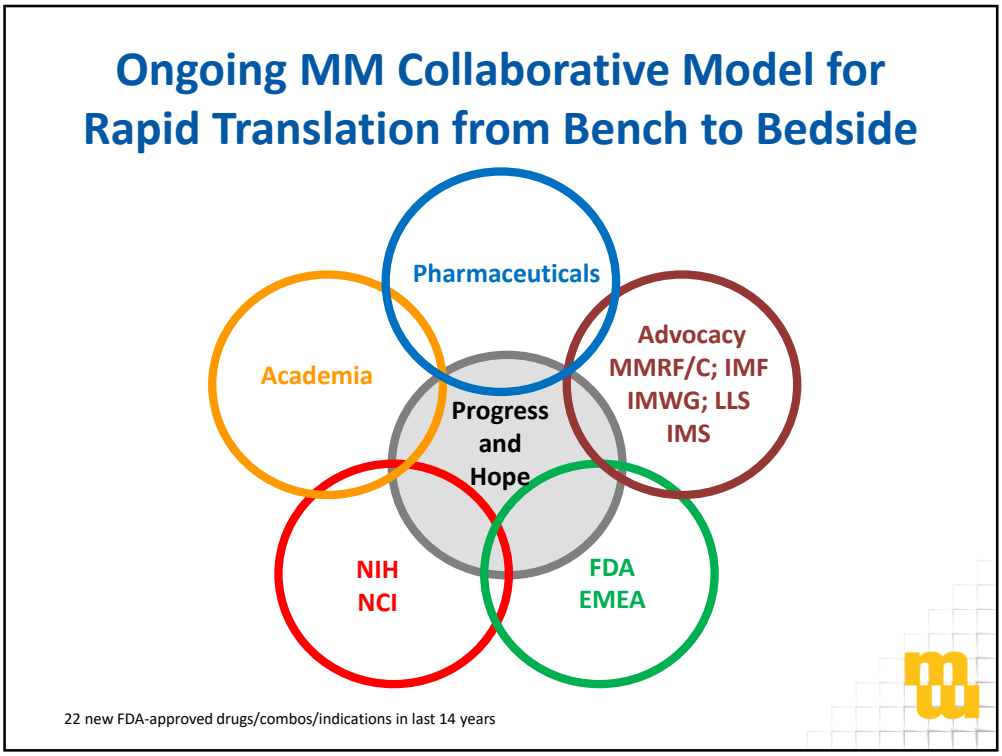


My last slide here is the continuing evolution of multiple myeloma treatment and selected new classes and targets through this last year, and what you can see is a whole host of them. They are all very promising and we are looking forward to a future that is characterized by yet further advances. In addition to what I mentioned about venetoclax, I do want to mention very promising data around selinexor. I also want to mention very promising data around a novel cytotoxic, melflufen. Finally, I want to close by mentioning excitement regarding a third-generation proteasome inhibitor called marizomib, as well as much more to come.

2016-2017: Integration and Impact of Novel Agents, Including Immune Therapies

- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS, OS
  - Recent approvals (eg, carfilzomib, ixazomib, HDACi, MoAbs) will augment this, with the next wave of therapies agnostic to mutational thrust
- Baseline immune function appears a key barrier to success and is targetable (eg, use of PD1/PDL1 blockade)
- MoAbs (Elo, DARA, ISA, MOR 202) active in high-risk disease, represent true new novel mechanisms, as well as other immuno-therapeutics (eg, checkpoint inhibitors, vaccines)
- Further refinement of prognostics and MRD will guide therapy

And with that in mind, I want to close by saying that as we think about the integration and impact of novel agents (including immunotherapies) in the RRMM setting, we have to recognize that these have produced wonderful improvements in PFS and OS, and recent approvals have augmented this. Baseline immune function appears a key barrier to success and we believe it is truly targetable. Monoclonal antibodies are really breakthroughs in this regard, and of course further refinements of prognostics and MRD testing and so forth will guide therapy.



With that in mind, I want to close by saying that the ongoing collaboration in myeloma research remains fundamental to successful progress and I especially want to acknowledge my co-investigators, pharma partners, our advocacy groups, and of course the partnership we enjoy with our regulators, for really an unprecedented period of progress over the last 14 years. Thank you very much for your kind attention.