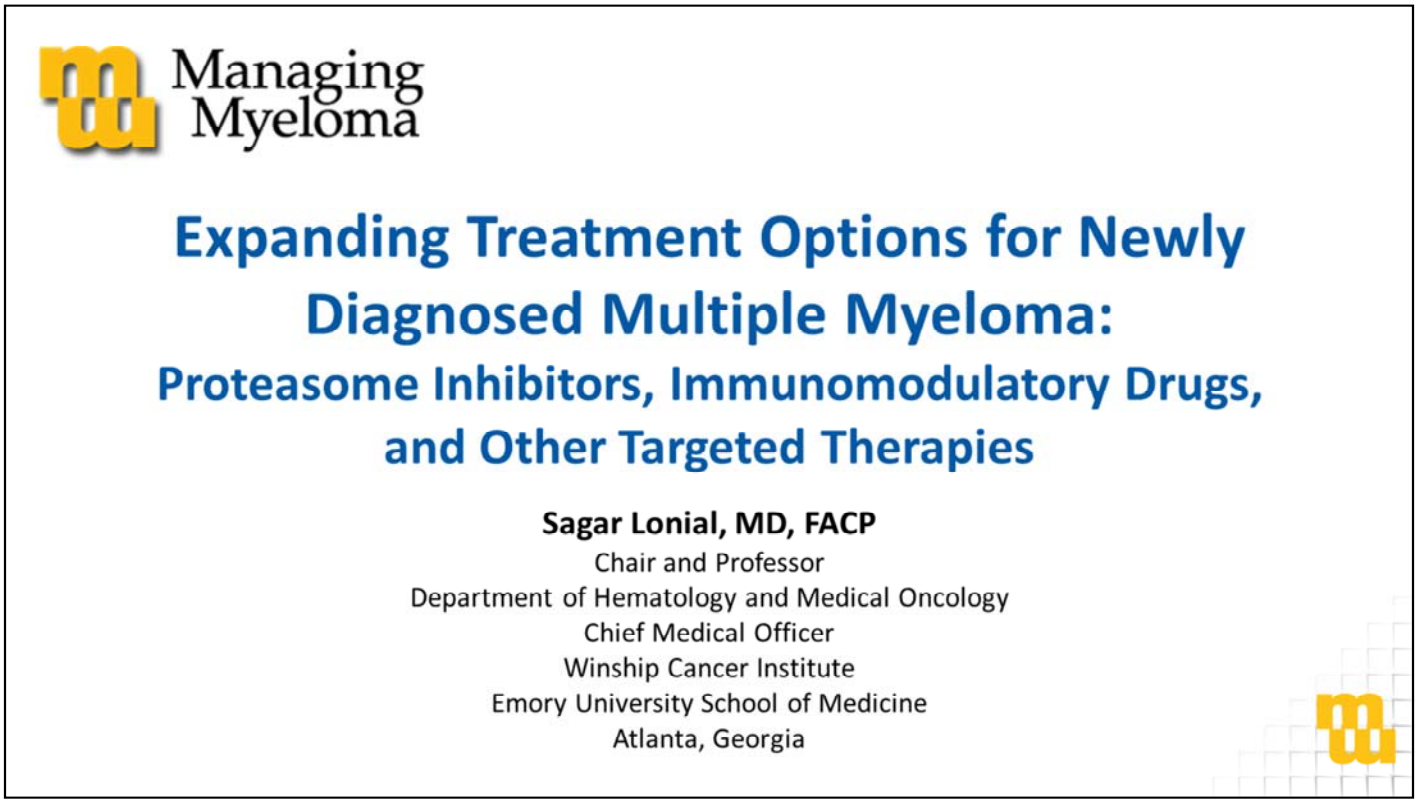
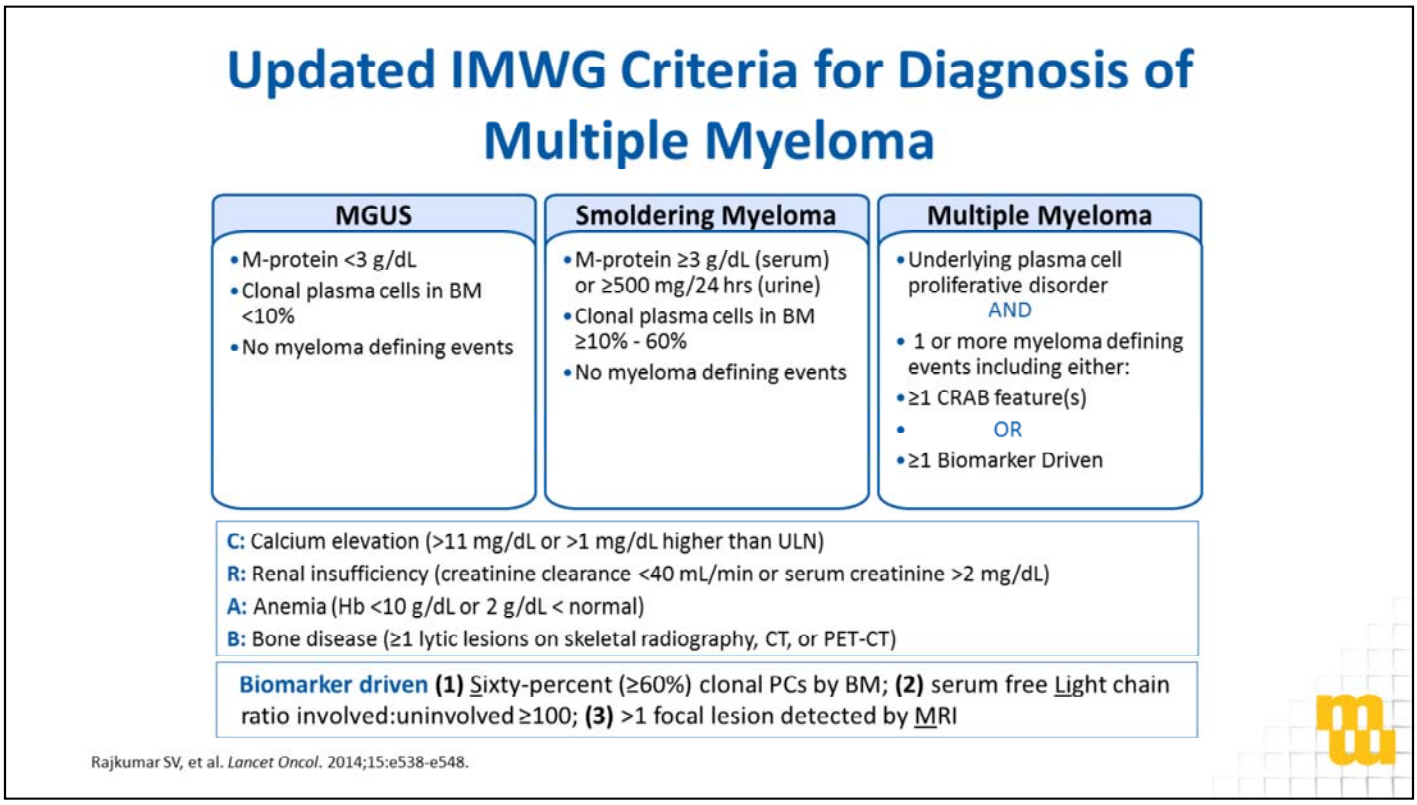
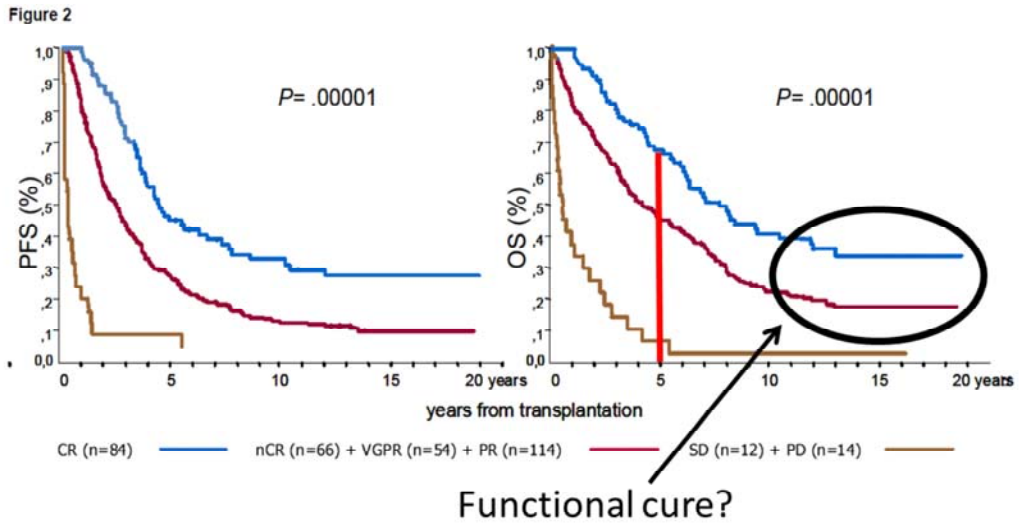


Welcome to *Managing Myeloma*. I am Dr. Sagar Lonial. In today's presentation, I will be discussing the treatment options for newly diagnosed multiple myeloma. I will specifically focus on the following topics: when to treat smoldering versus symptomatic myeloma, choice of induction regimen from the current standard of care to new options investigated in the clinical trial setting, and the role of high-dose therapy consolidation and maintenance therapy. Let's go ahead and begin.



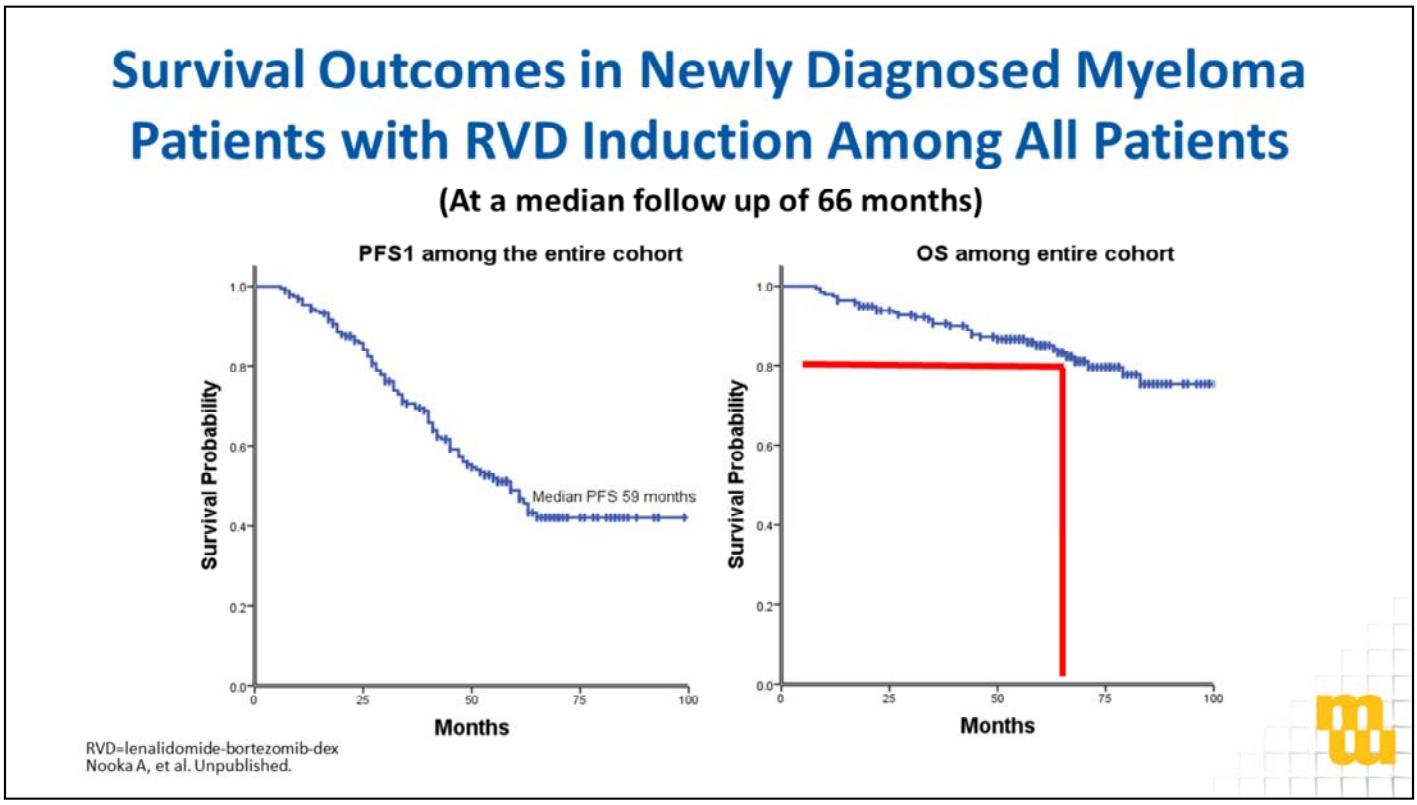
One of the first topics that I think is worth discussing is the importance of the updated IMWG criteria for the diagnosis of multiple myeloma. Historically, we have waited until symptomatic myeloma (as evidenced by the CRAB criteria: hypercalcemia, renal insufficiency, anemia, or bone disease) as a definition of when to initiate treatment. In the last two years, the International Myeloma Working Group created three different criteria – called the myeloma-defining criteria – that basically anticipate that patients with these side effects or symptoms will develop myeloma in a very rapid period of time. Therefore, there is not a reason or rationale to continue to watch them. These criteria include the biomarkers such as: greater than 60% plasma cells in the bone marrow, serum-free light chain ratio of greater than 100, and greater than one focal lesion by MRI. I think the important take-home message here is that imaging is really important for defining whether a patient is on observation or undergoes treatment. If you are going to subject a smoldering myeloma patient to observation, we should make sure that they have had aggressive imaging interventions – either with PET-CTs or MRIs – to make sure we are not missing early signs of bone disease. It is important to realize, however, that the standard of care for smoldering myeloma – even with the current definition where some of these patients have been moved into the symptomatic criteria – is observation or clinical trials. There is no current recommendation for early treatment of true smoldering myeloma.

PETHEMA Cure with Old Drugs

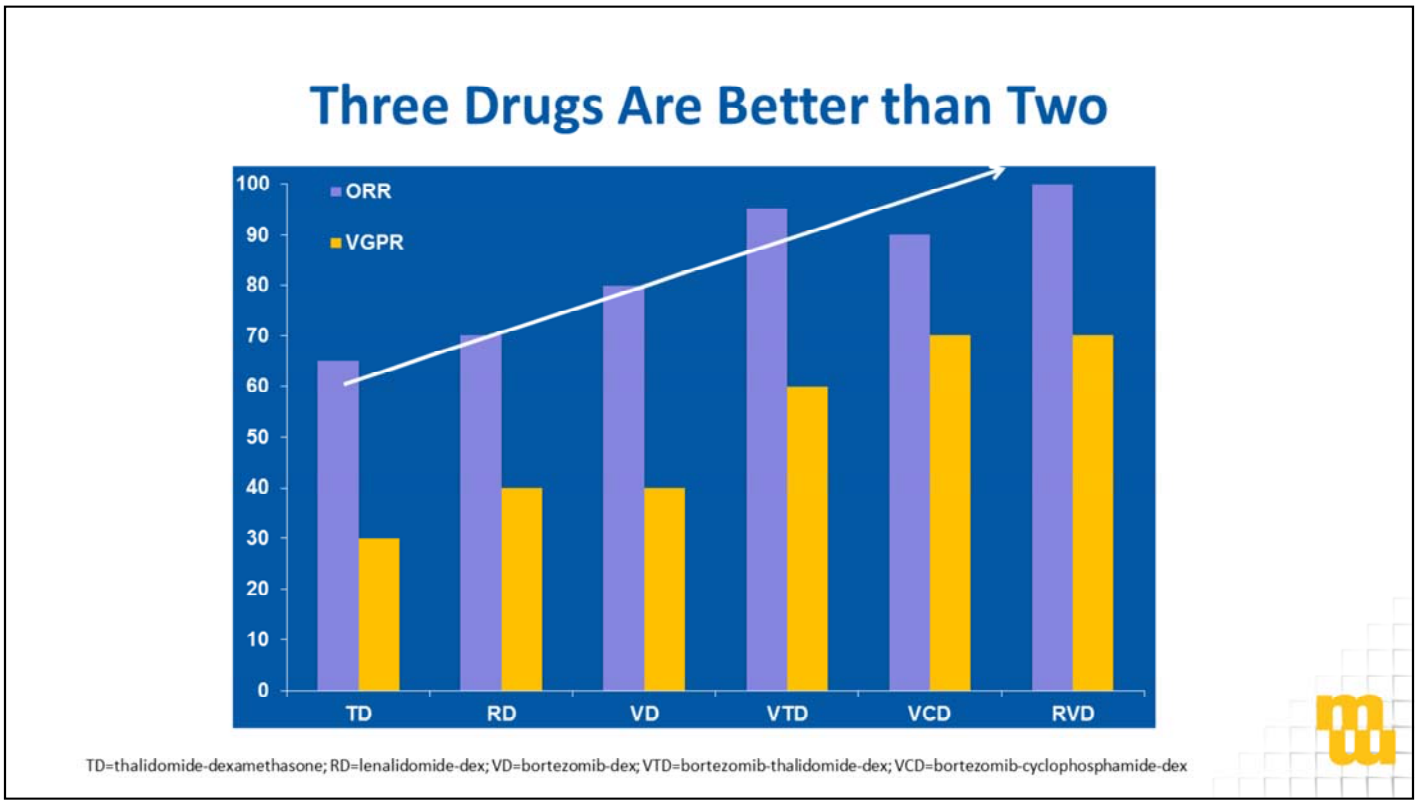


Martinez-Lopez J, et al. *Blood*. 2011;118(3)529-534.

I think it is also important to realize that with aggressive induction therapy, consolidation, maintenance, and using new drugs, there are subsets of patients that are, in fact, cured of myeloma. Currently, that percentage is probably 10% to 15%, maybe higher depending upon the age and the genetics of a given patient population. The idea that myeloma is an incurable disease, and that our goal is to gently treat this older frailer patient population, is not true for a significant fraction of myeloma patients. For this reason, I think having an aggressive treatment plan – even for patients well into their 70s but who have a good performance status – is critically important to offering patients the best options for long-term progression-free and overall survival.



As an example of this, I am showing you data from our group looking at a series of patients that all received RVD induction. As you can see, the median progression-free survival is right around 60 months, not dissimilar from the IFM study randomizing patients to early versus late transplant. The median overall survival is 80% at 5-year followup, suggesting again this is not the old-fashioned myeloma from a decade ago where the median survival was only 2 to 3 years. This is a very different disease where the median survival may be well over 10 years, particularly for good-risk subsets of patients.



When we think about induction therapy, there are number of principles that I think are important. The first is, clearly, more is better, as long as the "more" is well-tolerated. We know that in the induction therapy setting, the role of doublets has almost completely fallen away except for the truly frail, elderly patient. This was an example of that where we demonstrated that the use of three drugs (a proteosome inhibitor backbone with either an IMiD or alkylator) had a much higher overall response rate and a much higher VGPR or better rate when compared with using either lenalidomide or an IMiD in a doublet regimen.

Induction Regimens in MM

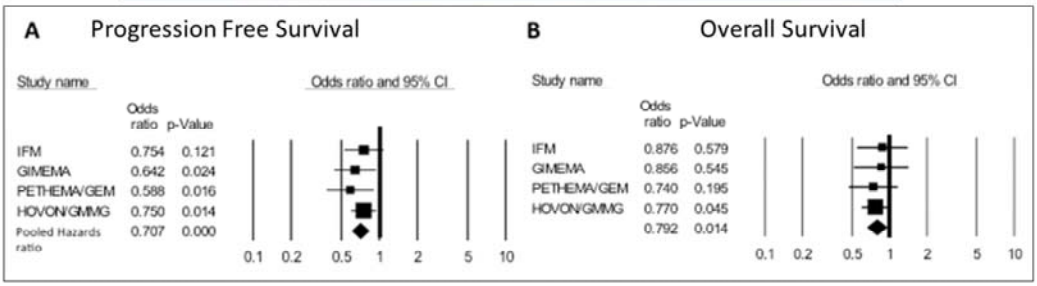
Original Article

Bortezomib-Containing Induction Regimens in Transplant-Eligible Myeloma Patients

A Meta-Analysis of Phase 3 Randomized Clinical Trials

Ajay K. Nooka, MD, MPH; Jonathan L. Kaufman, MD; Madhusmita Behera, PhD; Amelia Langston, MD; Edmund K. Waller, MD, PhD; Christopher R. Flowers, MD, MS; Charise Gleason, NP; Lawrence H. Boise, PhD; and Sagar Lonial, MD

BACKGROUND: The objective of this meta-analysis in patients with myeloma was to test the hypothesis that the addition of bortezomib to induction therapy not only improves the depth of response but also improves post-transplant progression-free survival (PFS) and overall survival (OS) outcomes. **METHODS:** Phase 3 trials that randomized newly diagnosed, transplant-eligible patients with myeloma to receive either a bortezomib-containing induction regimen (BCIR) or a nonbortezomib-containing induction regimen (NBCIR) were identified. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adapted for data synthesis, and comprehensive meta-analysis software was used to report pooled data as hazard ratios or odds ratios under a

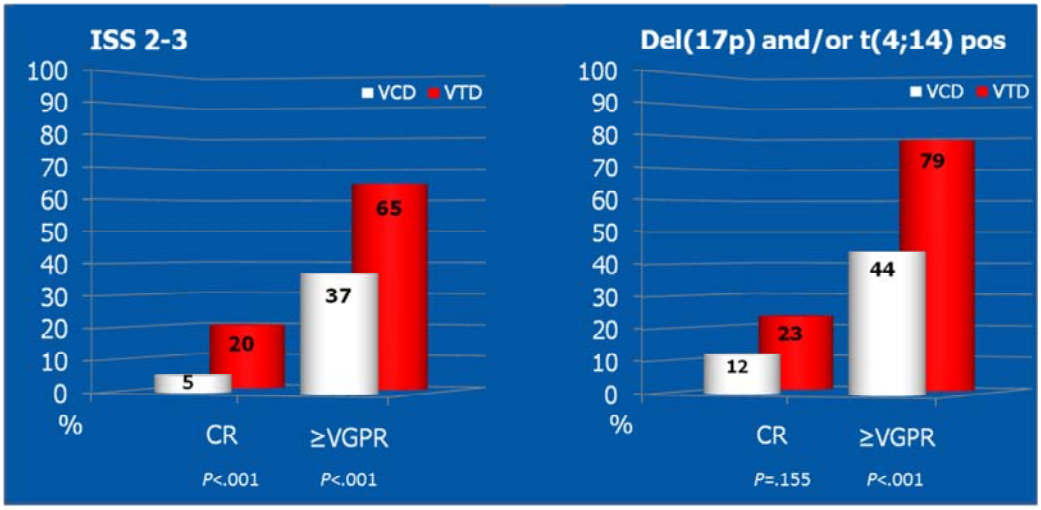


Nooka A, et al. *Cancer.* 2013;119(23):4119-4128.

We also know from a meta-analysis from Dr. Nooka and our group that patients who received bortezomib as part of their initial induction therapy have a better survival than patients who do not. This is critically important because it then begins to give us a backbone of induction therapy, which is the use of bortezomib-based induction therapy for patients across the board with newly diagnosed symptomatic myeloma.

CR and ≥ VGPR Rates in High-Risk Subgroups of Patients

Does it matter which 3 drugs are used?



Responses to both VTD and VCD were reassessed centrally.
Cavo M, et al. *Leukemia.* 2016.

Does it matter which three drugs are used? There has been a large controversy over the use of VCD (cyclophosphamide in combination with bortezomib and dexamethasone), versus bortezomib with an IMiD (either thalidomide in Europe or lenalidomide in the United States). What you can see from this retrospective analysis from the European Myeloma Group is that the response rate and VGPR or better rate for high-risk and standard-risk myeloma is higher for the IMiD and proteasome inhibitor combination moving forward.

Randomized Trial VTD vs VCD Shows Superiority of IMiD/PI

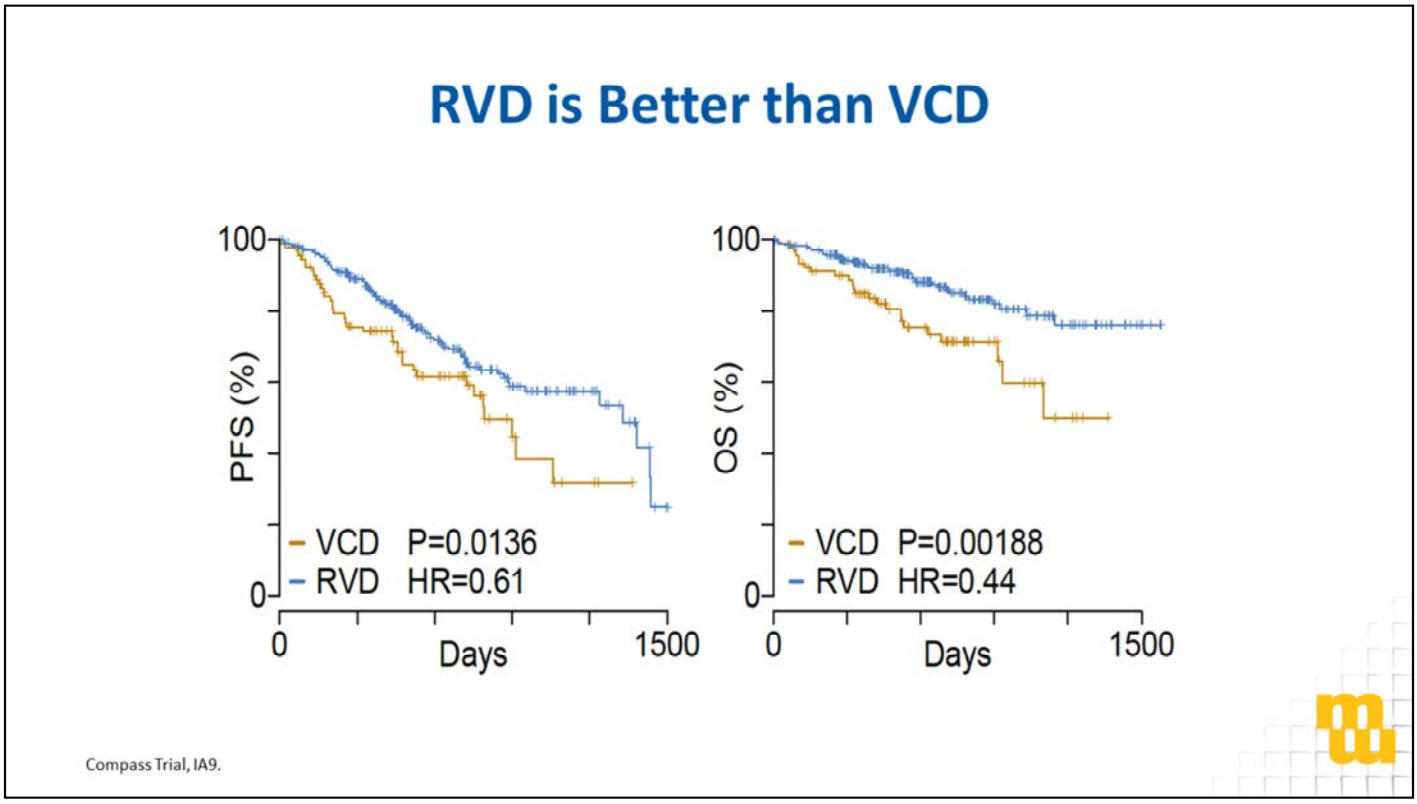
Response to Induction

	VTD (n = 169)	VCD (n = 169)	*P* value
Intent to treat			
≥CR	13.0%	8.9%	.22
≥VGPR	66.3%	56.2%	.05
≥PR	92.3%	83.4%	.01
Per protocol	n = 157	n = 154	
≥CR	14.0%	9.1%	.17
≥VGPR	70.7%	60.4%	.05
≥PR	98.7%	90.3%	.001

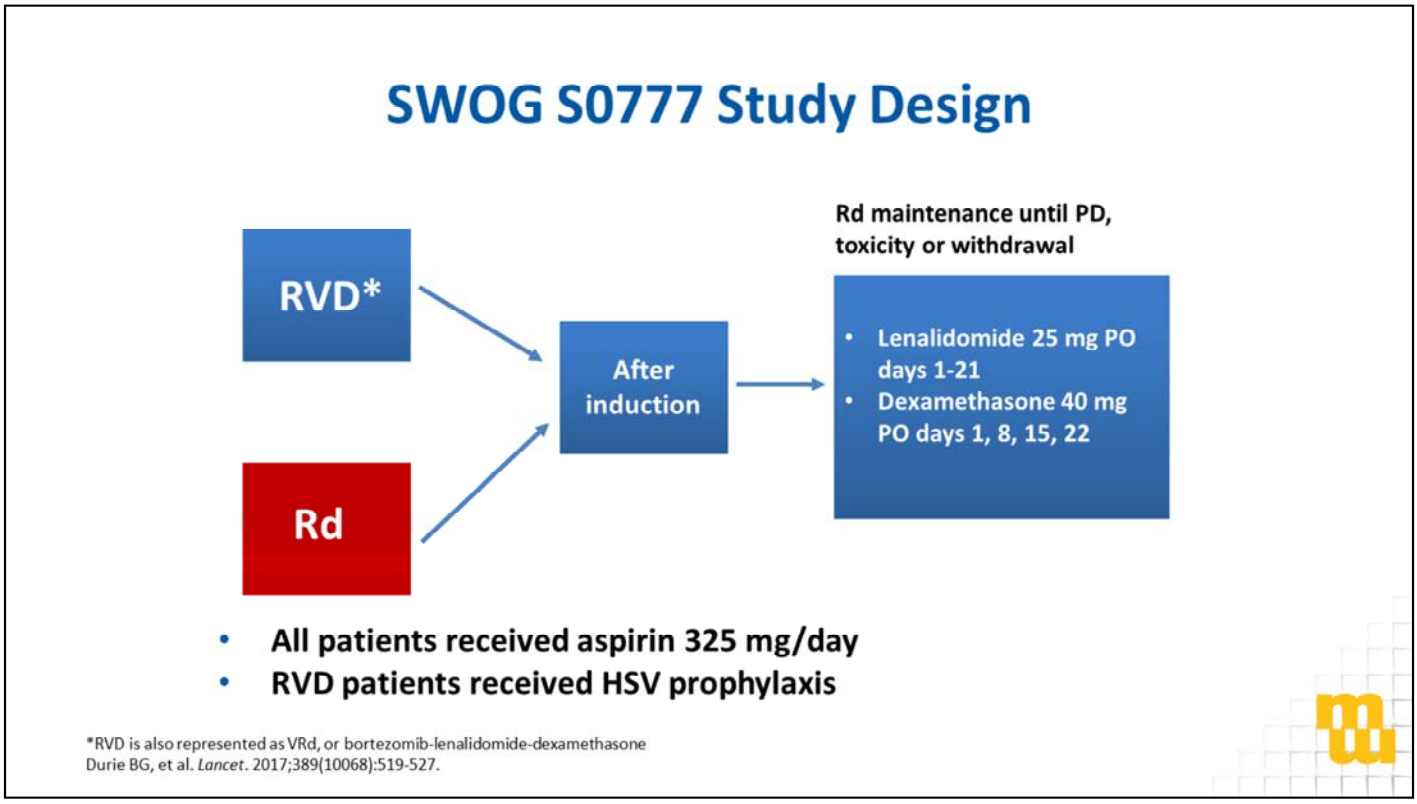
VCD is no longer a reasonable induction choice

Moreau P, et al. *Blood*. 2016;127(21):2569-2574.

Now, the French actually did a randomized trial trying to evaluate VTD versus VCD (the alkylator or the IMiD partner) for newly diagnosed symptomatic myeloma in patients receiving bortezomib. Their endpoint was VGPR or better after 4 cycles of therapy. What they nicely showed is that the VGPR or better rate was significantly higher for the IMiD and proteosome inhibitor combination. In our view, this suggests that VCD is no longer a good primary choice for patients with newly diagnosed symptomatic myeloma. A question that often comes up is, “What about for patients who present with renal failure?” I will tell you we have actually had very, very good success with VTD for patients who present with renal failure, as opposed to VCD. This avoids the alkylator, potentially minimizing the complications of DNA damage-induced complications of myeloma therapy.



In our group, we also went back and looked at the COMPASS trial, which is a 1000-patient newly diagnosed myeloma trial. We looked at just progression-free and overall survival for the IMiD and proteasome inhibitor combination of RVD versus VCD, cyclophosphamide with bortezomib and dexamethasone. What was demonstrated in this non-randomized trial (this is just a retrospective look at cohorts of patients) is that the progression-free survival and the overall survival is significantly better for patients who receive an IMiD and a proteasome inhibitor together. In my view, this data really sets up the trial that evaluates the use of an IMiD and proteasome inhibitor triplet versus just an IMiD and corticosteroids.



This was the SWOG trial, RVD versus Rd, trying to evaluate doublet versus triplet in the context of a randomized phase 3 trial.

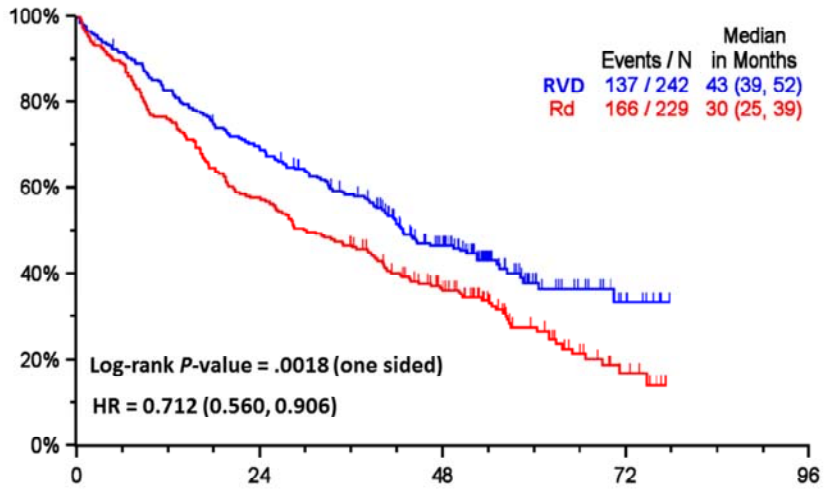
Confirmed Response: RVD vs Rd

	RVD	Rd
CR	15.7%	8.4%
VGPR	27.8%	23.4%
PR	38%	39.7%
ORR (PR or better)	81.5%	71.5%
SD	15.7%	24.3%
SD or better	97.2%	95.8%
PD or death	2.8%	4.2%

Durie BG, et al. *Lancet*. 2017;389(10068):519-527.

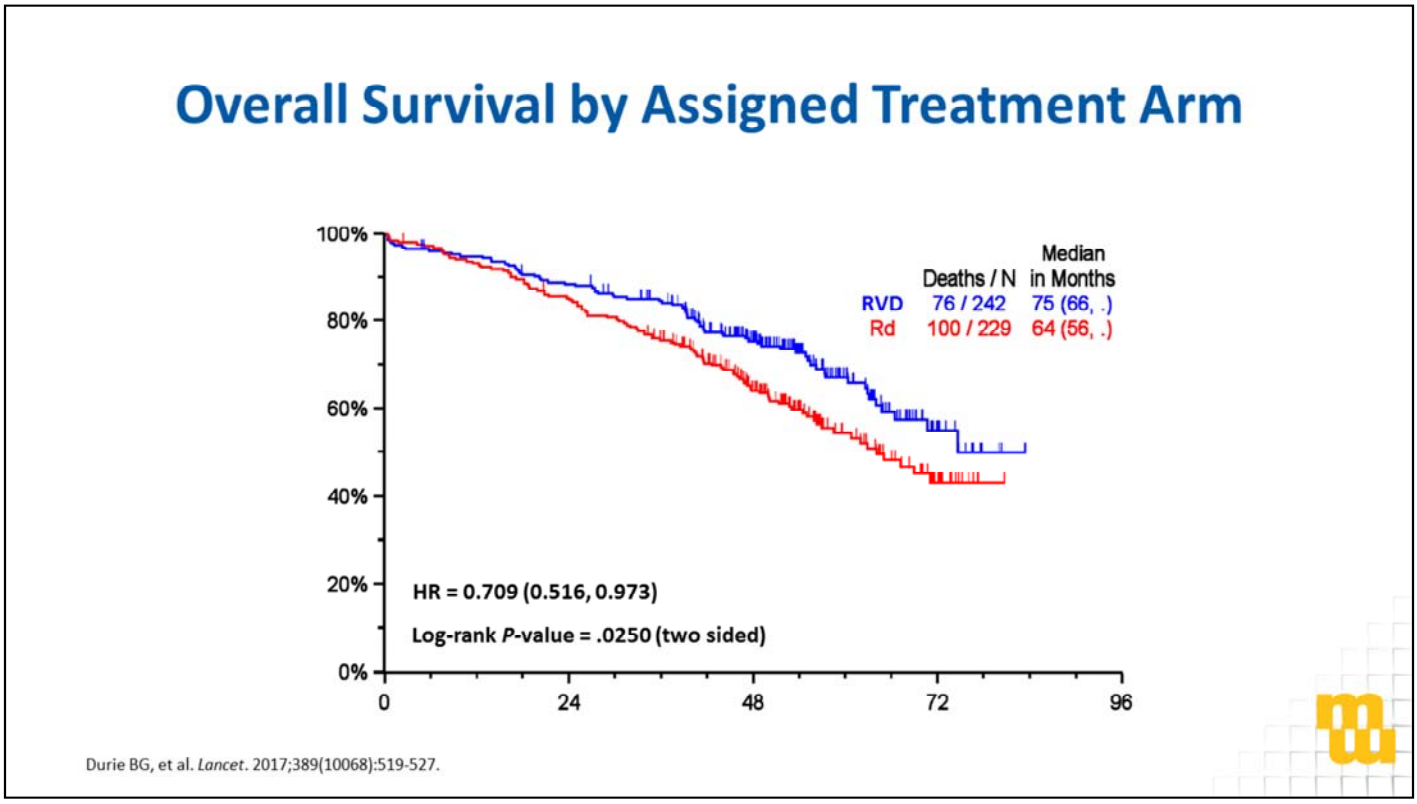
What was demonstrated from this was a clear improvement in CR, VGPR, and overall response rate favoring the use of the triplet over the doublet.

Progression-Free Survival by Assigned Treatment



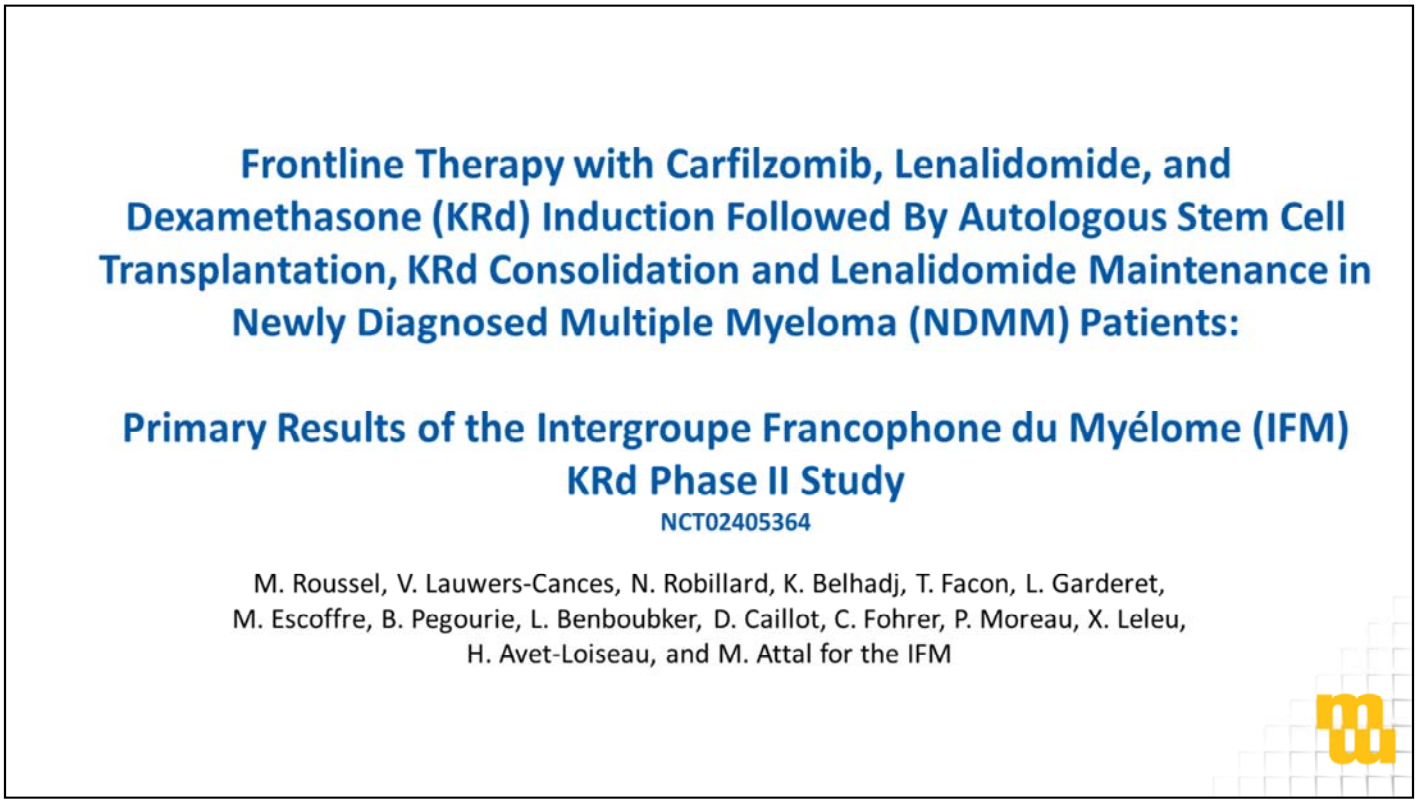
Durie BG, et al. *Lancet*. 2017;389(10068):519-527.

This translated into an improvement in progression-free survival.



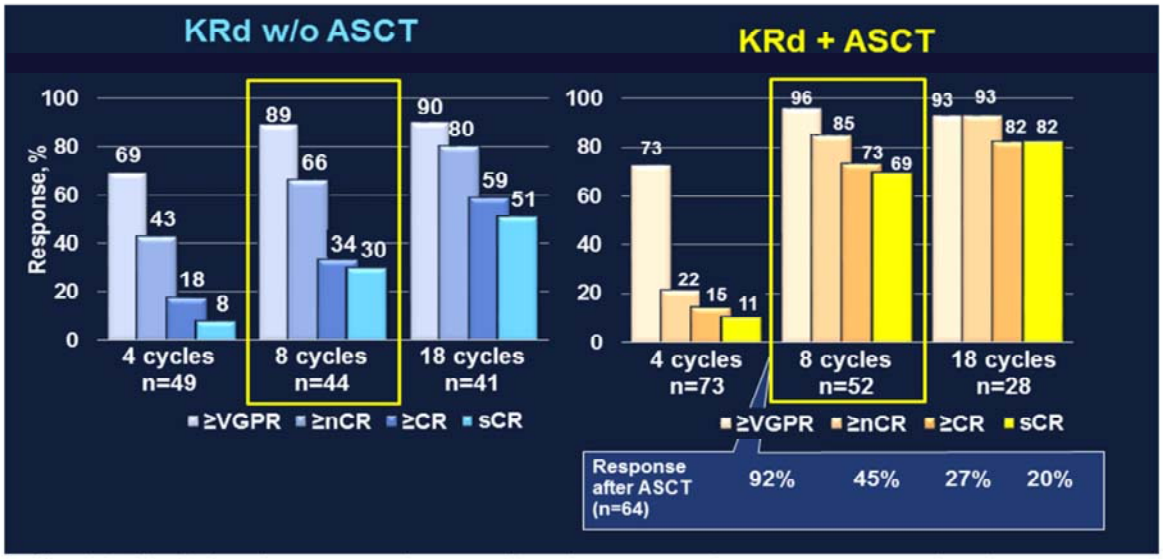
Surprisingly, it also translated into an improvement in overall survival. Based on these data that I have now shown you, I think it is reasonable to establish that RVD or the IMiD proteasome inhibitor induction therapy has become a standard of care for patients around the world based on randomized phase 3 data. There is actually no phase 3 data supporting the use of VCD at all, and so, I think, again, this does become a standard of care.

A question that arose as we have developed a larger armamentarium of new drugs for patients with myeloma is, “What is the optimal proteasome inhibitor?” We agreed that an IMiD/PI is the best backbone, but are there better PIs to potentially combine with an IMiD for newly diagnosed myeloma?



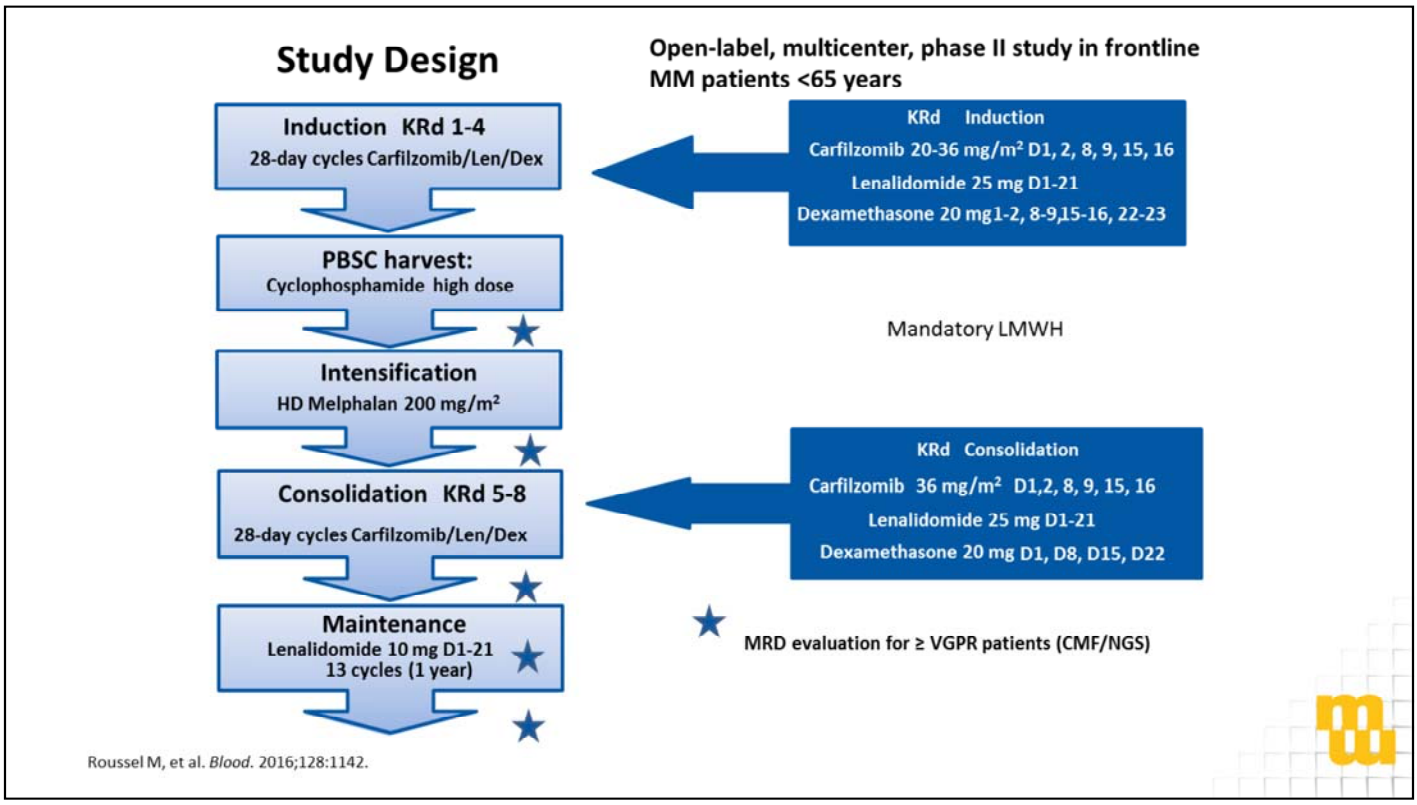
There have been a number of trials that have tried to look at this. There was a pilot study from France looking at KRd, the combination of carfilzomib with lenalidomide and dexamethasone for newly diagnosed myeloma.

KRd for Newly Diagnosed Myeloma



KRd=carfilzomib-lenalidomide-dexamethasone; ASCT=autologous stem cell transplant; nCR=near complete response; VGPR=very good partial response
Roussel M, et al. *Blood*. 2016;128:1142.

This was a very small phase 2 study built on data from Andrzej Jakubowiak looking at KRd with and without transplant, showing a very high overall response rate, and a very high depth of response rate in a small phase 2 clinical trial.



Based on that, the French created a pilot study, similar to what they have done for other large randomized phase 3 trials, where they did induction, stem cell collection, transplantation, consolidation, and maintenance, as you can see outlined on the slide here.

Response Rates at the Completion of Consolidation

N=46	n	%
sCR	26	57
MRD - CMF	32	70
MRD - NGS	23/34	
At least CR	28	61
At least VGPR	39	85
ORR	41	89
PD	1	2

4 patients were not evaluable due to toxicities

MRD CMF $10^{-4}/10^{-5}$
MRD NGS clonoSEQ Adaptive 10^{-6}

Roussel M, et al. *Blood*. 2016;128:1142.

Now what we know is that the response rate and depth of response was actually quite high. 57% of patients achieved a stringent CR, 70% of patients were MRD negative by flow cytometry (granted this was 10 to the power of -5 as the cutoff), and a significant fraction of patients achieved next-generation sequencing (NGS) MRD negativity following consolidation, suggesting that this was a very effective and very rapidly inducing regimen overall.

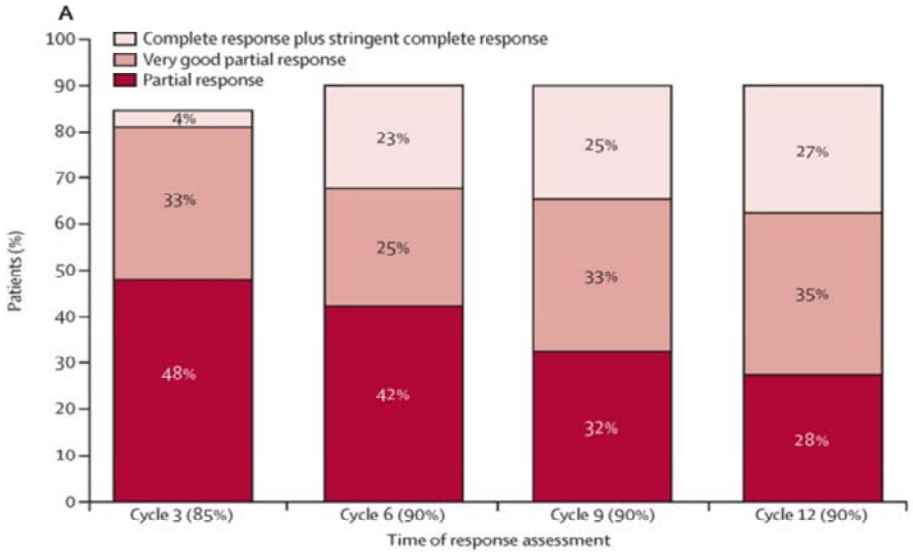
Cardiovascular + Pulmonary Toxicities (All Grades)

25 CARDIAC AND VASCULAR EVENTS	Total	
	No of events	No of patients (%)
Cardiac Failure	2	2 (4)
Pulmonary Embolism	2	2 (4)
Venous Thrombosis	2	2 (4)
Intra Cardiac Thrombus	1	1 (2)
Superficial Thrombosis	8	8 (17)
Bradycardia	2	2 (4)
Arrhythmia	1	1 (2)
Atrial Fibrillation	1	1 (2)
Tachycardia	1	1 (2)
Hypertension	5	4 (9)
Cough	11	9 (20)
Dyspnea	5	5 (11)

Roussel M, et al. *Blood*. 2016;128:1142.

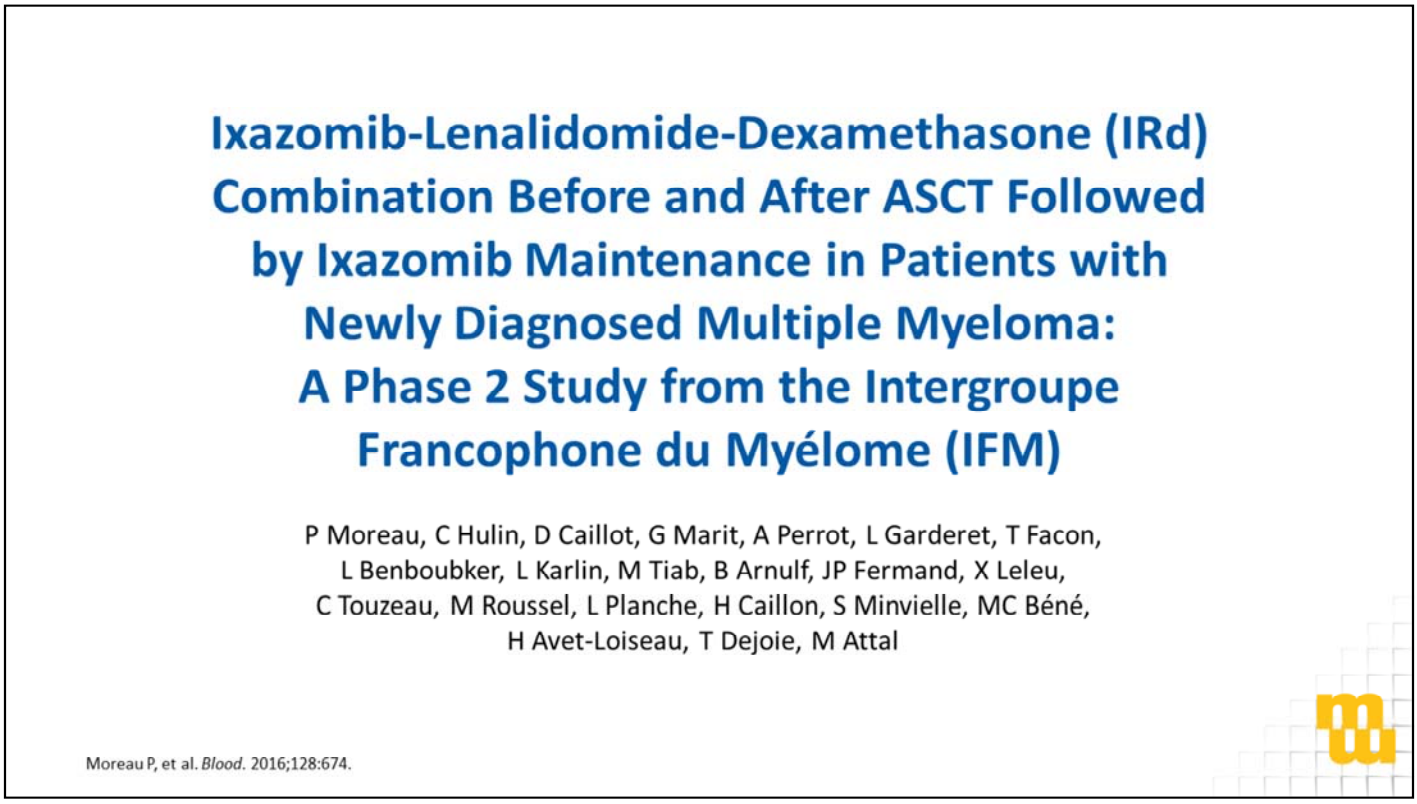
This was not a regimen that came without side effects or toxicities. As you can see, there were 25 cardiac and/or vascular toxicities. Few of them were grade 3, but certainly this bears some further evaluation in a large randomized phase 3 trial. There is currently an ECOG trial evaluating KRd versus RVD for newly diagnosed symptomatic myeloma. I think we need the results of this trial to really understand whether carfilzomib has effectively supplanted bortezomib as the optimal PI for induction therapy of myeloma across the board.

IRd Response Rates



IRd=ixazomib-lenalidomide-dexamethasone
Kumar SK, et al. *Lancet Oncol.* 2014;15(13):1503-1512.

The other PI that is available now is the oral bortezomib-like agent, ixazomib. IRd was tested in a phase 1/2 trial by Dr. Kumar and colleagues, and also demonstrated a very high overall response rate and rapidity of response.



Based on this, the IFM also did a pilot study, evaluating IRd as induction followed by transplant, consolidation, and maintenance with an ixazomib-based approach.

Study Design

1. Induction: 3 cycles of ixazomib Rd, every 28 days
   - Ixazomib 4 mg/d; D1, 8, 15
   - Lenalidomide 25 mg/d; D1 to 21
   - Dexamethasone 40 mg/d; D1, 8, 15, 22
2. PBSC harvest
   Mobilization: cyclophosphamide 3 g/m^2 and G-CSF 5 mcg/kg
3. Peripheral stem cell transplantation
   Melphalan 200 mg/m^2
4. Early consolidation: 2 cycles of ixazomib/len/dex, every 28 days
5. Late consolidation: 6 cycles of ixazomib/len (without dex), every 28 days
6. **Maintenance therapy for 1 year (13 cycles)**
   Ixazomib weekly 4 mg D1, 8, 15, every 28 days

Moreau P, et al. *Blood*. 2016;128:674.

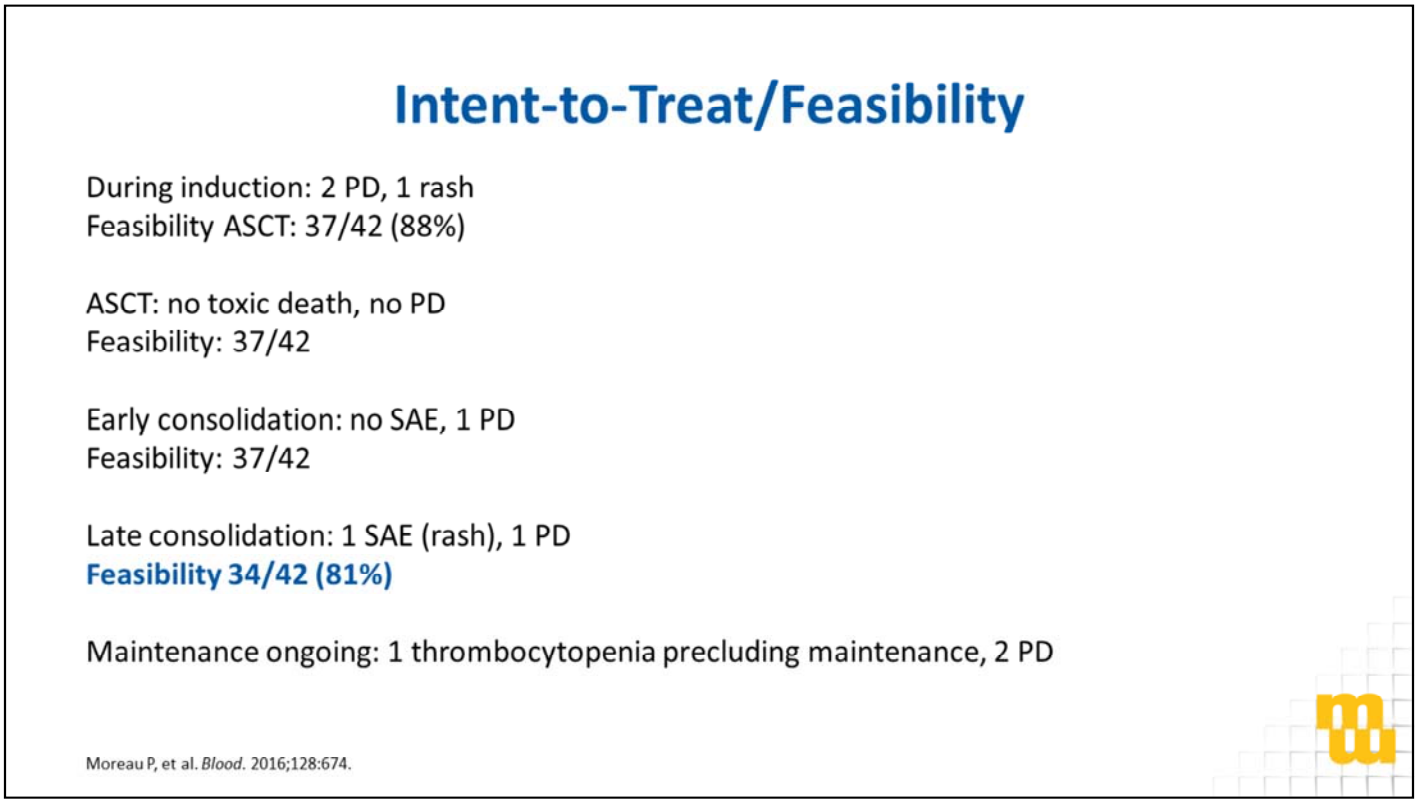
As you can see, IRd for 3 cycles, stem cell collection, transplant, consolidation for 2 cycles with IRd and then late consolidation with IR with no dexamethasone and then maintenance therapy following that.

Responses Intent-to-Treat

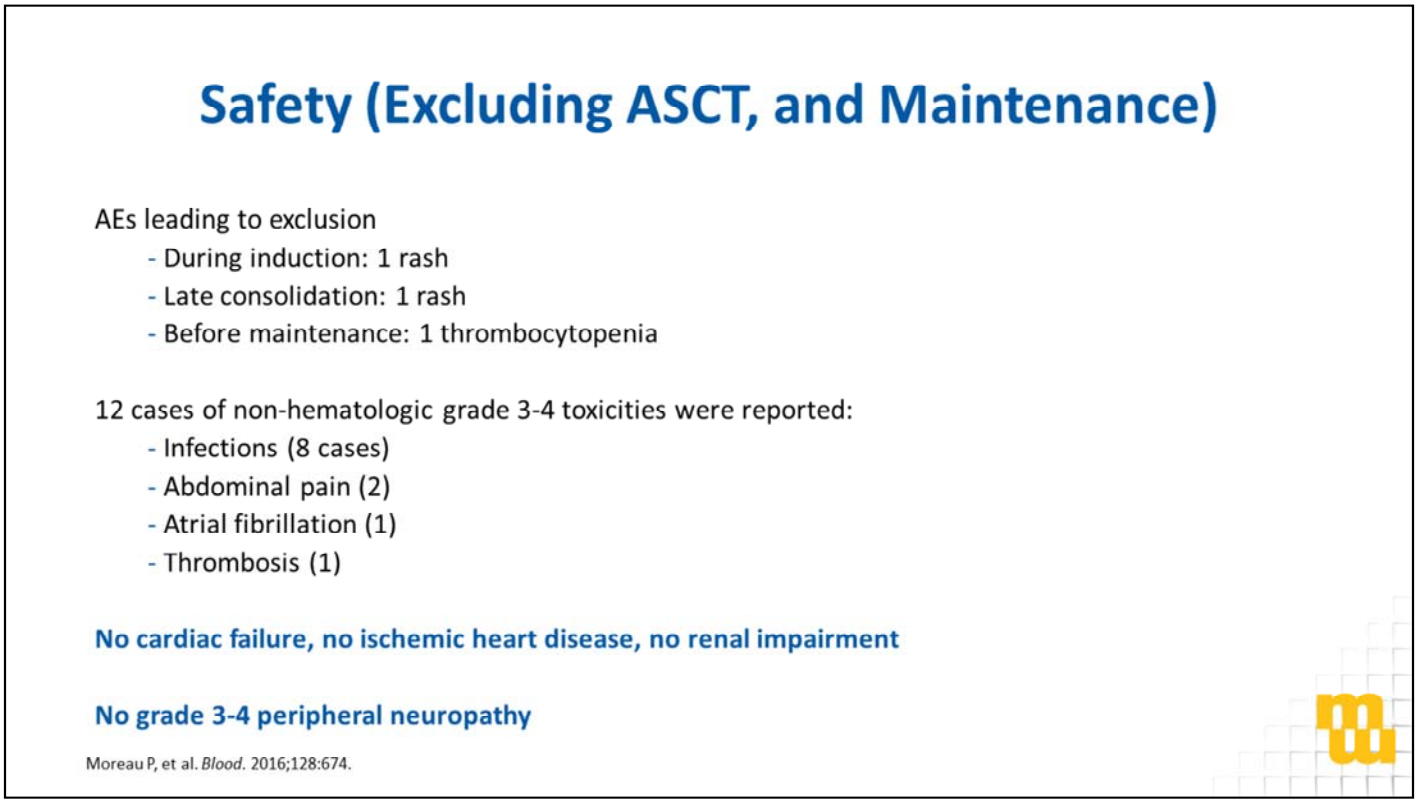
	Post-induction N = 42	Post-ASCT N = 42	Post-early Conso N = 42	Post-late Conso N = 42
sCR (%)	**2.4**	**10.8**	**27**	**31**
CR (%)	9.5	8.1	5.4	4.8
VGPR (%)	23.8	51.4	43.2	26.2
PR (%)	42.9	24.3	21.6	14.3
Stable (%)	14.3	5.4	0	0
PD (%)	4.8	0	2.7	4.8
NE (%)	2.4	0	0	19
> PR (%)	81	94.6	97.3	76.2
> VGPR (%)	38.1	70.3	75.7	61.9
> CR (%)	**11.9**	**18.9**	**32.4**	**35.7**

Moreau P, et al. *Blood*. 2016;128:674.

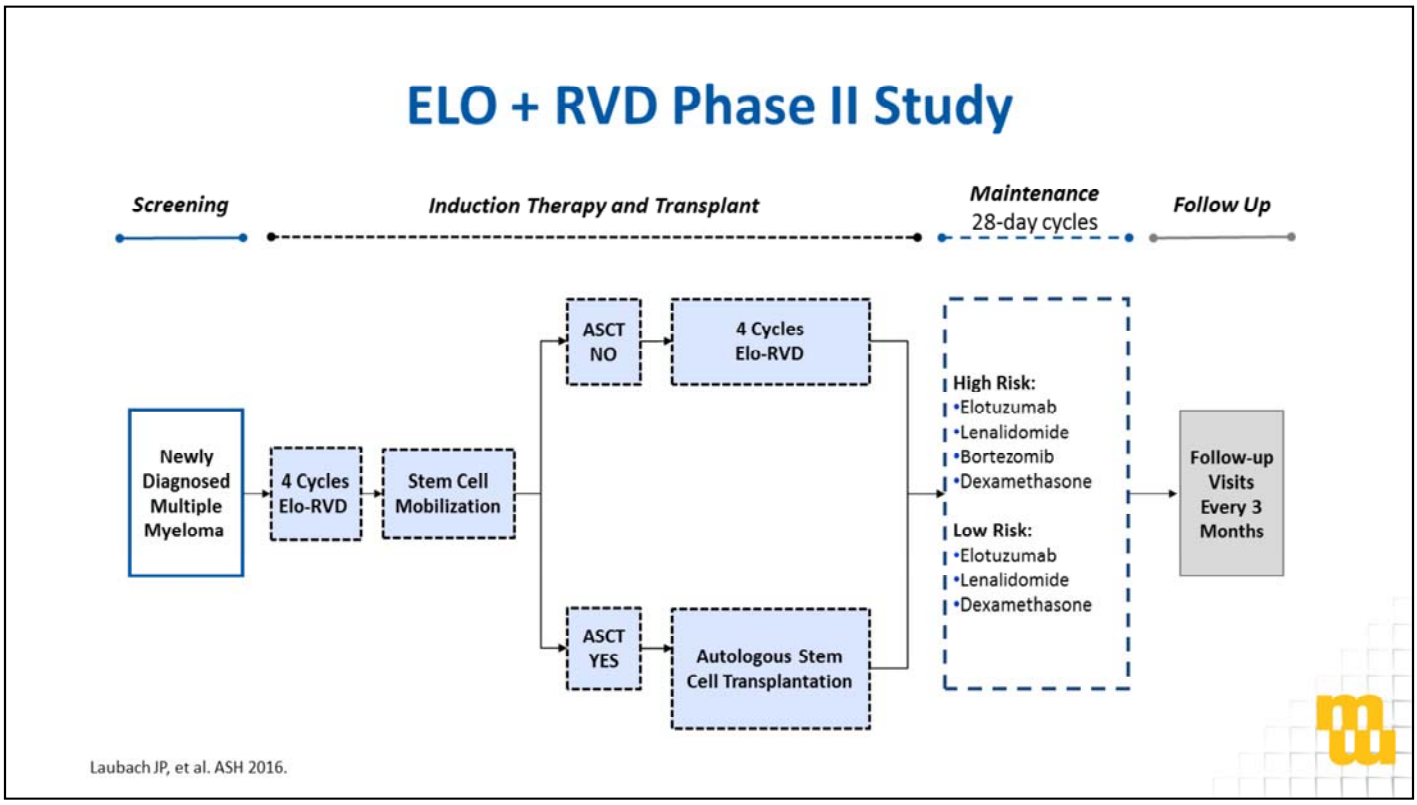
Again, you can see the response rate on the intent-to-treat group here. What is somewhat striking is that the depth of response was not quite as good as one would have hoped, or certainly with what we have seen, particularly with the carfilzomib-based approach.



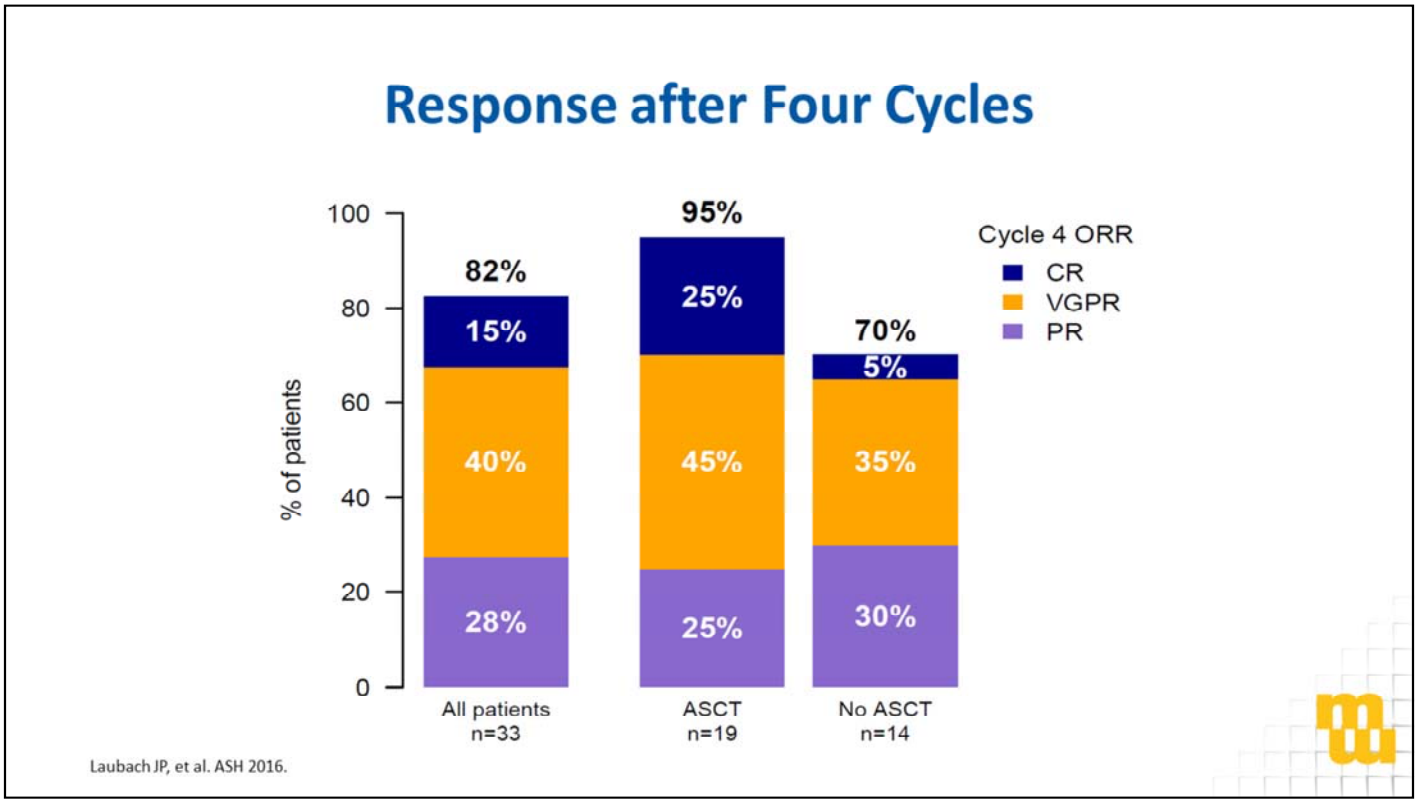
There was a feasibility concern, with a few patients actually progressing or developing significant thrombocytopenia associated with ixazomib, that I think has limited the enthusiasm of this in this current form to replace RVD as a standard induction regimen. The French are now doing a pilot of IRd with twice-a-week dosing of ixazomib. This is still more convenient than bortezomib because it is an oral agent, and we need additional data to determine whether ixazomib can, in fact, supplant bortezomib as the alternative PI for newly diagnosed symptomatic myeloma.



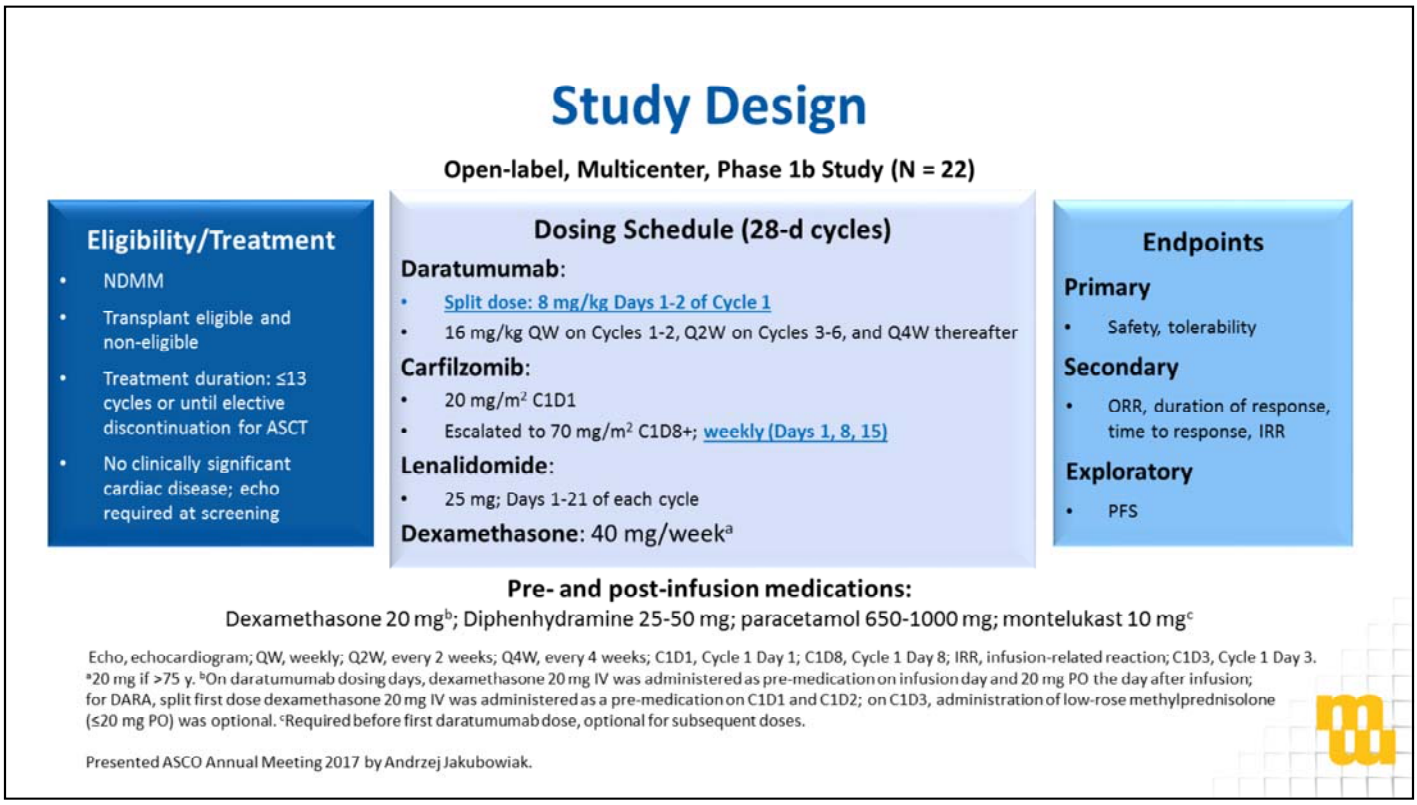
Again, there were no cardiac issues, no renal issues associated with this regimen. Patients did not develop neuropathy. There were some cases of grade 3/4 toxicities, including infection, abdominal pain, atrial fibrillation, and one case of thrombosis.



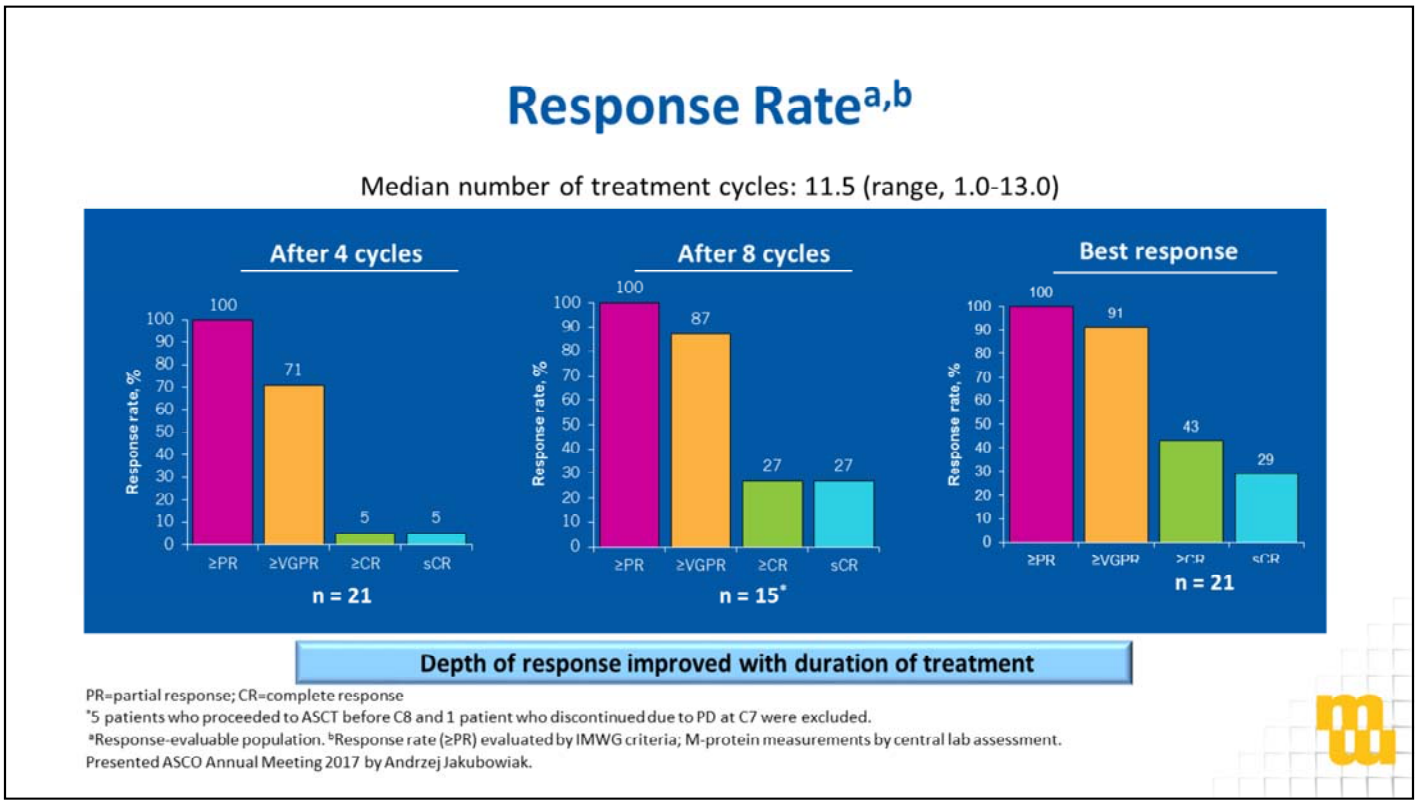
What about other approaches trying to include the new monoclonal antibodies into treatment for patients with symptomatic myeloma? Jacob Laubach from the Dana-Farber Cancer Institute presented a multicenter trial looking at RVd plus elotuzumab, and you can see the schema outlined here. It was basically 4 cycles of elo plus RVd, followed by stem cell collection, and an opportunity for patients to either continue on elo and RVd or to go on to a transplant.



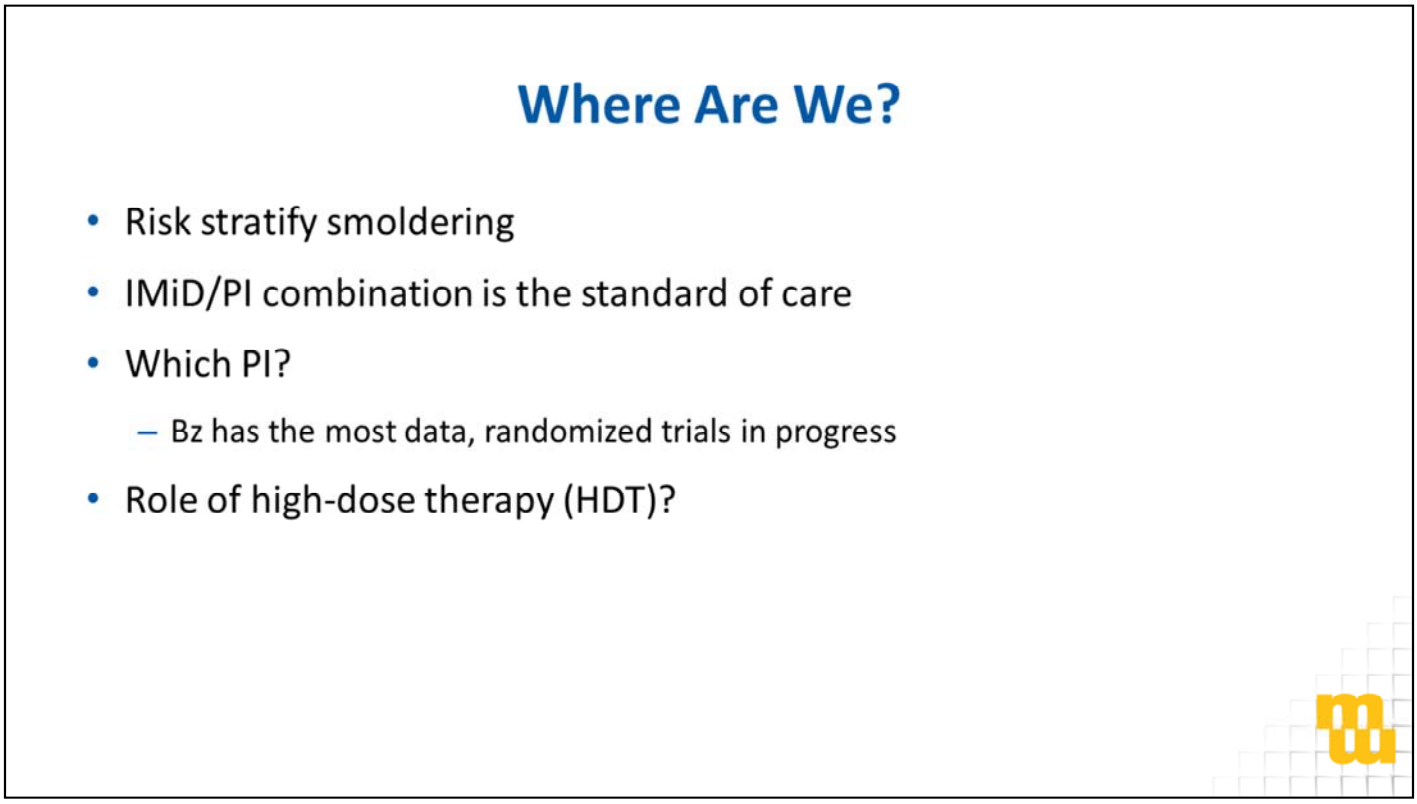
As you can see, the overall response rate was quite high. The depth of response was quite high, and it occurred relatively quickly, also again in a small pilot study.



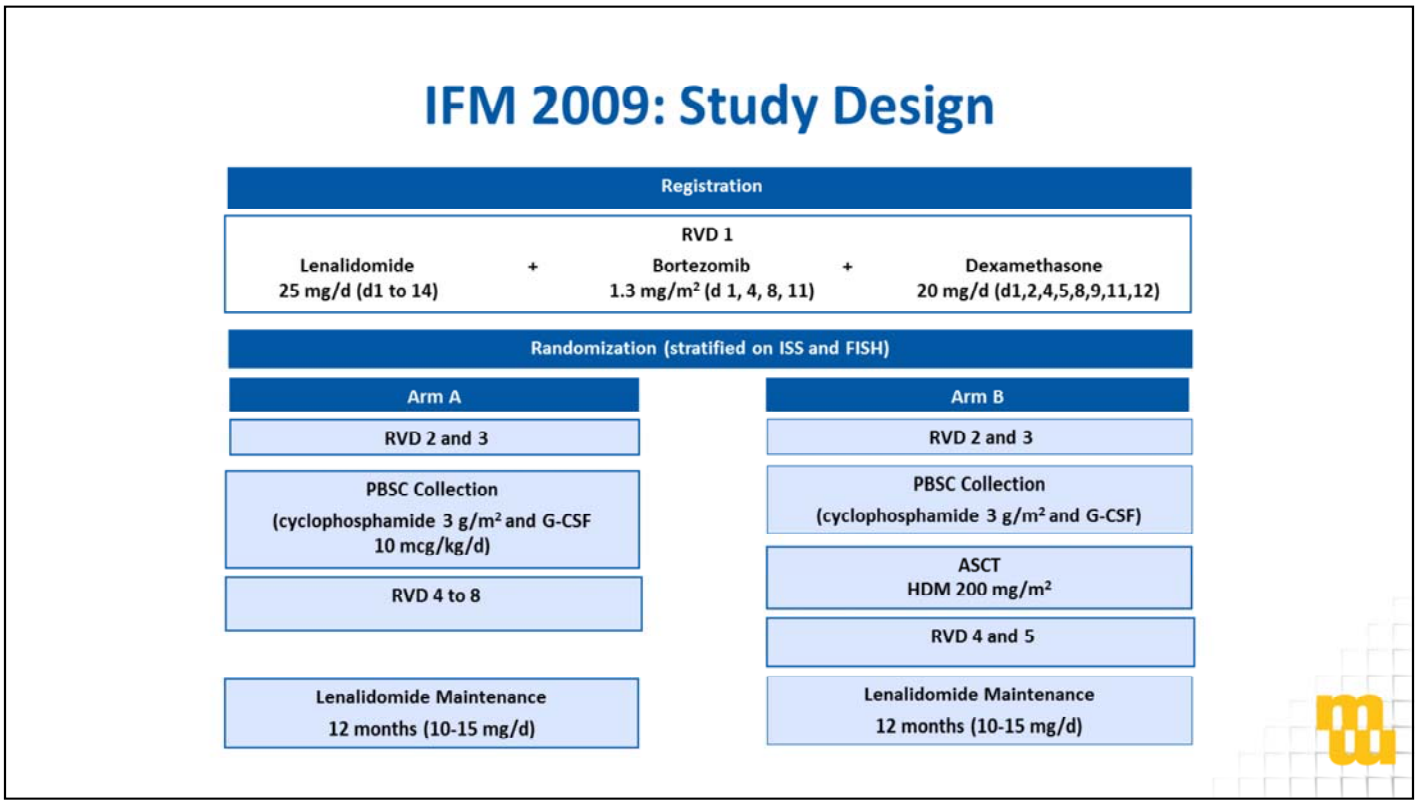
We know that elo is not the only antibody out there. We know that daratumumab is an effective antibody as well. There was a trial presented by Dr. Jakubowiak looking at KRd with weekly dosing of carfilzomib in combination with daratumumab. This was an idea trying to incorporate daratumumab into induction therapy.



Again, what you see is overall response rates were quite high, VGPR or better rate early on was quite high. Response rate continued to improve with longer duration of therapy. Some patients did go off therapy for a transplant. Some patients stayed on for a maximum of 13 cycles of therapy. I think these are encouraging data demonstrating that antibodies can be introduced. There were some adverse events associated with both of these trials with the introduction of a monoclonal antibody, but overall, the treatment was tolerated relatively well.



I think we looked forward to additional trials evaluating the role of antibodies in the context of induction therapy. What about the role of high-dose therapy and autologous transplant?

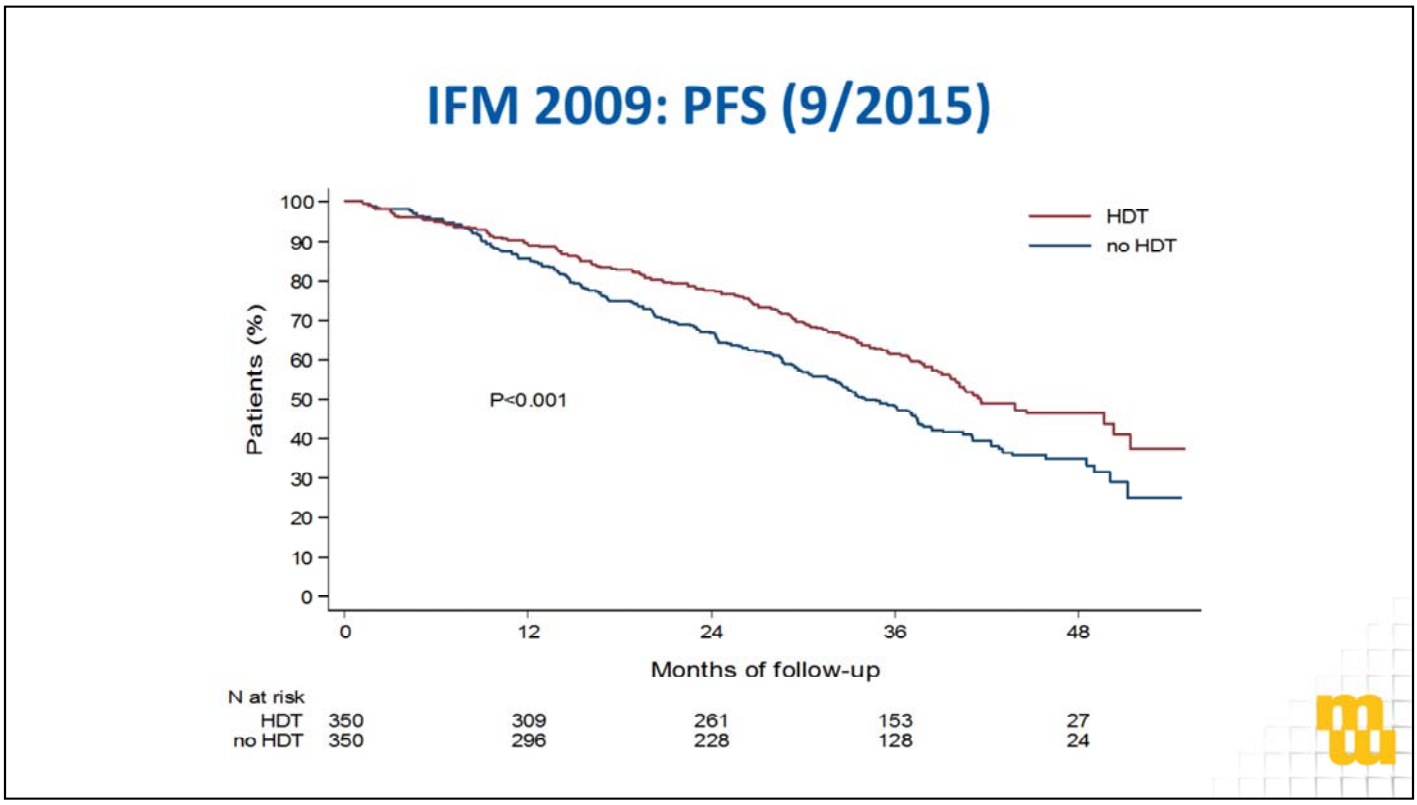


The most recent trial we have data from is the IFM 2009 trial. This was RVd for every patient upfront, followed by a randomization to early versus delayed transplant with post-transplant consolidation and then maintenance after that.

IFM 2009: Best Response

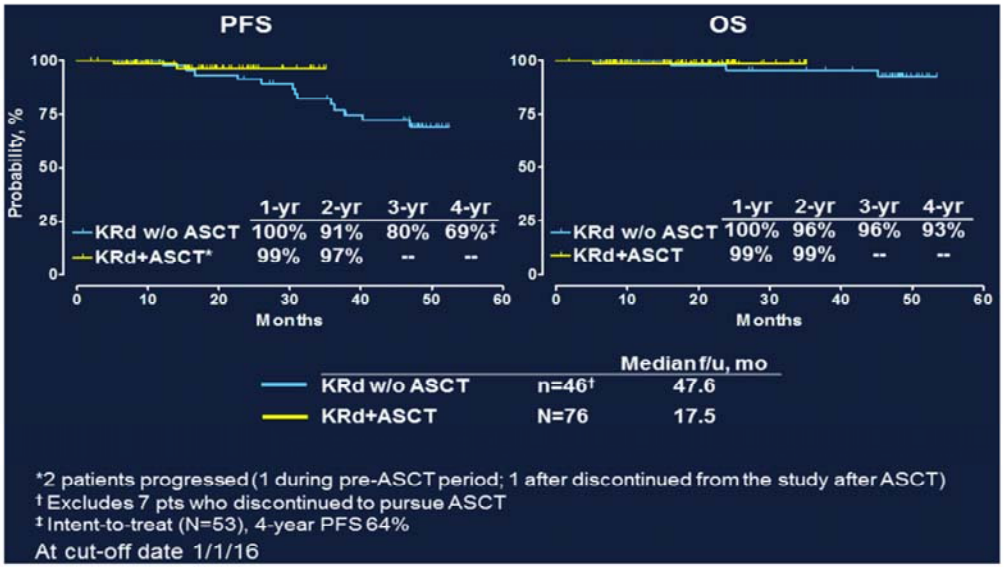
	RVD arm N=350	Transplant arm N=350	*P*-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

As you can see, the group that received a transplant had a higher overall response rate and a higher depth of response.



This translated into an improved progression-free survival with an early followup of only 3 years. There was no difference in overall survival, but clearly, a big difference in progression-free survival. Given that our goal is to try and improve the duration of first remission, this continues to support the role of high-dose therapy and autologous transplantation.

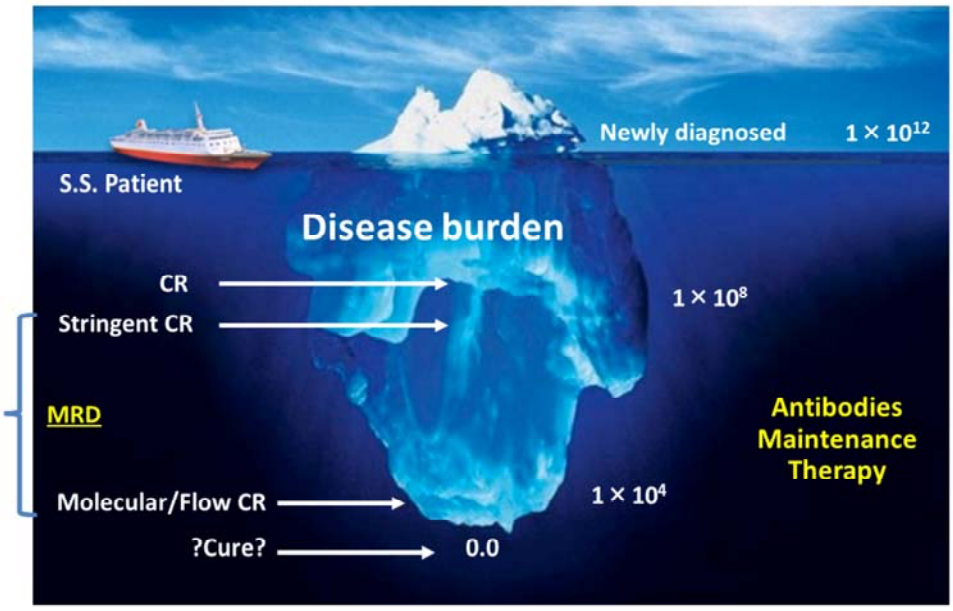
KRd Outcomes by Transplant Status



Jakubowiak A, et al. EHA 2016.

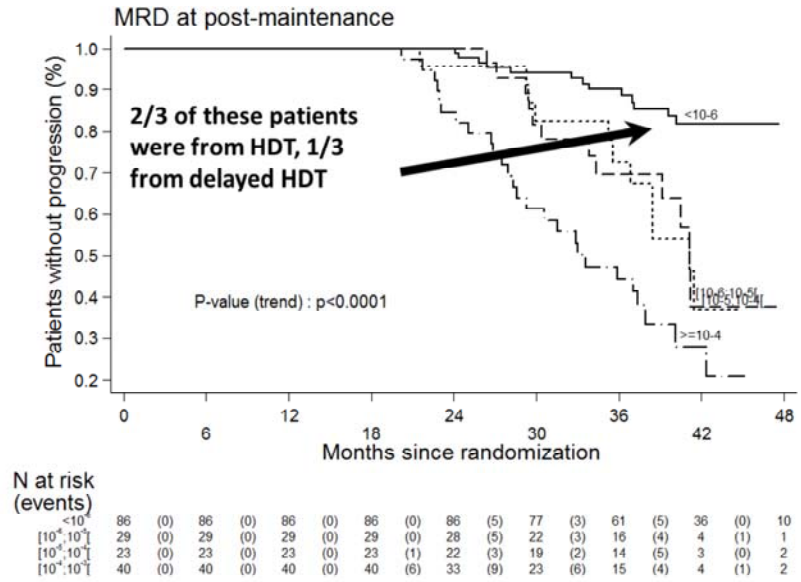
One would argue that if you use better regimens, perhaps you do not need to think about transplant as often. I use this slide to reiterate the point that even with KRd, which may be a more depth-inducing induction regimen, the role of transplantation improves the progression-free survival for these patients. Just because you have a better, more potent induction does not mean that transplant may have less of a role. In fact, it may continue to have an even greater role because some of those patients who are in CR but not MRD negative CR may be pushed into MRD-negative complete remission, and we know this is likely the case with data from the IFM.

Getting to Minimal Residual Disease (MRD): New Definitions for CR

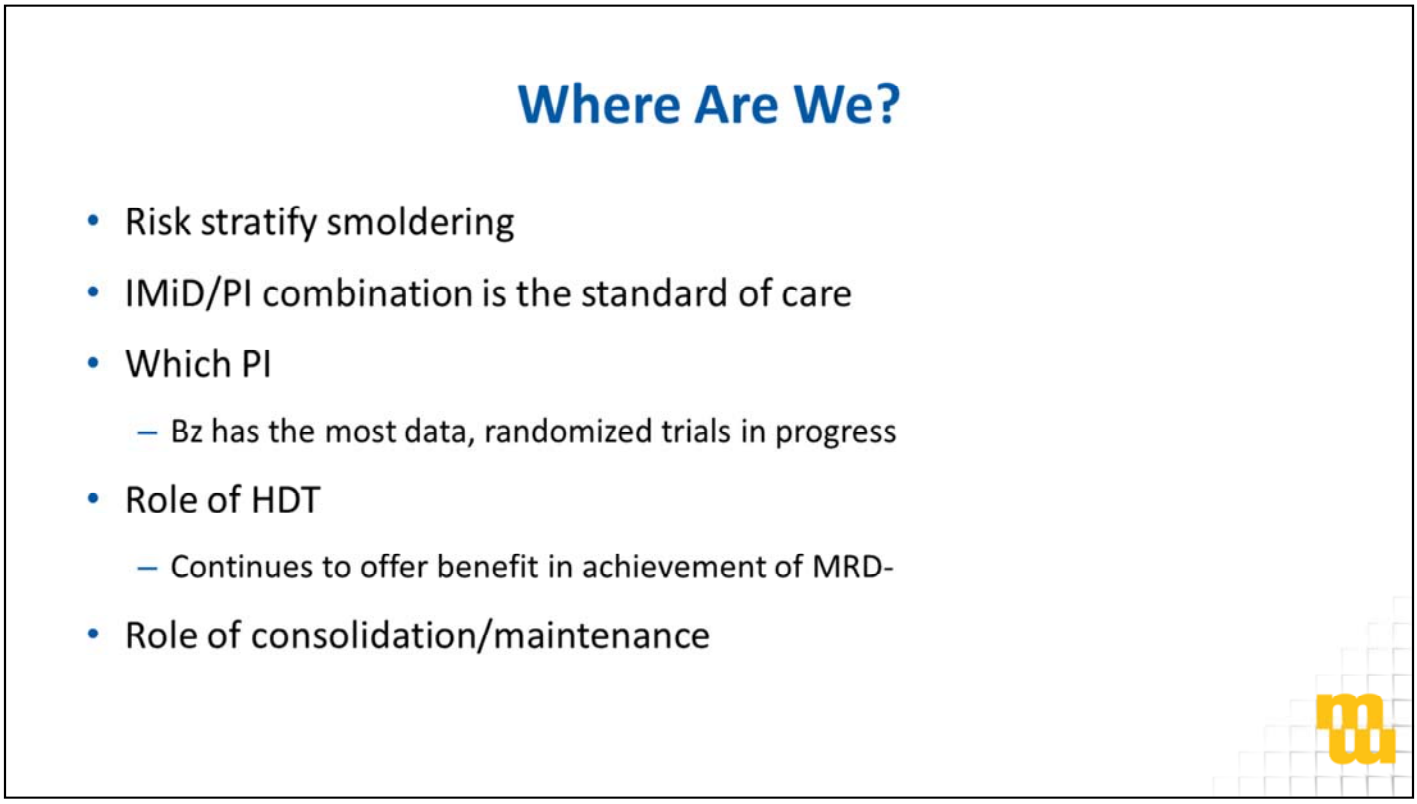


What is the rationale for transplant even in patients who achieved complete remission? The rationale is to try and drive them lower down on that iceberg to get a higher fraction of patients into MRD negative complete remission, and ultimately, increase the fraction of patients that we cure with our therapy.

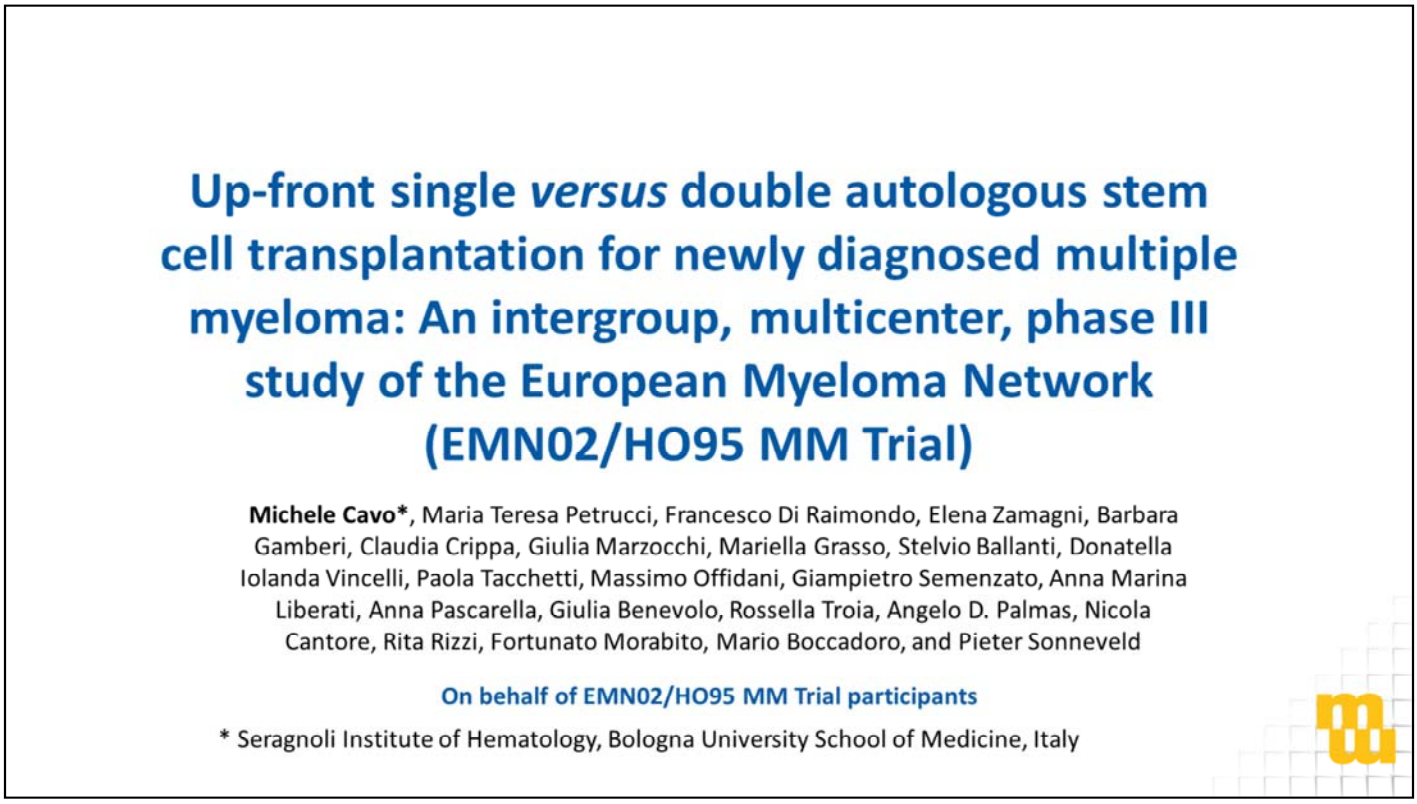
Outcomes for Patients Are the Same if they Achieved MRD Negativity



Now in that French trial that I talked about a moment ago, in early versus delayed transplant, if you look at the curve of patients who achieved MRD negativity at 10 to the power of -6, their outcomes were clearly better than every other patient group in the evaluation. At 18 months, they had a better outcome. However, two-thirds of those patients got there with a transplant. Only one-third got there without a transplant, and you do not know this result until 18 months after diagnosis. You have to make a commitment early on, and I think it is important to make that commitment in the context of what we know is the most effective, best therapy for patients going forward.



Again, I think there continues to be a role for high-dose therapy in the context of improving depth of response, and ultimately improving long-term outcomes for patients with myeloma.



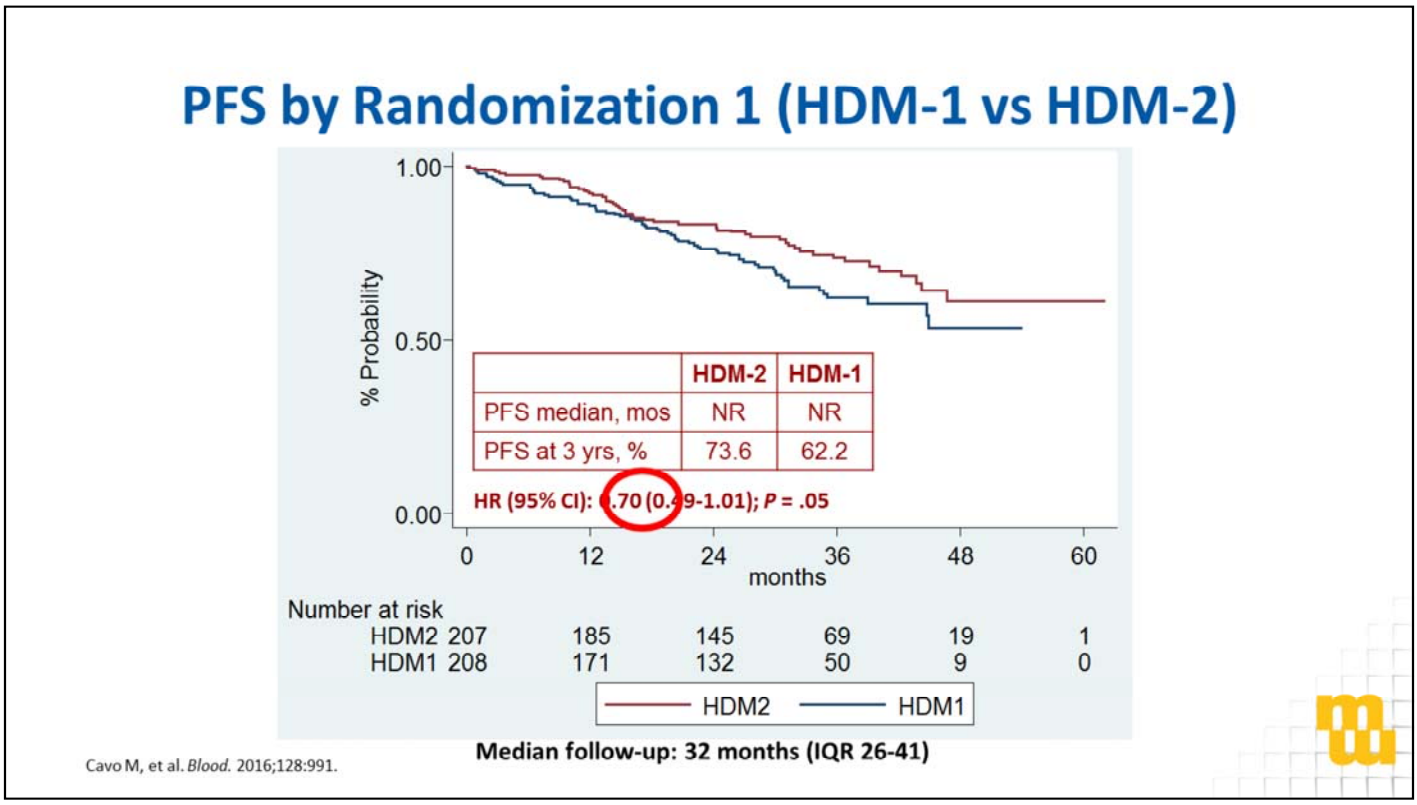
Up-front single *versus* double autologous stem cell transplantation for newly diagnosed multiple myeloma: An intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial)

Michele Cavo*, Maria Teresa Petrucci, Francesco Di Raimondo, Elena Zamagni, Barbara Gamberi, Claudia Crippa, Giulia Marzocchi, Mariella Grasso, Stelvio Ballanti, Donatella Iolanda Vincelli, Paola Tacchetti, Massimo Offidani, Giampietro Semenzato, Anna Marina Liberati, Anna Pascarella, Giulia Benevolo, Rossella Troia, Angelo D. Palmas, Nicola Cantore, Rita Rizzi, Fortunato Morabito, Mario Boccadoro, and Pieter Sonneveld

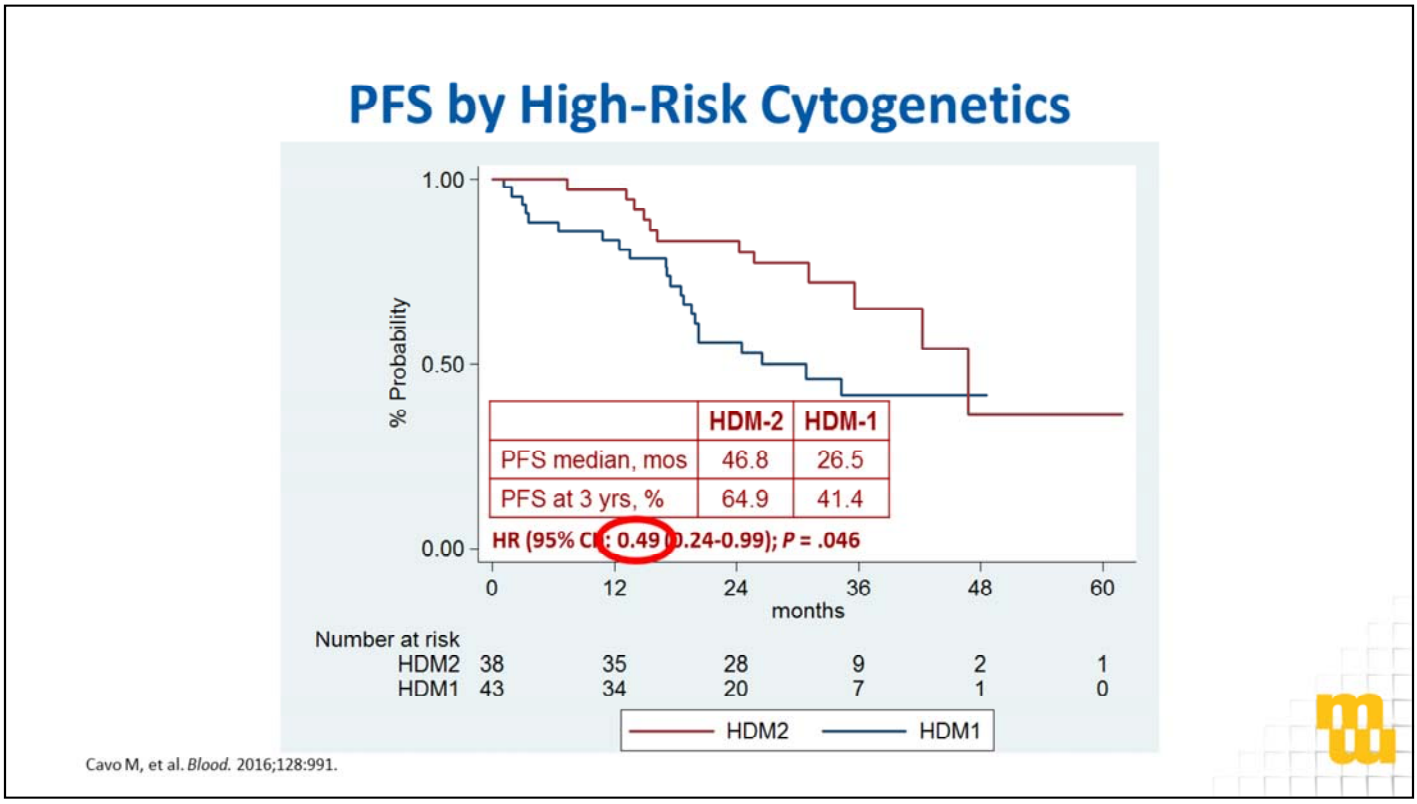
On behalf of EMN02/HO95 MM Trial participants

* Seragnoli Institute of Hematology, Bologna University School of Medicine, Italy

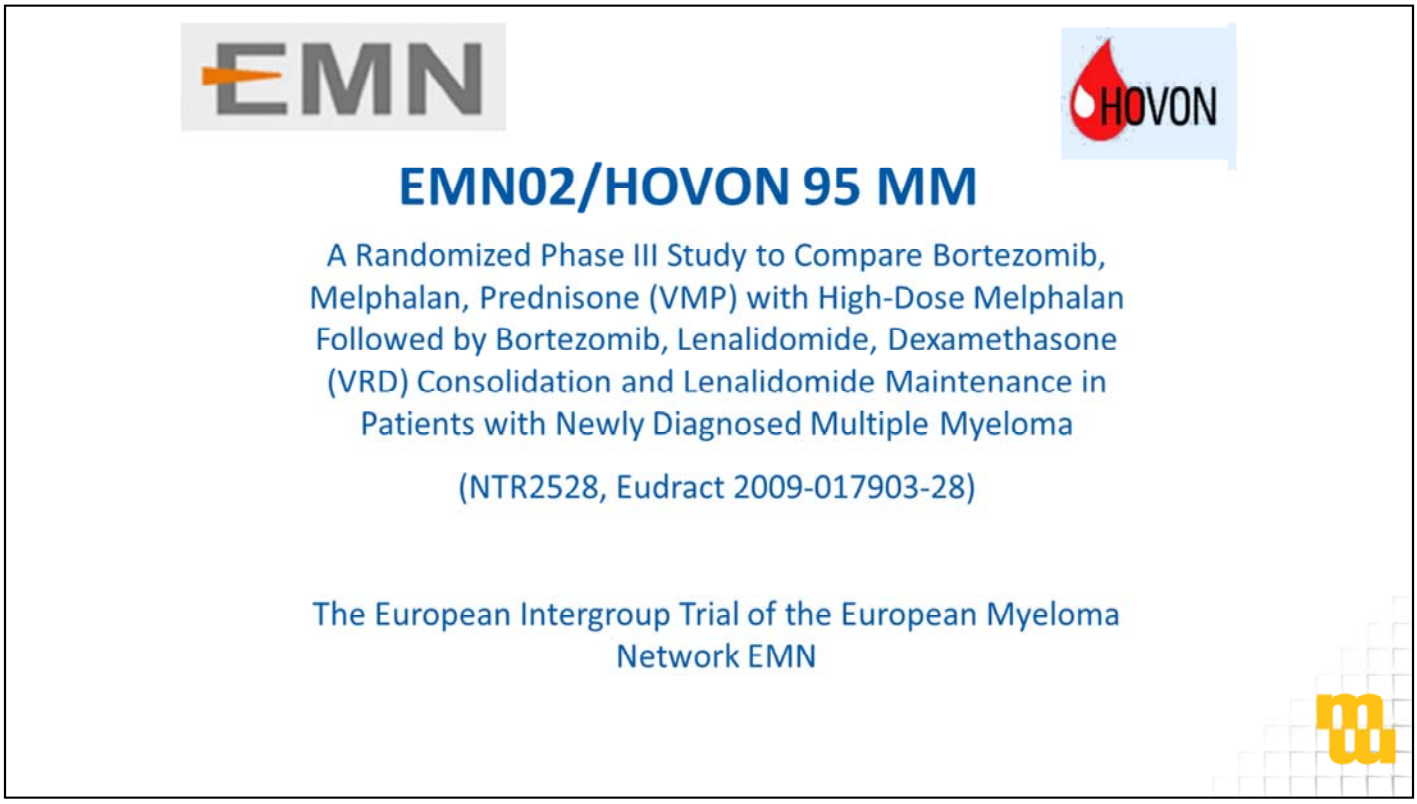
What about the role of consolidation and maintenance? This is a little bit more controversial. There are two trials, one done in Europe and one done in the United States. They give us somewhat conflicting data on the role of consolidation. The first trial is a trial from the European group evaluating single versus double transplant in the context of newly diagnosed myeloma.



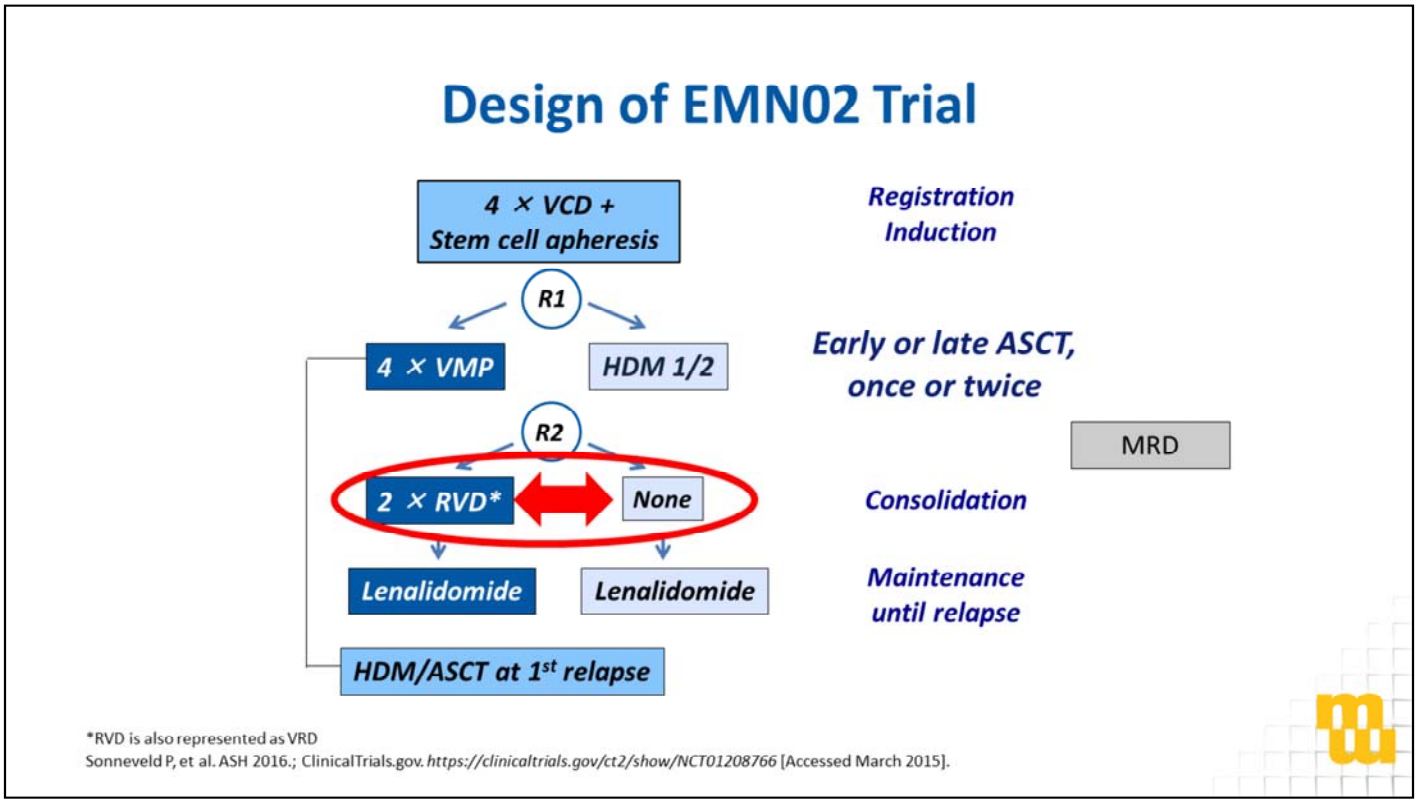
As you can see in this randomization, the Europeans suggest that patients who had two transplants had a better progression-free survival compared to patients who only had one transplant.



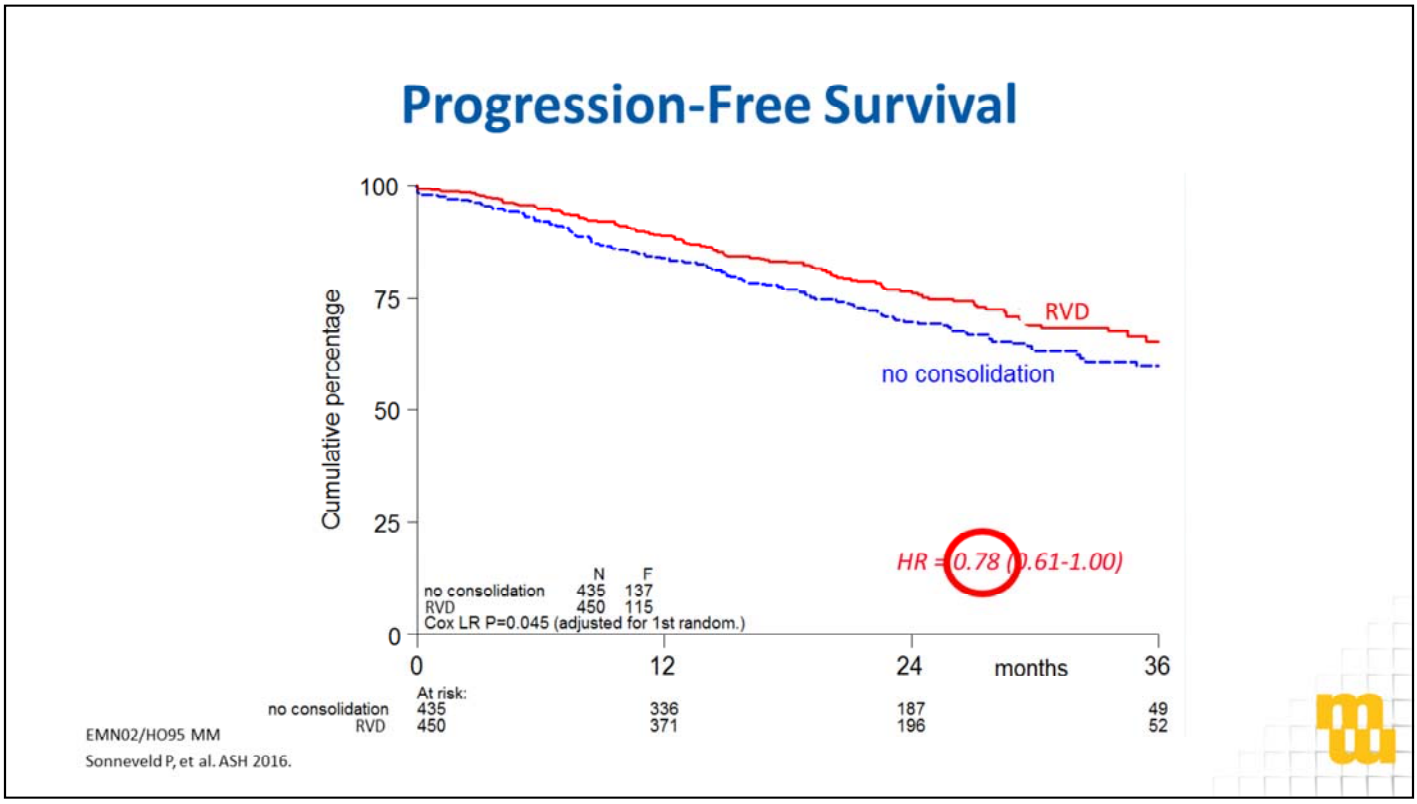
This was particularly notable for patients with high-risk genetics. Now understand that, in many areas, they are talking about not using transplant for patients with high-risk genetics. I think that is too much of an extreme, but I am also not convinced by the data suggesting that two transplants is necessarily better either. We are going to get to caveats in just a moment.



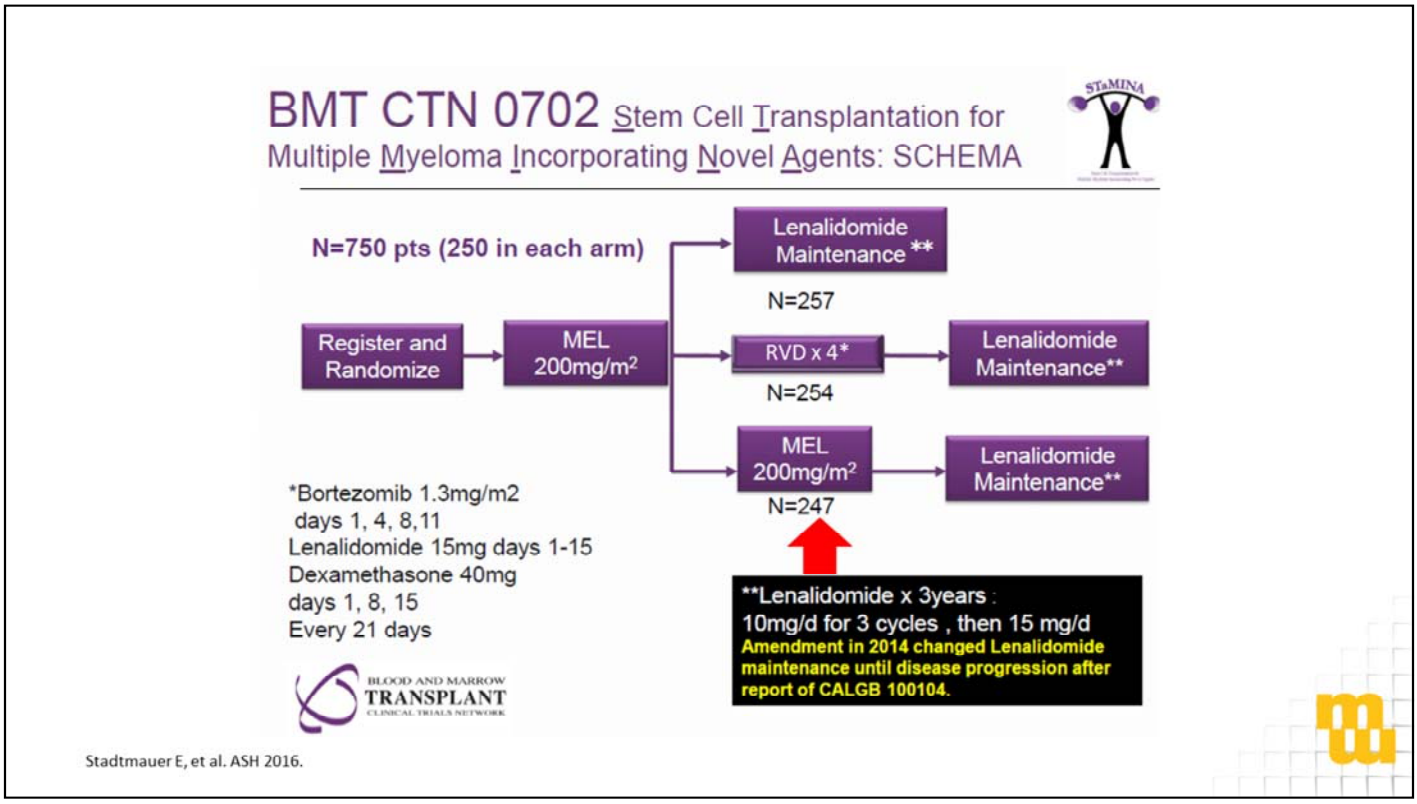
Let's look at the other European trial. This was a randomized trial of consolidation versus no consolidation.



You can see the schema. Everybody got VCD, and it is important to note that in the previous trial of one versus two transplants, everybody also got VCD. In both European trials, they got what we know is an inferior induction regimen. Access is a big issue when trying to interpret European trials. You can see that patients were randomized to either transplant versus VMP and then there was a second randomization to consolidation versus no consolidation. Every patient received maintenance.

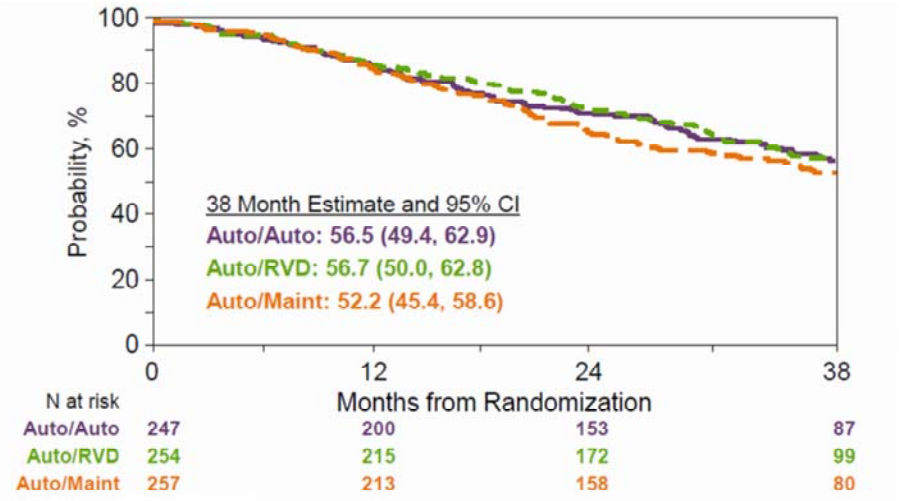


If you look at progression-free survival, there was clearly a superior PFS for patients who received RVD consolidation versus no RVD consolidation, if you got VCD as your initial treatment. Remember induction regimen does in fact potentially impact how to interpret other trials.



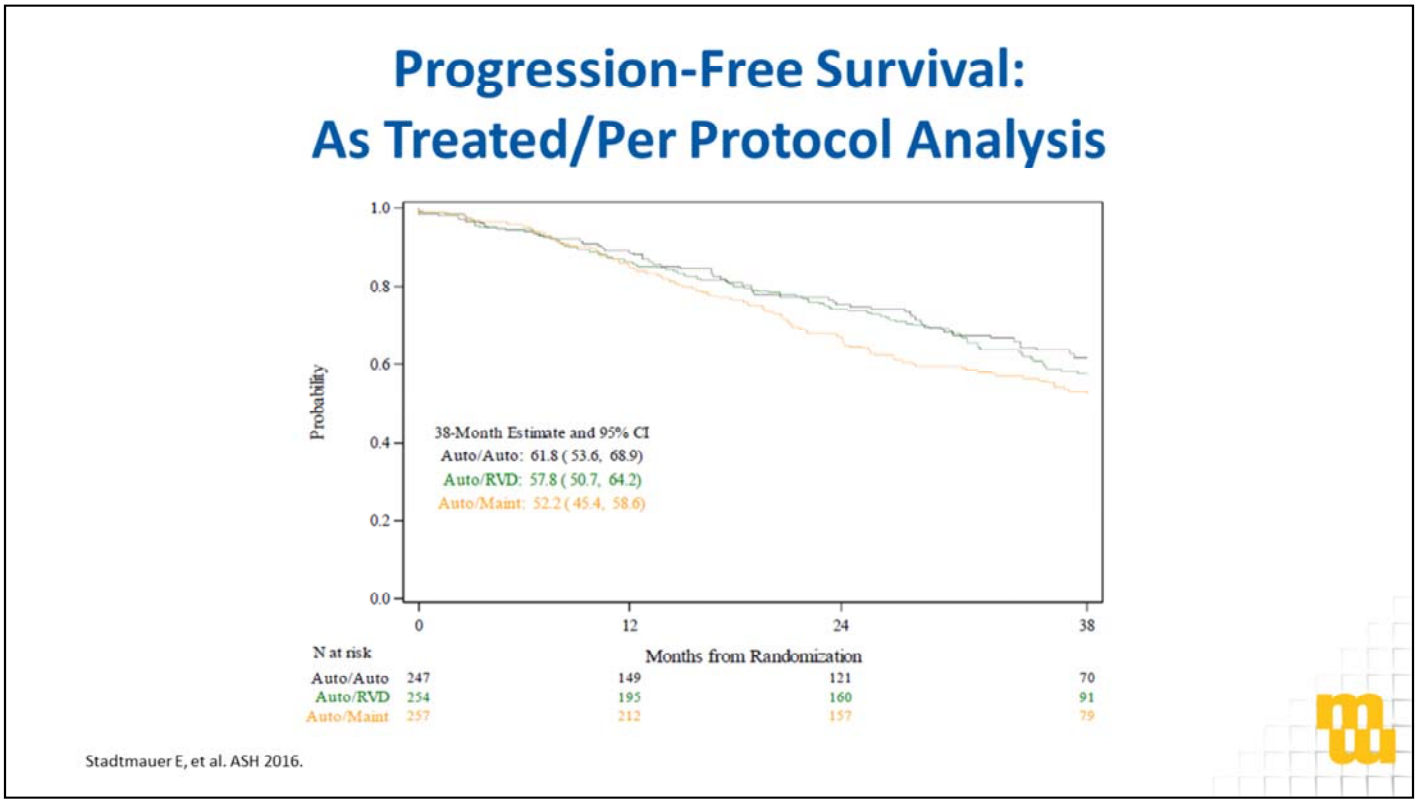
This was the U.S. trial. In this trial, they did not dictate induction regimen, but as you can see most patients received RVD. Over two-thirds of patients in this trial received RVD, not VCD, as the induction therapy. There was then a randomization: two transplants, one transplant with consolidation with RVD, or one transplant followed by going straight to lenalidomide maintenance.

Primary Endpoint: Progression-Free Survival

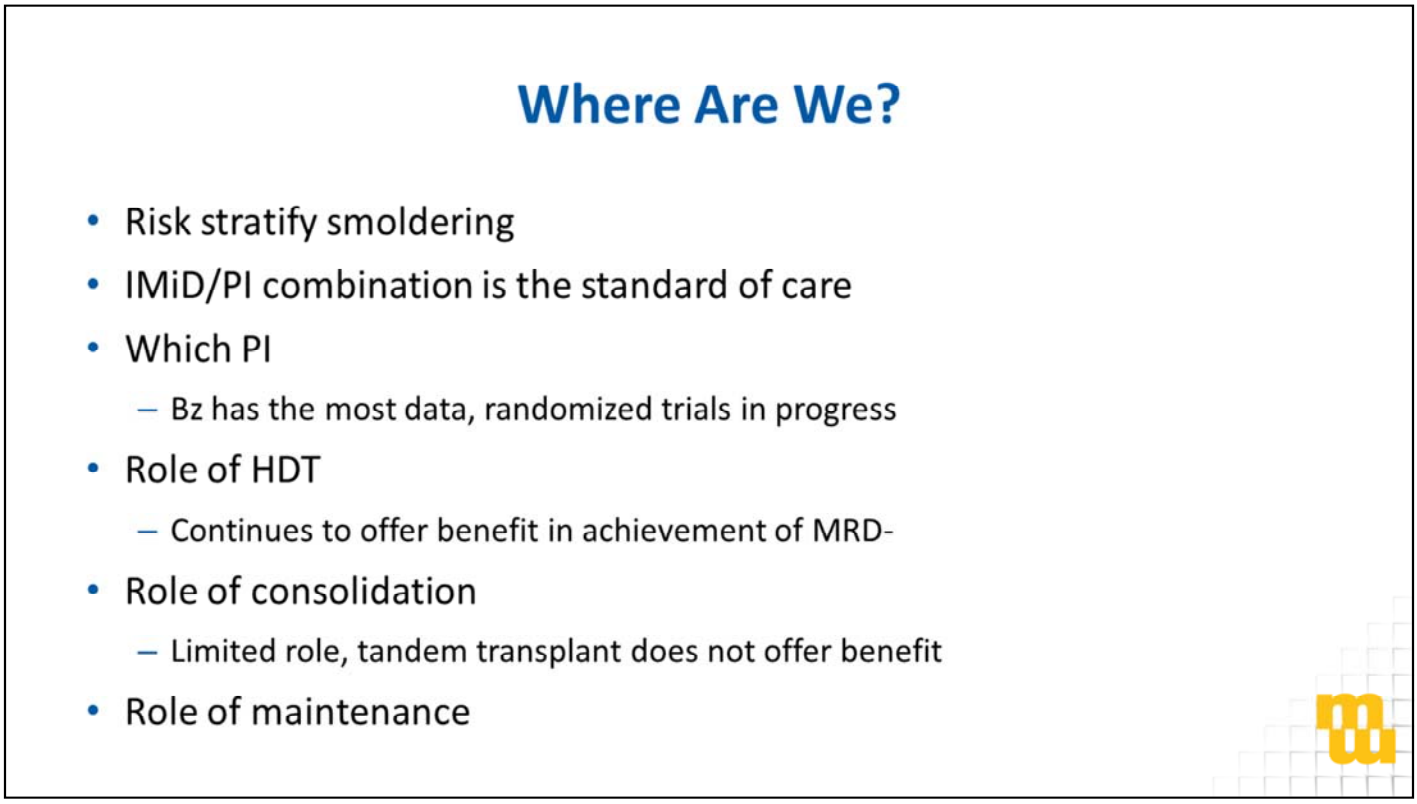


RVD or VRD or VRd
Stadtmauer E, et al. ASH 2016.

This one trial asked the questions that the two European trials did before. There was no difference in progression-free survival and no difference in overall survival either.



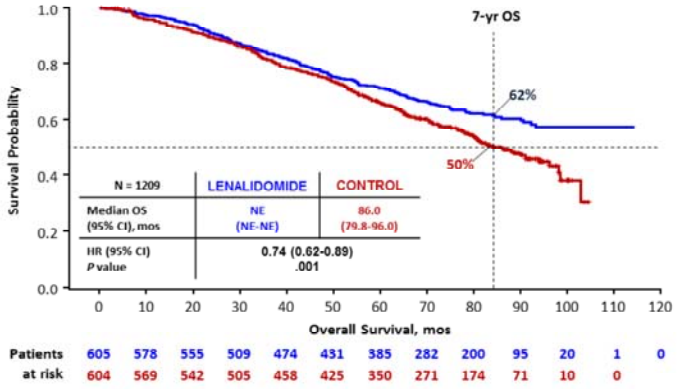
Why is one trial showing a benefit for consolidation and tandem transplant and one trial is not? The answer quite simply is induction regimen. The European trial used VCD, the U.S. trial used RVD. If you use a better induction, you do not need two transplants and you do not need consolidation with RVD. We also have better access to new drugs here, particularly the IMiDs in the maintenance and consolidation and salvage setting in the U.S. That may affect both progression-free and overall survival curves in the U.S. In my simple summary, there is no role for tandem transplant in the U.S. treated patients, and there is no role for consolidation at this point, based on the data we have from the StaMINA study.



Now, what about the role of maintenance therapy? Again, we have trials done in the U.S. and in Europe that evaluate the role of maintenance therapy. I think it is important to realize that maintenance therapy is something that we now have a meta-analysis evaluating.

Overall Survival: Median Follow-Up of 80 Months

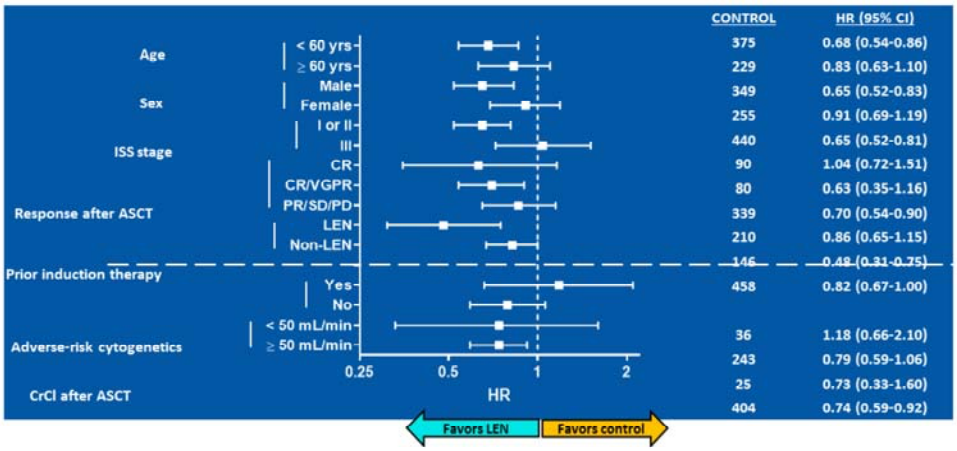
There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival[a]



[a]Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74.)
HR=hazard ratio; NE=not estimable; OS=overall survival
McCarthy PL, et al. *J Clin Oncol*. 2017 Jul 25:JCO2017726679.

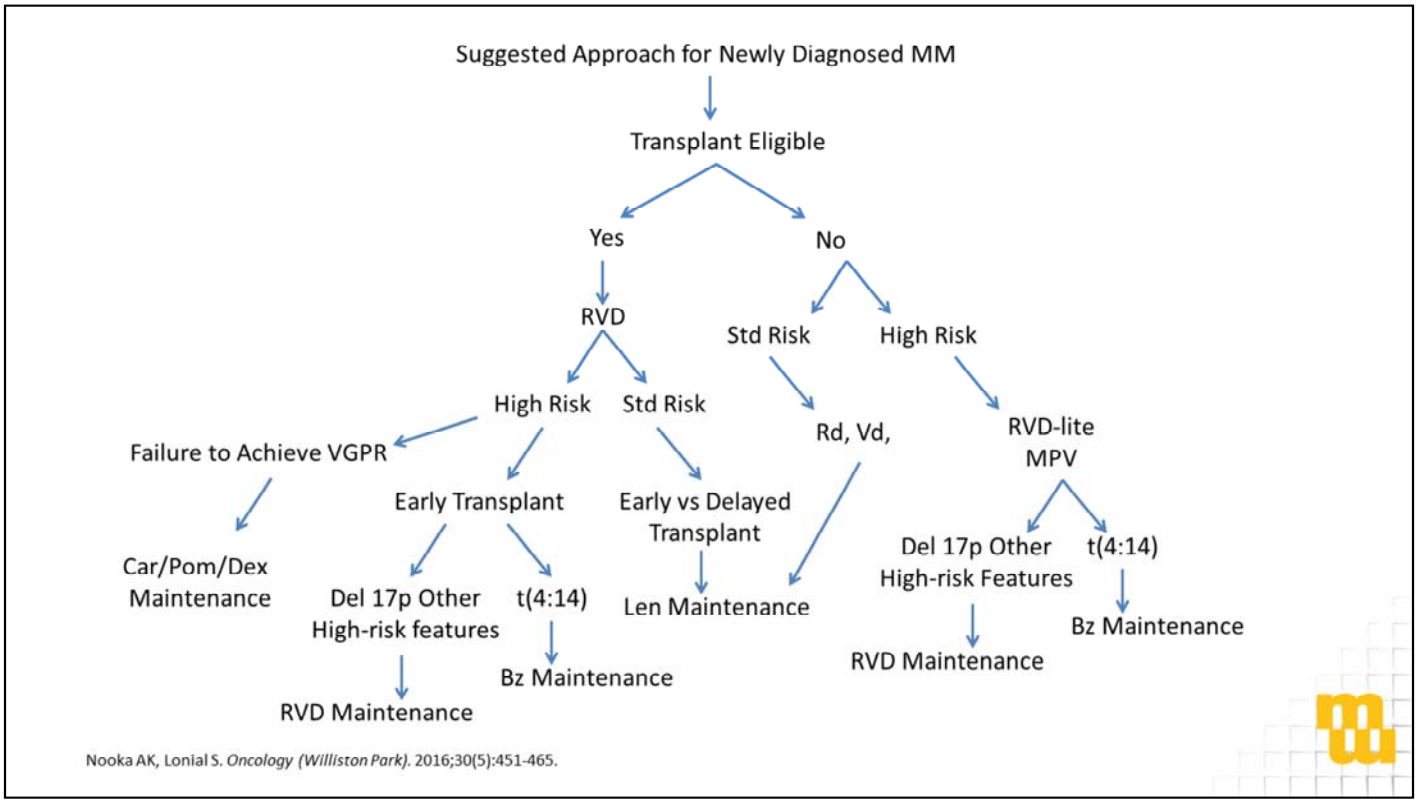
This is being published and has been presented at a number of meetings now suggesting that there is a difference not only in progression-free survival, but overall survival with a median followup of 80 months. This suggests that, across the board, maintenance therapy with lenalidomide does improve not just PFS or duration of remission, but actually overall survival.

Overall Survival: Subgroup Analysis

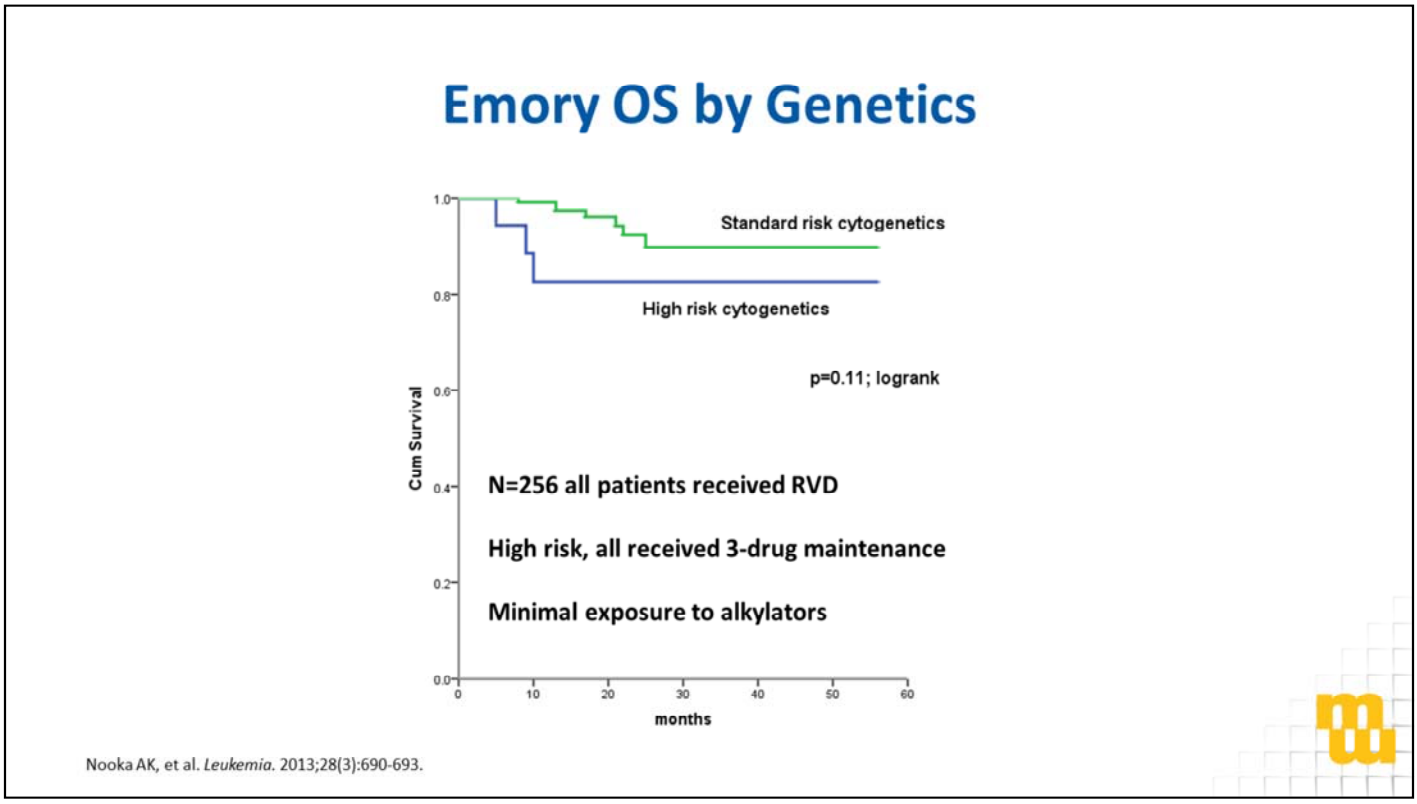


McCarthy PL, et al. *J Clin Oncol*. 2017 Jul 25:JCO2017726679.

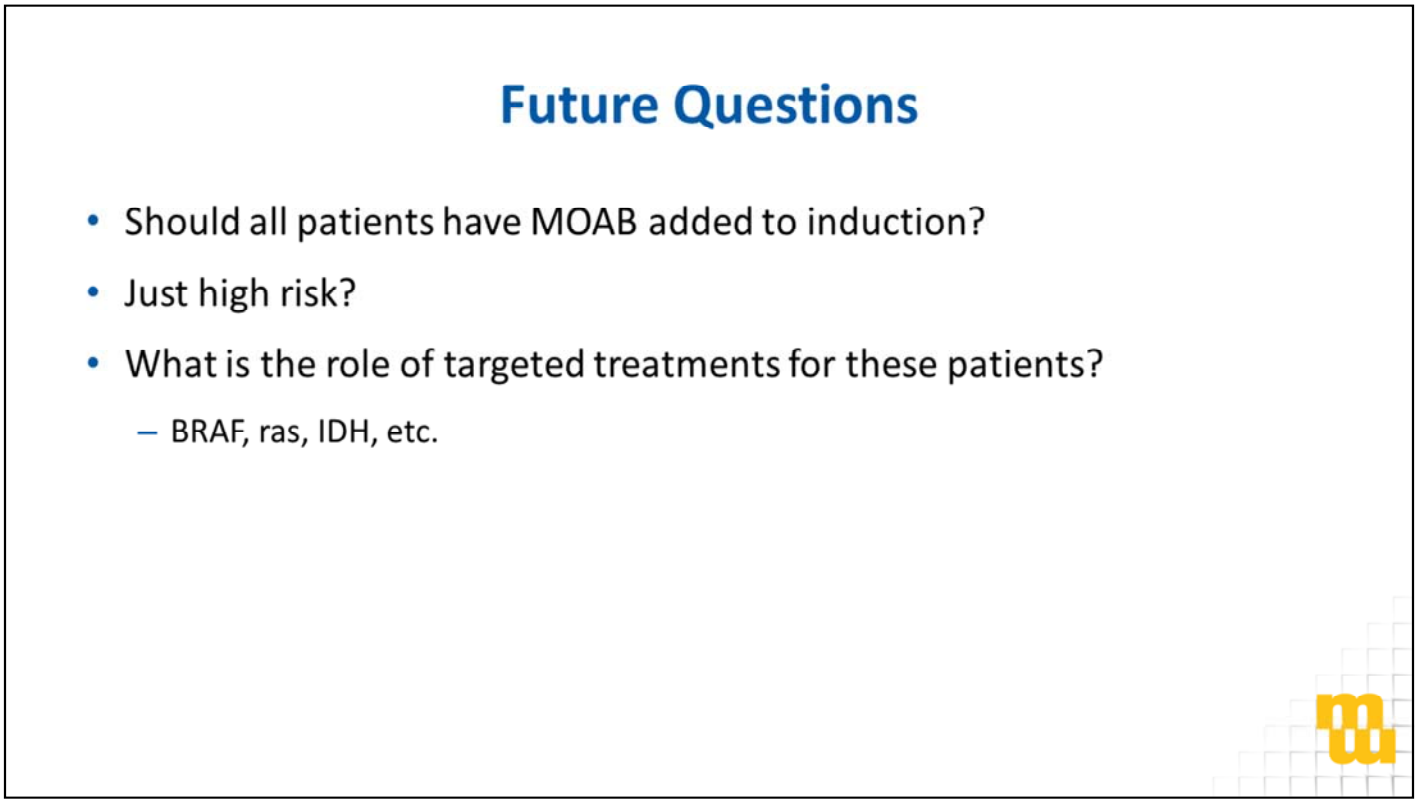
If you look at that one step further and try and understand the impact of this in terms of who really gets the most or least benefit overall, it is important to realize that the high-risk subset of patients do not appear to get as much benefit from the use of lenalidomide as a single agent as all the other patients do seem to get. That is not a surprise because we do not think about lenalidomide as being highly effective in the context of high-risk myeloma.



An alternative way to think about this is an algorithm that our group published in the *Journal of Oncology Practice* a couple of years ago that evaluates our approach based on risk-adapted maintenance therapy. As you can see, patients that have high-risk 17p deleted myeloma receive RVD as consolidation (we published this data in *Leukemia* a few years ago), patients with 4;14 get bortezomib or ixazomib or carfilzomib as maintenance therapy, and patients that have standard risk clearly seemed to benefit from lenalidomide maintenance. This is some data that I think we use as our daily practice and can be very useful to you in your overall daily practice.



By approaching this from a risk-adapted maintenance setting, what you see quite nicely is that one can, in fact, have a big narrowing of that difference in overall survival between high-risk and standard-risk when you use a risk-adapted maintenance approach. I think that this does provide you with some guidelines on how to approach maintenance therapy based on risk in your own practice.



What are future questions? I think future questions involve the role of an antibody in the context of induction therapy. Should we do it just in high risk? Should we do it in all patients? Is there a sequence for how to approach this or when to approach this? What is the role of targeted treatments? We know that subsets of patients with myeloma have BRAF mutations or IDH mutations or Ras, Raf, or MAP kinase mutations. Do we use these combinations with what we know really works to try and improve the depth of response and ultimately increase the cure fraction? These are all questions that are coming in the future as we begin to evaluate how to treat patients with myeloma.

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And many others who
are part of the B-cell team

I think you have gotten a good summary of how to do this and what the important options and questions are, and I hope that this approach has really helped you in your day-to-day care of patients with newly diagnosed myeloma. Thank you for your attention.