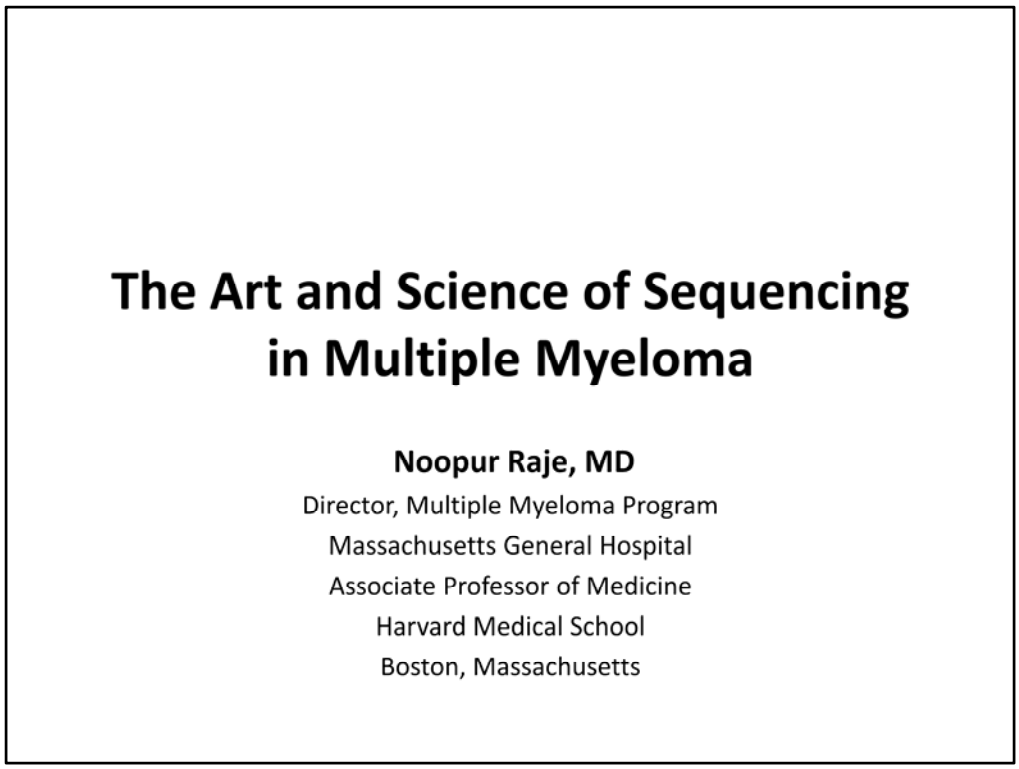
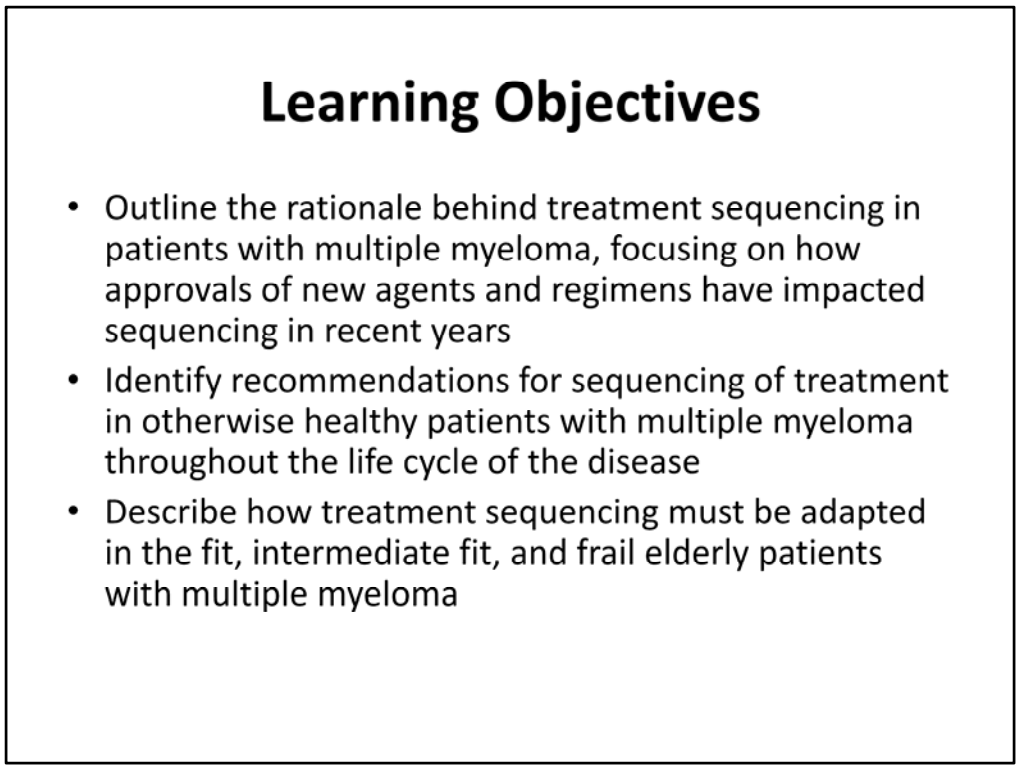
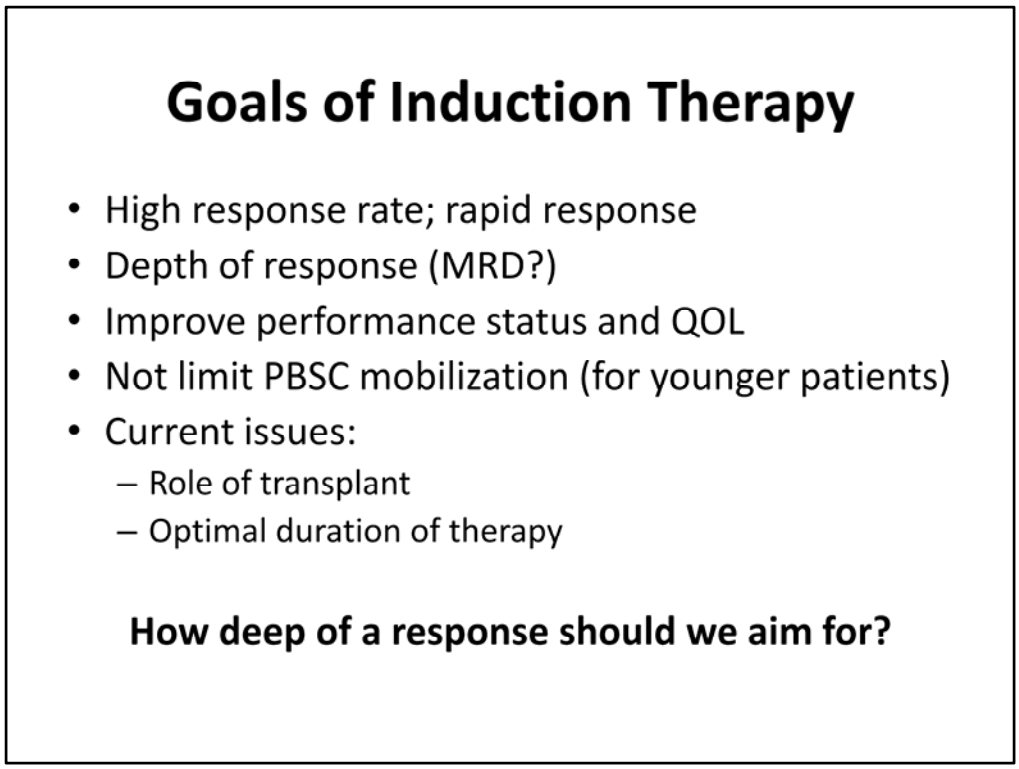
The Art and Science of Sequencing in Multiple Myeloma



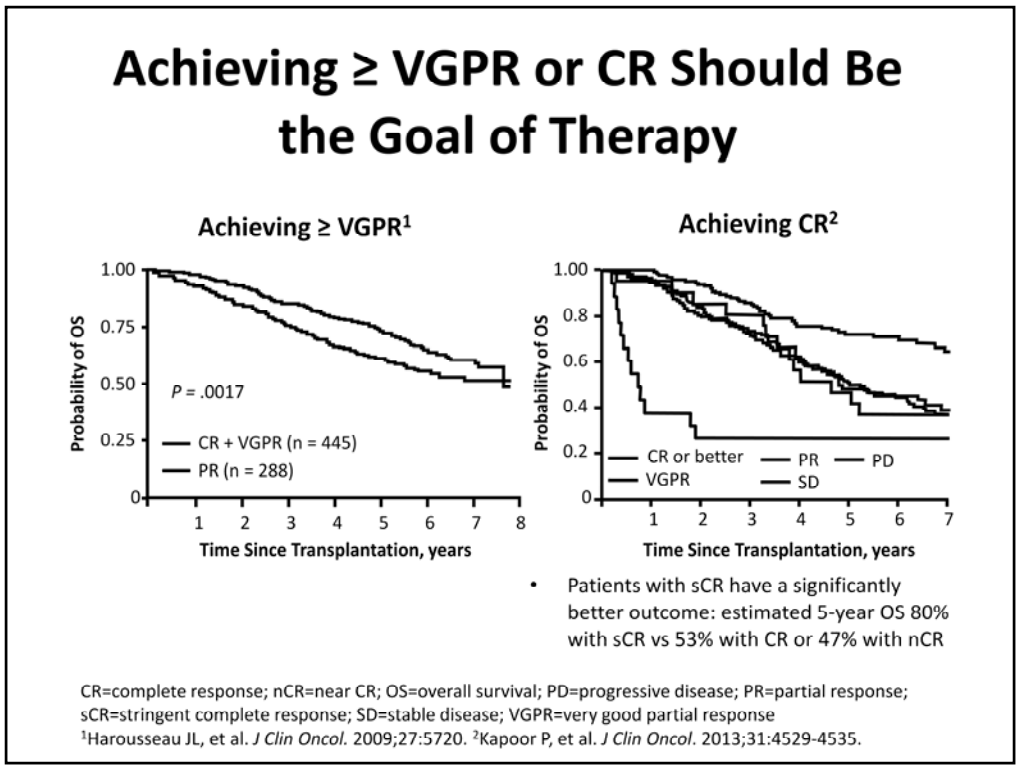
Welcome to *Managing Myeloma*. My name is Noopur Raje. I am the Director of the Center for Multiple Myeloma at Mass General in Boston. I am going to be talking to you about *The Art and Science of Sequencing in Multiple Myeloma.*



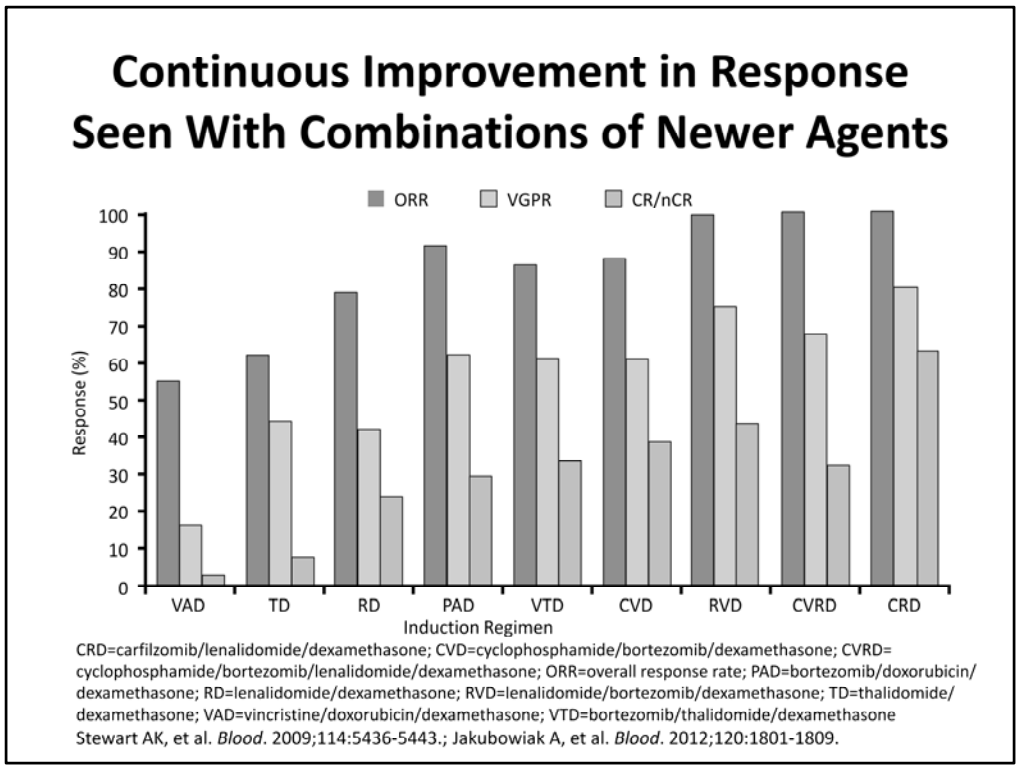
The learning objectives for today include outlining the rationale for treatment sequencing, focusing specifically on the many new drug approvals we've had recently, and the expanded number of treatments for patients with multiple myeloma. We are also going to identify recommendations for sequencing of treatment in an otherwise healthy patient with multiple myeloma. More importantly, we will also discuss sequencing treatment in the more common situation, where we have an older patient who may have associated comorbidities and may not be absolutely fit to undergo all of the available treatments for myeloma.



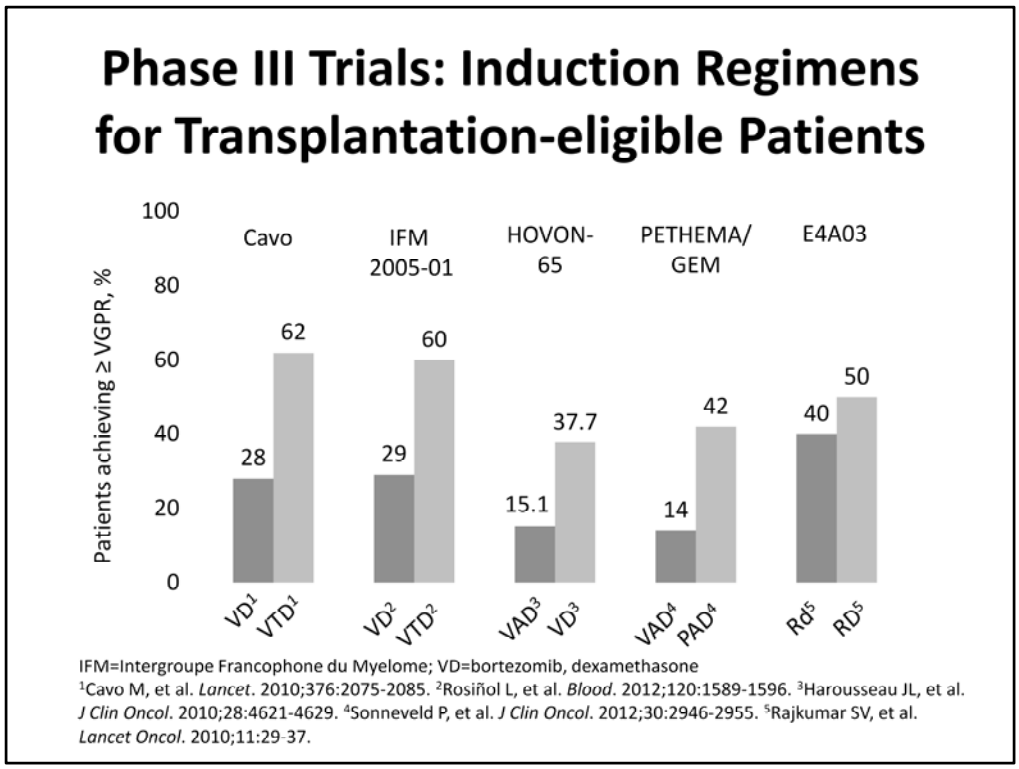
The goals of induction treatment for multiple myeloma should, however, remain the same. Always, we want to achieve a high response rate, and a rapid response rate in patients. Obviously, over the last several years, we've started thinking about depth of response in patients with multiple myeloma, so we'll talk a little bit about minimal residual disease status achievement in patients with this disease. Along with those high response rates, we want to see an improvement in performance status in patients, and we also want to improve the quality of life of our patients. Specifically in younger patients who may be transplant eligible, you want to make sure that you are not going to be limiting peripheral blood stem cell mobilization. The current issues still remain; we're still questioning the role of transplant, and we'll talk about that a little bit. The optimal duration of treatment still remains an issue, and I am not sure we necessarily have the answers to that. Again, we will be talking about depth of response, as well.



So, when you look at the younger fit patient, there is a lot of data where we have looked at responses and outcomes. There is French data, as well as the meta-analysis from Mayo Clinic which looked at achieving a complete response (CR) or a very good partial response (VGPR) or better. Suffice it to say that if you achieve a very good partial response or better, the outcome of the patient is likely to be much better in that situation. This again underscores or highlights the fact that our goal of treatment should be to achieve the best possible response in patients with multiple myeloma.

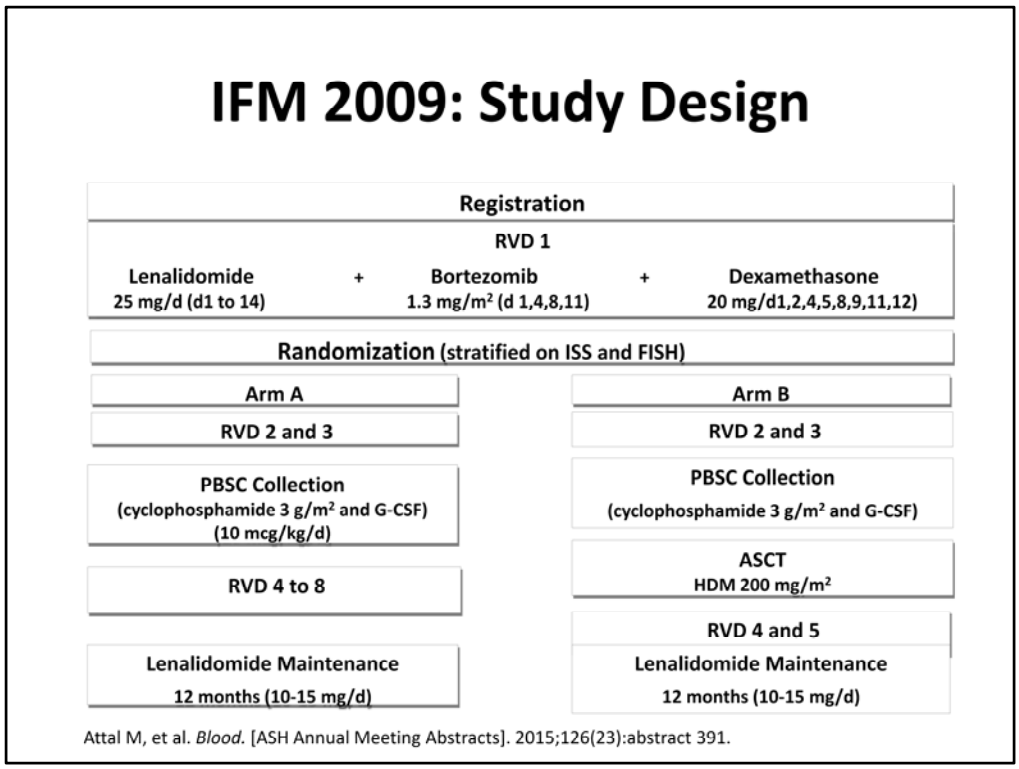


Over the last several years, we have used many different combinations, and as we have used new drugs in these combinations, we are beginning to see 100% response rates in most of our patients. So, with combinations like RVD, which includes lenalidomide, bortezomib, and dexamethasone, or KRd which is carfilzomib, lenalidomide, and dexamethasone, the overall response rate is 100%, and we are seeing VGPR or better rates of close to 70% and 80% in our patients.



IFM=Intergroupe Francophone du Myelome; VD=bortezomib, dexamethasone
[1]Cavo M, et al. *Lancet*. 2010;376:2075-2085. [2]Rosiñol L, et al. *Blood*. 2012;120:1589-1596. [3]Harousseau JL, et al. *J Clin Oncol*. 2010;28:4621-4629. [4]Sonneveld P, et al. *J Clin Oncol*. 2012;30:2946-2955. [5]Rajkumar SV, et al. *Lancet Oncol*. 2010;11:29-37.

There have been several large randomized trials where induction treatments have included novel drugs. The bottom line here is that patients who are transplant eligible should be receiving treatment that with combinations that include new drugs. As long as a new drug is incorporated in the treatment of myeloma patients, the response rates are much better when one uses either a proteosome inhibitor or an IMiD-based treatment for multiple myeloma patients.



Attal M, et al. *Blood.* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 391.

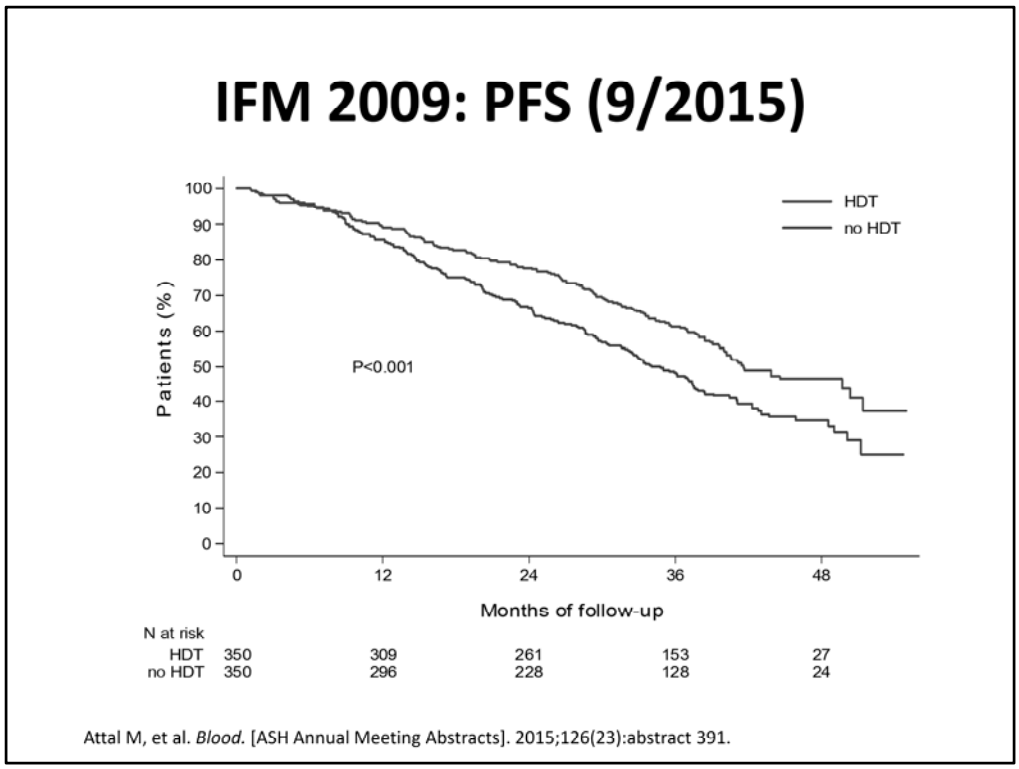
Now to answer the question of the role of transplant, given that we have seen such high response rates in patients with multiple myeloma, the IFM/DFCI has conducted a trial wherein everybody receives a combination of new drugs. In this case, the induction regimen is RVD which is lenalidomide, bortezomib, and dexamethasone, and subsequently after one cycle, they are randomized based on risk stratification of ISS, as well as cytogenetics. Everybody undergoes PBSC collection after 3 cycles, but one arm continues with RVD followed by a year's worth of maintenance. In contrast, the other arm, which is arm B in this case, is consolidated with an autologous stem cell transplant followed by 2 cycles of RVD and then maintenance for approximately a year.

IFM 2009: Best Response

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

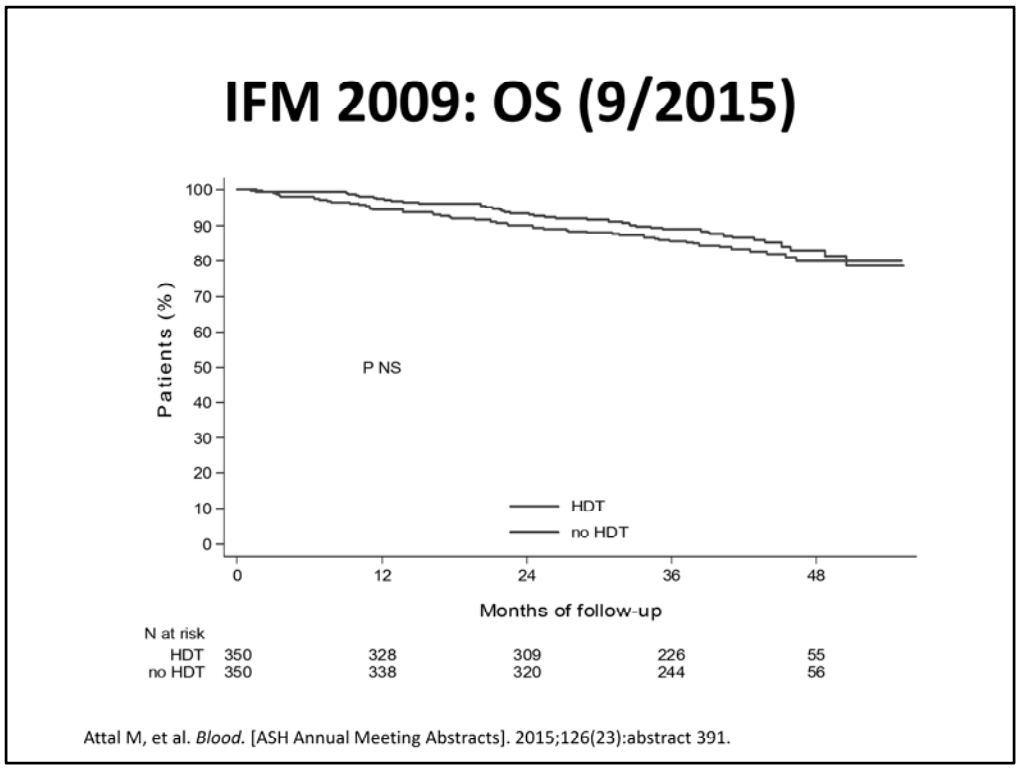
Attal M, et al. *Blood.* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 391.

If you look at the response data for this study, you will notice that the complete response rate is higher and is better than VGPR response rate in patients who are getting a transplant. This was statistically significant, and what was noted here was looking at minimal residual disease status (MRD), we saw that a higher number of patients had MRD negativity on the transplant arm, and this obviously translated into a progression-free survival benefit.



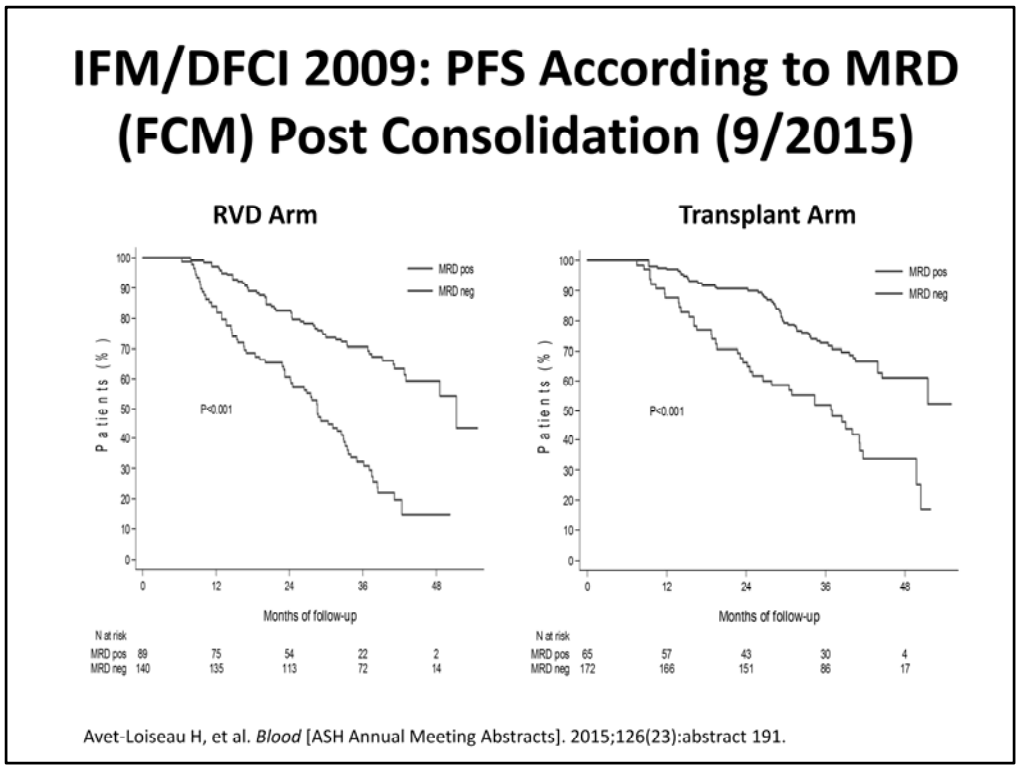
Attal M, et al. *Blood.* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 391.

As a result, the patients who received high-dose chemotherapy had a median progression-free survival of close to 40-45 months, compared to about 36 months in the non-transplant patient population.



Attal M, et al. *Blood.* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 391.

However, if you look at the overall survival of these patients, there was really no difference between an autologous transplant versus no transplant. This again underscores the fact that this question still remains unanswered, granted that the PFS survival benefit was there. One caveat with this study is that the maintenance in the French trial lasted for approximately 12 months. The ongoing trial in the United States, which is the DETERMINATION trial, is continuing maintenance for up until progression, and we will see whether or not we can translate more of these patients into MRD negativity without the transplant in itself. We will also see whether or not we can decrease that progression-free survival benefit which has been seen with transplant, but as of right now, based on this data at least, transplant certainly has a role in the context of new drugs in multiple myeloma, and transplant should be considered as part of the care of younger fit patients with multiple myeloma.



They also looked at MRD by two methods. What I am showing you here is MRD by flow cytometry, and what you can see is that any patient who achieved an MRD negative status did much better, regardless of whether they were in the RVD arm or whether they were in the transplant arm. This again underscores what we've seen with responses: the deeper the response, the better the outcome.

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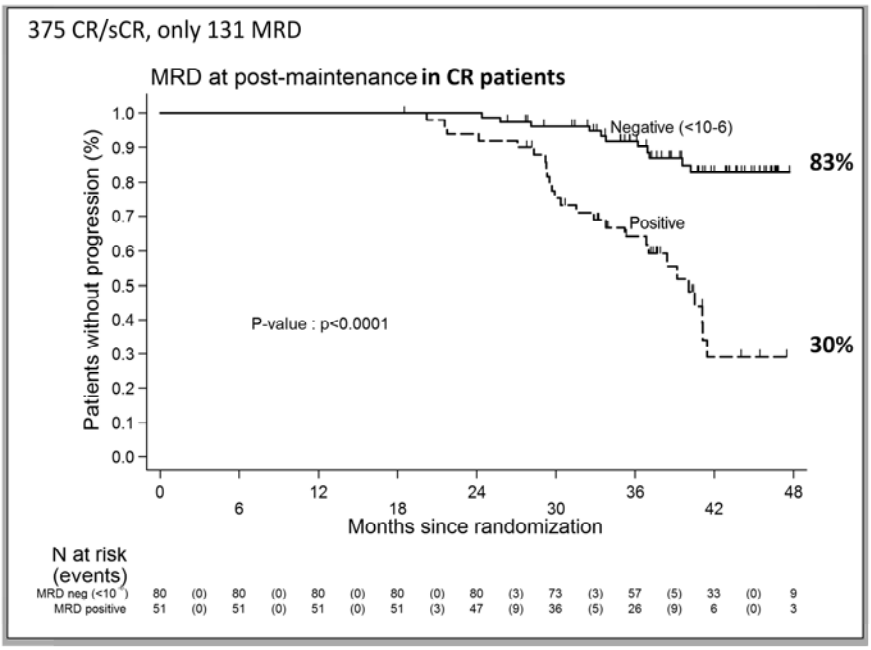
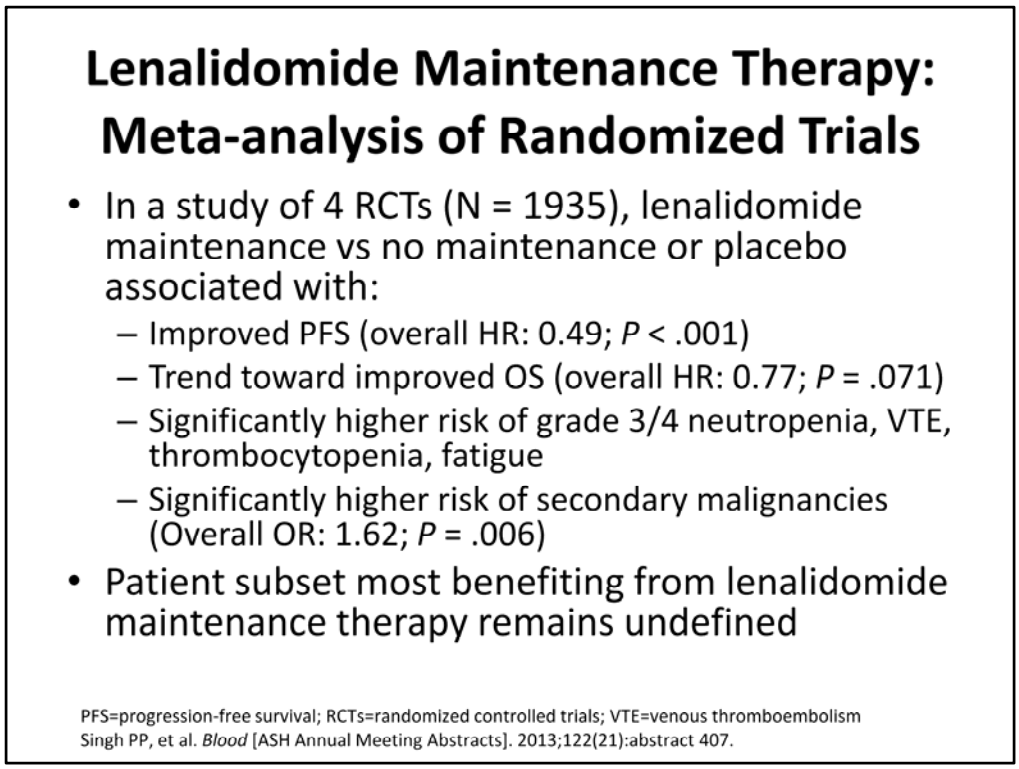
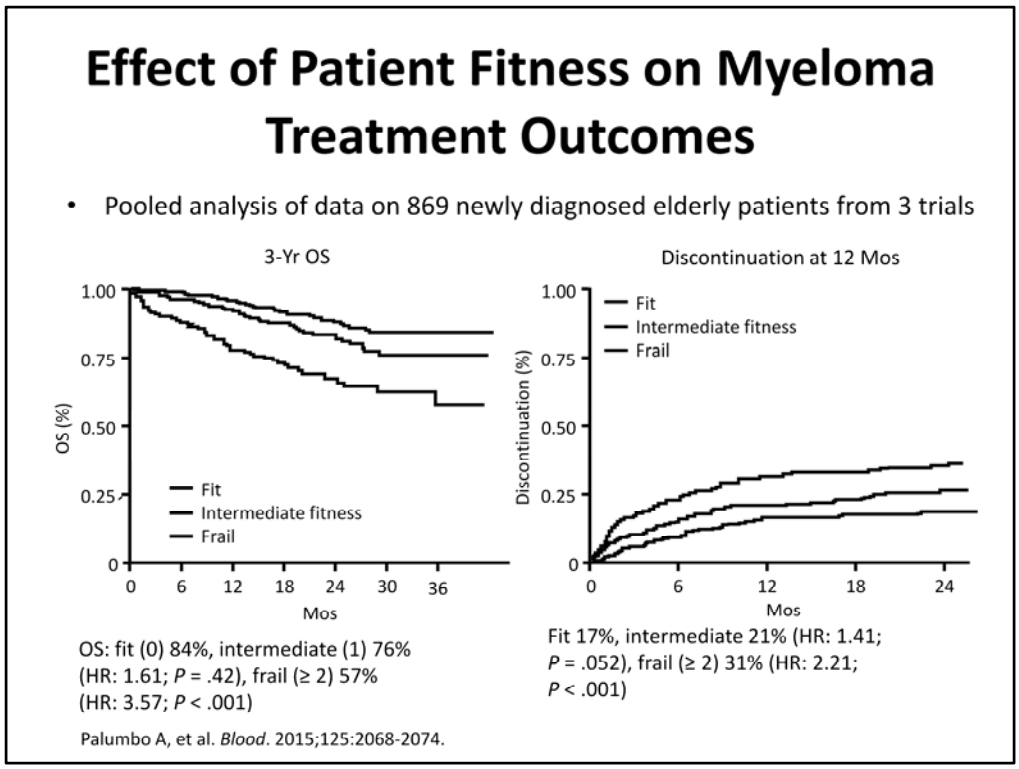


Avet-Loiseau H, et al. *Blood* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 191.

Another method of achieving MRD negativity is by genotypic methods. The genotypic method of achieving MRD negativity also translates into better progression-free survival. Again, this underscores the fact that the best response will be through achieving an MRD negative status, whether it be by flow cytometry or by genotypic methods, and this should be the goal of our treatment in the younger, fit patient.



We have used maintenance treatment for a long time, and as I alluded to in the French study, maintenance lenalidomide was continued for approximately one year. The practice in the United States is continuing maintenance lenalidomide up until progression. There has been a large meta-analysis done with four large randomized trials with close to 2,000 patients, and what this suggests is that adding on maintenance does improve progression-free survival, and does decrease the potential of relapse with multiple myeloma. What we have also seen is that continued maintenance does actually increase the depth of response in patients. Hopefully, with this knowledge, we will be able to convert more patients into MRD negative status.



So, what about older patients with multiple myeloma? As you all know, the median age for diagnosis in multiple myeloma is close to 67-70 years. So, the majority of patients tend to be non-transplant eligible, and what Dr. Palumbo has very nicely done is divided these patients based on their frailty score. This includes looking at age, comorbidities, etc., so that if you look the overall survival of fit patients, it is always much better than those patients who are more frail. This may also be related to the kind of treatment we are able to institute in these patients and also their ability to tolerate some of this treatment. I do think you have to consider the patient's fitness level when prescribing medications, and you may need to alter dosing to reflect a patient's frailty.

Myeloma in Octogenarians: The Era of Modern Myeloma Therapy

- More moderate to severe renal impairment
- Worsening PS (≥ 2)
- More frequent ISS 3 disease
- Cytogenetics different; less frequently del(17p) and t(4;14)
- Efficacy comparisons between those < 65 vs ≥ 80 years of age

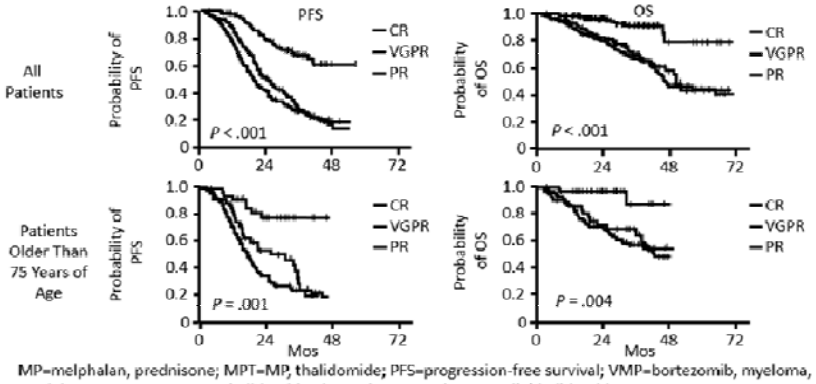
Outcome	Pts < 65 Yrs of Age	Pts ≥ 80 Yrs of Age
Response to therapy, %	85	63
Median PFS, mos	31	11
OS	66% at 5 yrs	Median 19.5 mos
Early mortality at 2 mos, %	3	14

ISS=International Staging System
Dimopoulos M, et al. *Blood* [ASH Annual Meeting Abstracts]. 2014;124(21):abstract 4738.

As all of us are getting older now, we are seeing more and more patients in their 80s with multiple myeloma, and the difference between patients in their 80s and much younger patients is obviously because of their associated comorbidities. We tend to see more renal impairment in these patients; we also see worsening performance status in these patients, as well as higher stages. We have not really seen much in terms of worsened cytogenetic prognostic factors; it is primarily the comorbidities which compound problems and which can impact how we treat these patients with multiple myeloma.

CR Correlates With Long-term Survival in Elderly Patients Treated With Novel Agents

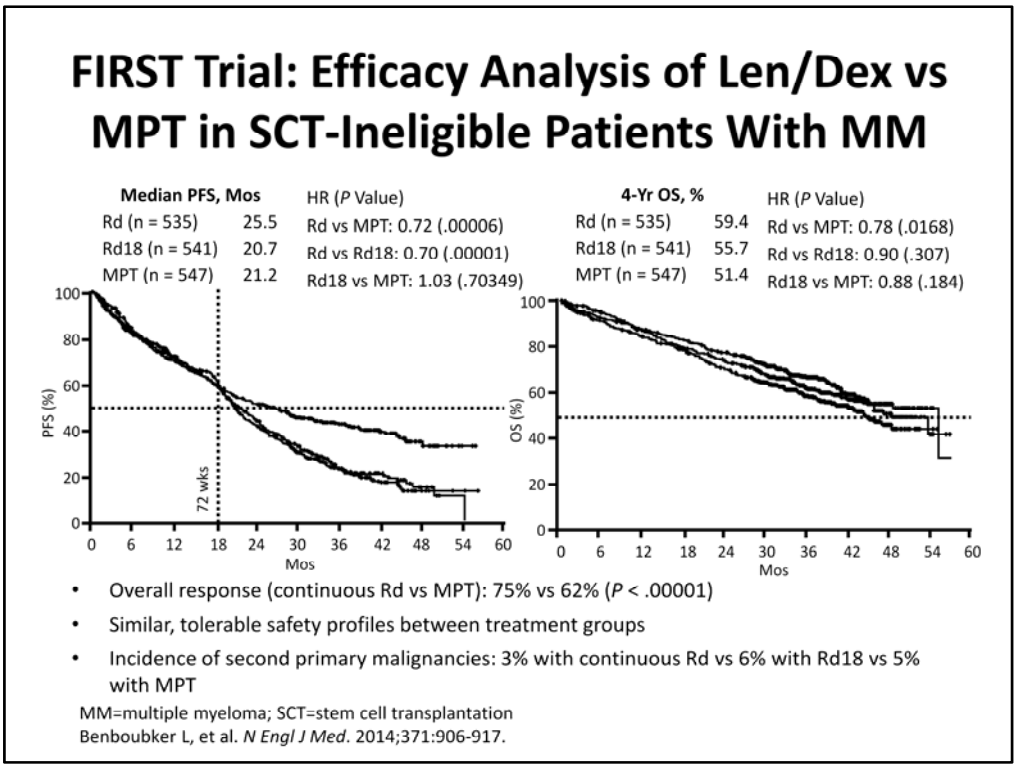
- Retrospective analysis: 3 randomized trials of GIMEMA and HOVON (N = 1175)
  - First-line treatment: MP (n = 332), MPT (n = 332), VMP (n = 257), VMPT-VT (n = 254)



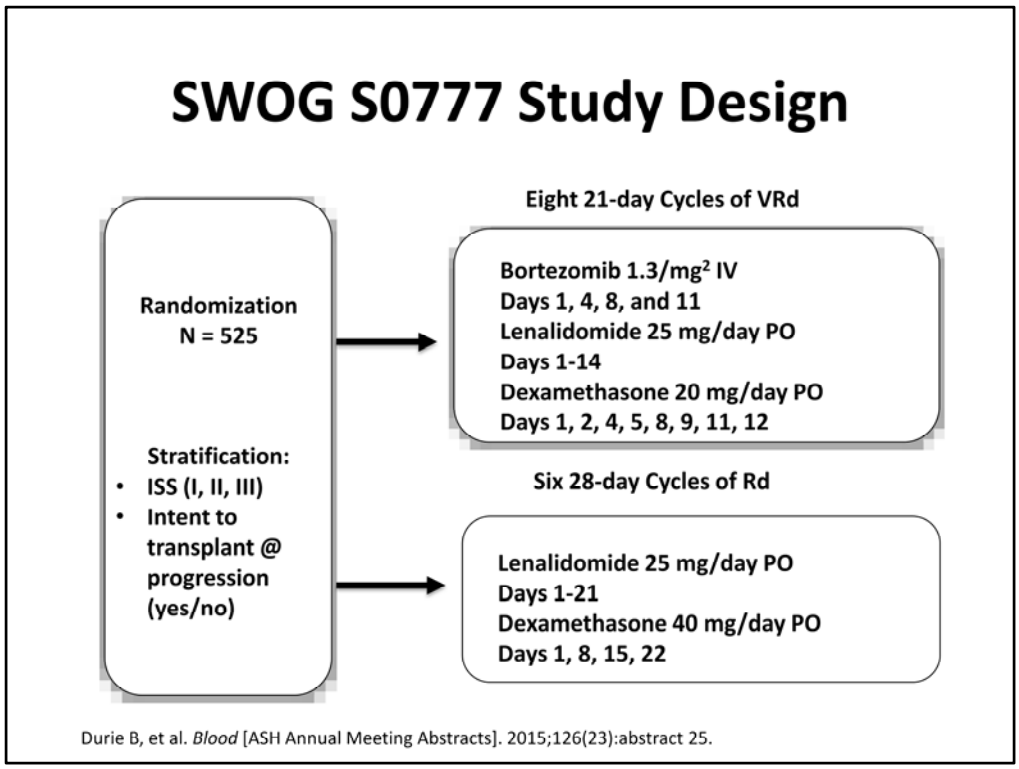
MP=melphalan, prednisone; MPT=MP, thalidomide; PFS=progression-free survival; VMP=bortezomib, myeloma, prednisone; VMPT-VT=VMP, thalidomide plus maintenance bortezomib/thalidomide

Gay F, et al. *Blood*. 2011;117:3025-3031.

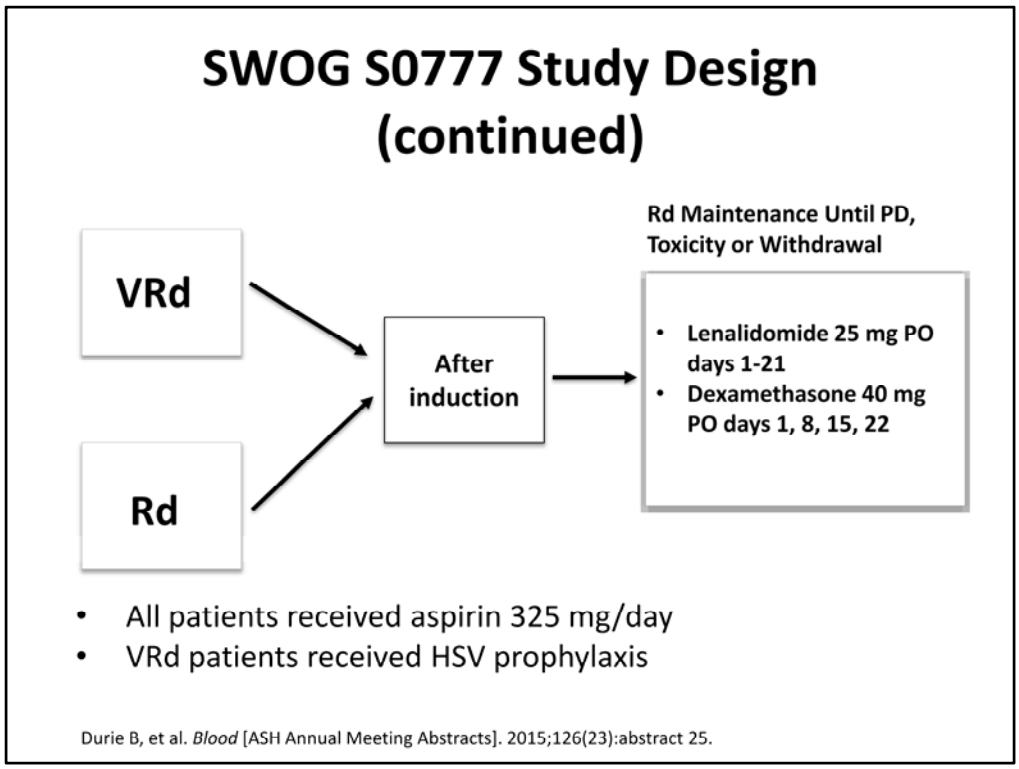
So, it is really quite important to identify the dosing schedule for these patients. Nonetheless, even in these older patients, similar to the data from younger patients that I showed you previously, response does matter. If you can get patients into a complete response, whether they are old or young, their outcome is significantly improved compared to patients who achieve a PR or less. Even in an older patient in their 70s or 80s, I think the goal of treatment for multiple myeloma should be to try and achieve the best possible response. One will need to take into account dose modifications based on comorbidities, renal dysfunction, cardiac history, and so on and so forth, before picking the optimal treatment for these patients.



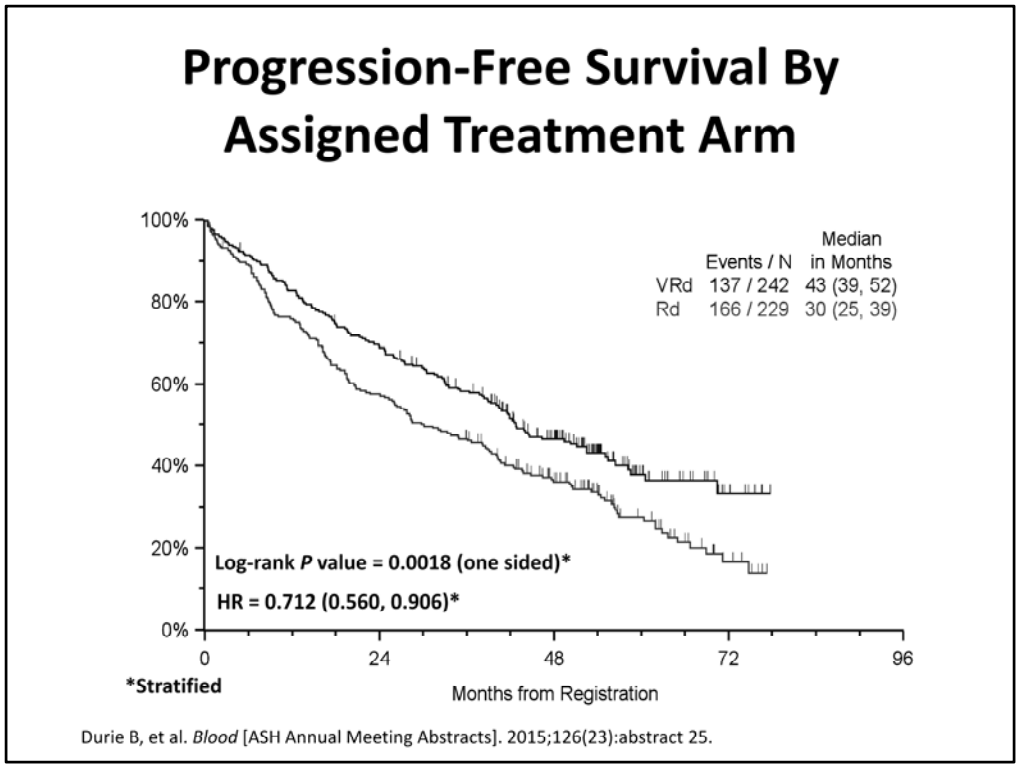
And again, we have seen data from the FIRST trial, where Dr. Thierry Facon looked at nearly 1,500 non-transplant eligible patients in a very large randomized trial. Patients were randomized to receive either lenalidomide-dexamethasone or the old standard of MPT for 18 months. What was overwhelmingly seen was that, if patients continued on treatment, there was a significant improvement in progression-free survival, which also translated into an overall survival benefit. Again, this underscores the fact that you have to continue treatment and maintaining people on continued lenalidomide actually deepens their responses, which translates into both better disease control as well as overall survival.



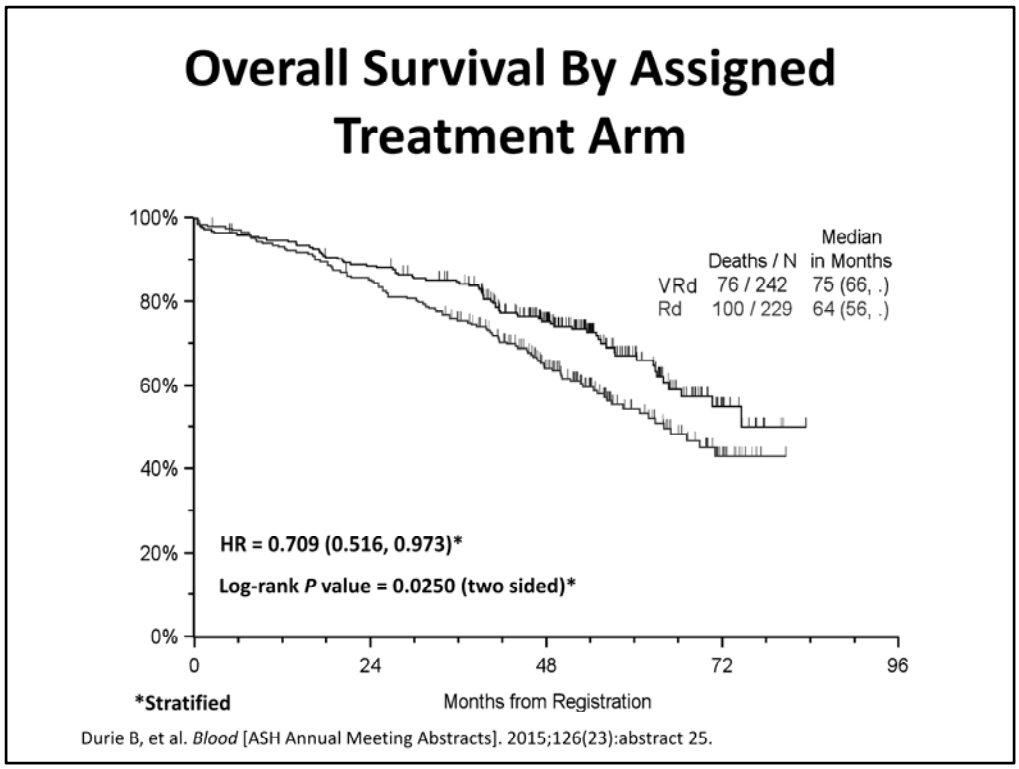
Dr. Durie presented the SWOG S0777 study at ASH, in which more than 500 non-transplant-eligible patients were randomized to receive lenalidomide-dexamethasone, similar to the FIRST trial, versus the triplet combination of lenalidomide, bortezomib, and dexamethasone.



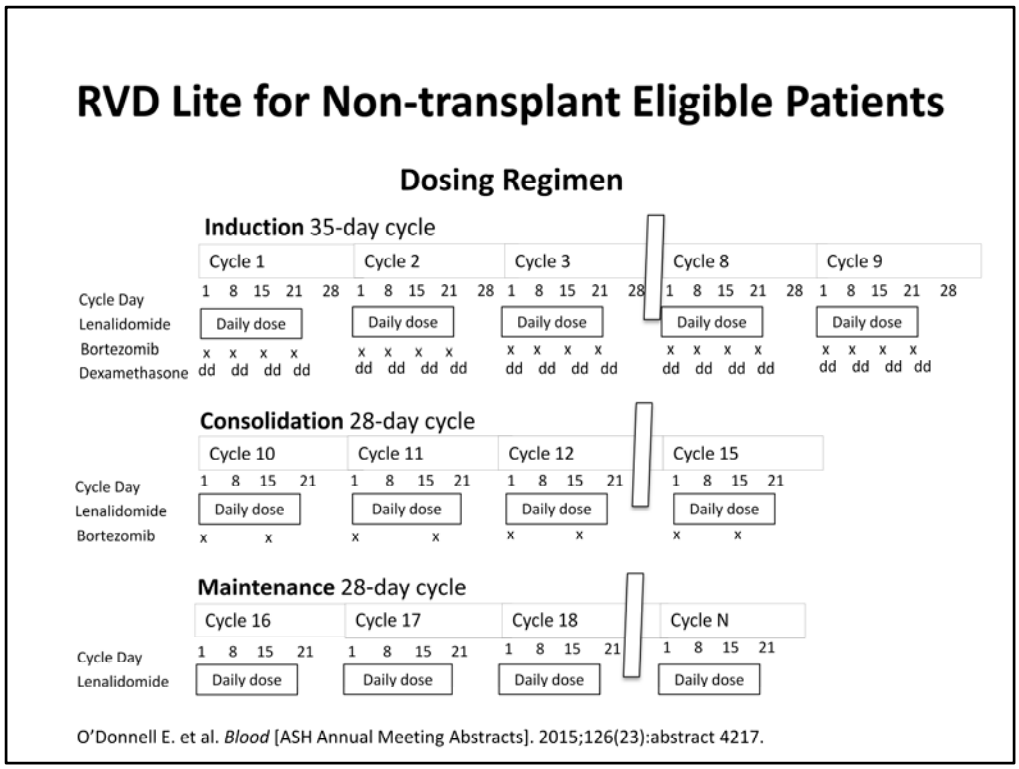
After induction, these patients were allowed to go on to lenalidomide maintenance.



And what was seen was a significant progression-free survival benefit in patients who were in the triplet arm. So, bortezomib, lenalidomide, and dexamethasone did much better in terms of progression-free survival outcomes, compared to the doublet of lenalidomide-dexamethasone.



What was most telling, however, was the overall survival data. If you look at the overall survival data, you see a statistically significant improvement in overall survival in patients who received the triplet, versus those who received RD.



So, these are older patients who have not gotten a transplant. At our center, we are using RVD-Lite, because as I mentioned, as patients get older, we need to modify doses of both lenalidomide and bortezomib. What we have done in this RVD-Lite schedule is use weekly bortezomib given in a subcutaneous fashion, lower doses of lenalidomide at 15 mg and lower doses of dexamethasone. With this, we have seen VGPR better than 90% or so, and most patients tolerate this extremely well. So again, underscoring the need for dose adjusting in patients with multiple myeloma.

Suggested Empiric Age-Adjusted Dose Reduction in Patients With Myeloma

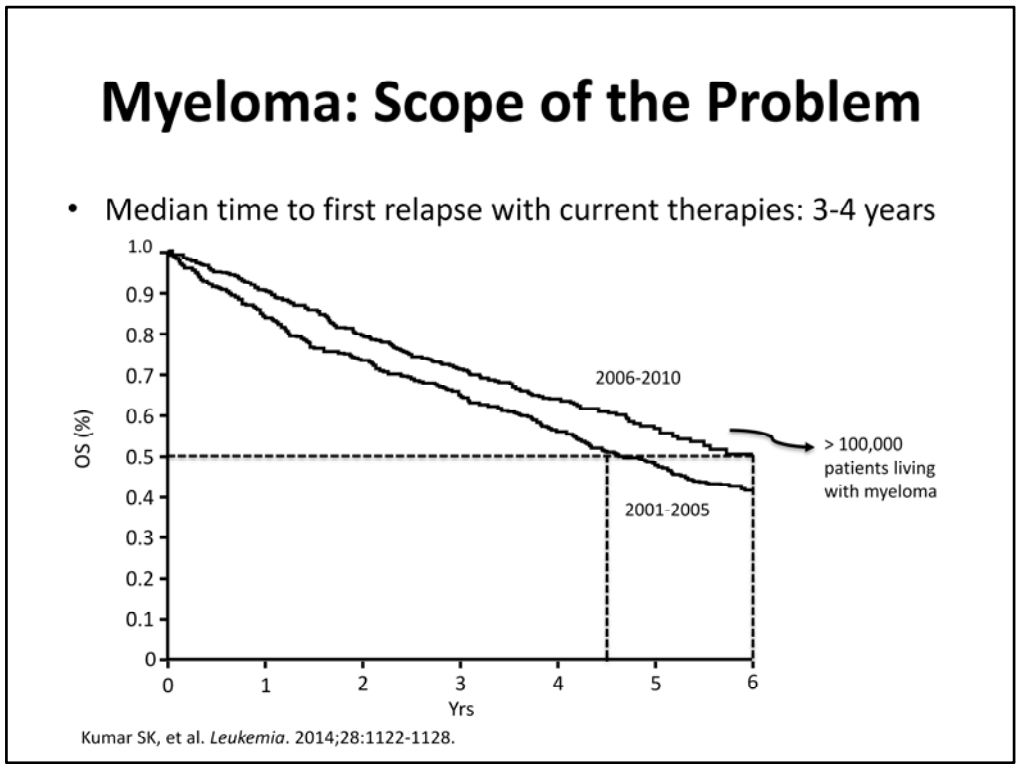
Agent	Younger Than 65 Years	65-75 Years	Older Than 75 Years
Dexamethasone	40 mg/day on Days 1-4, 15-18 q4w ***or*** Days 1, 8, 15, 22 q4w	40 mg/day on Days 1, 8, 15, 22 q4w	20 mg/day on Days 1, 8, 15, 22 q4w
Melphalan	0.25 mg/kg on Days 1-4 q6w	0.25 mg/kg on Days 1-4 q6w ***or*** 0.18 mg/kg on Days 1-4 q4w	0.18 mg/kg on Days 1-4 q6w ***or*** 0.13 mg/kg on Days 1-4 q4w
Cyclophosphamide	300 mg/day on Days 1, 8, 15, 22 q4w	300 mg/day on Days 1, 8, 15 q4w ***or*** 50 mg/day on Days 1-21 q4w	50 mg/day on Days 1-21 q4w ***or*** 50 mg/day QOD on Days 1-21 q4w
Thalidomide	200 mg/day	100 mg/day ***or*** 200 mg/day	50 mg/day to 100 mg/day
Lenalidomide	25 mg/day on Days 1-21 q4w	15-25 mg/day on Days 1-21 q4w	10-25 mg/day on Days 1-21 q4w
Bortezomib	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 q3w	1.3 mg/m^2 bolus on Days 1, 4, 8, 11 q3w ***or*** on Days 1, 8, 15, 22 q5w	1.0- 1.3 mg/m^2 bolus on Days 1, 8, 15, 22 q5w

Palumbo A, et al. *N Engl J Med*. 2011;364:1046-1060.

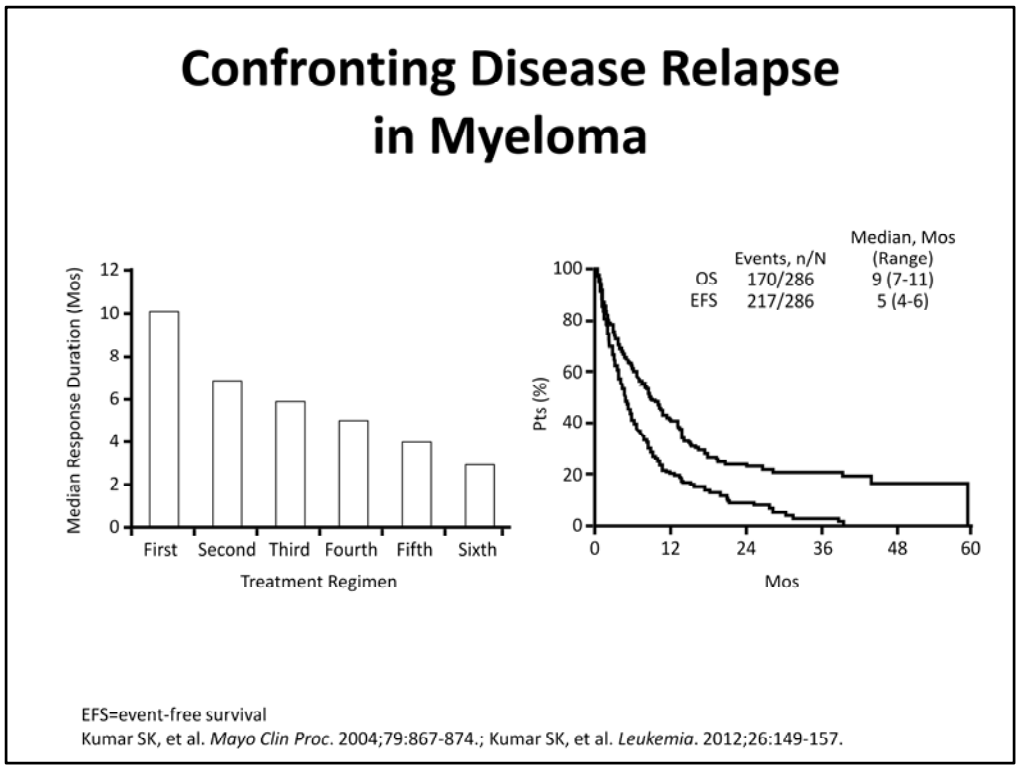
There was a very nice article published by Drs. Antonio Palumbo and Ken Anderson in *The New England Journal of Medicine* focusing on age-adjusted dose reduction in multiple myeloma patients. I would encourage everybody to look at this paper because it highlights how important it is to modify doses depending on the age of patients for those individuals between ages 65 and 75, as well as those older than 75. The article also demonstrates how important it is to keep patients on treatment for protracted periods of time, as has been seen in the FIRST trial.

Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med.* 2011;364(11):1046-60. *http://www.nejm.org/doi/full/10.1056/NEJMra1011442*

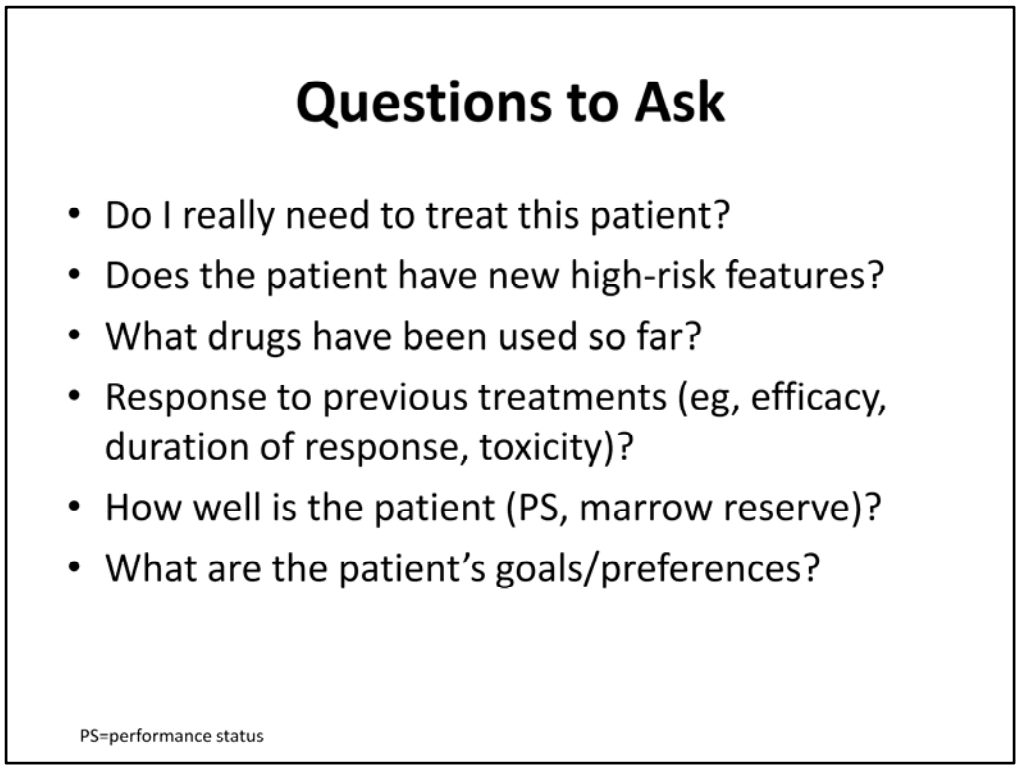
See also Palumbo A, Bringhen S, Ludwig H, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). *Blood*. 2011;118(17):4519-4529. *http://www.bloodjournal.org/content/118/17/4519.long*



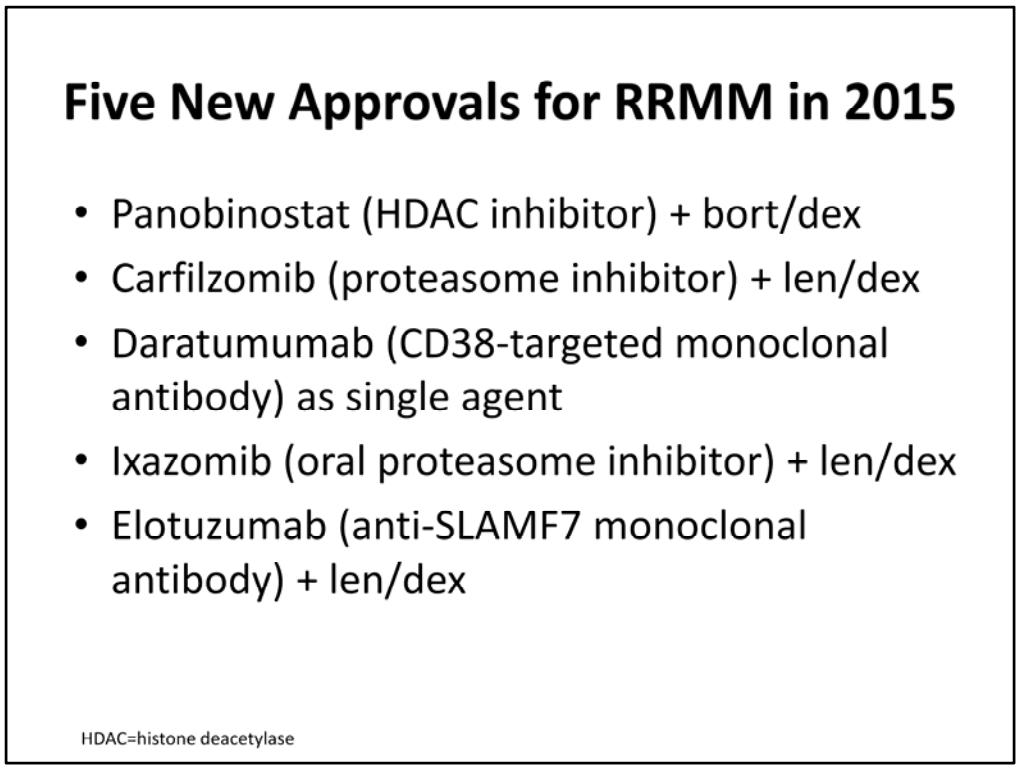
What we are beginning to see is that multiple myeloma patients regardless of stage are living much, much longer – anywhere between 7 and 14 years, currently. This survival continues to improve as we see newer and better treatments and, today, typically, the first relapse occurs at about 3 to 4 years. At any given time, we have about 100,000 or more patients now with multiple myeloma living in the United States.



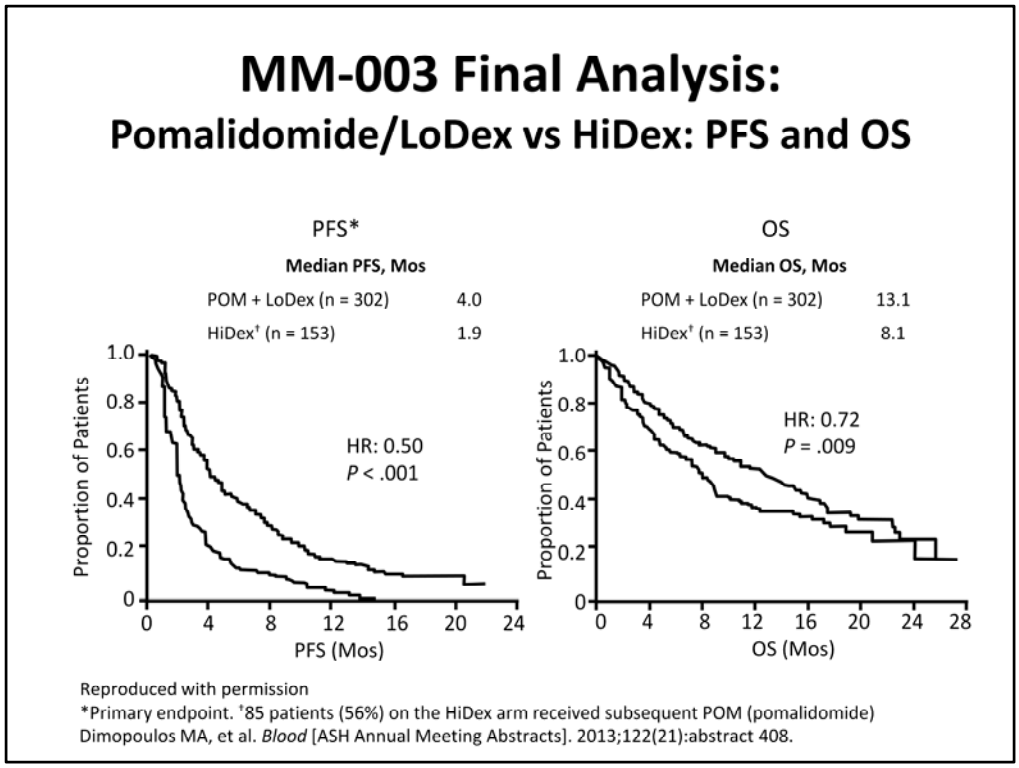
We also know that, with every relapse, patient response will generally decrease. Patients do tend to respond to treatment after relapse, but their response will be reduced after subsequent relapses, and the duration of remission keeps tending to get smaller. This is something we must consider when sequencing these drugs, especially now when we have a whole plethora of agents that we can choose from in the treatment of relapsed/refractory myeloma.



Before you treat a patient with relapsed/refractory myeloma, though, I think it is important to address several questions. The first question to ask is, do you really need to treat this patient? Or is this just a biochemical relapse where you are seeing a slight increase in M-protein, all the light chains, and can you just follow this patient along? At the time of relapse, does this patient have new high-risk features? In my opinion, it is really quite important to repeat a bone marrow, because, as we all know, patients with myeloma will evolve genetically. It is important to see what happens at the time of relapse and repeat bone marrows for that reason. It is also important to see what drugs they have received in the past, what was the nature of their response, how well did they tolerate those treatments, and how long was the response to those treatments. Again, very important to understand what the toxicity from the previous treatment is, so that you can modify what you are going to use. And then obviously, the few questions you have to ask about the patient themselves is, what is the performance status at the time of this relapse, what is the matter observed, is this patient going to be able to tolerate treatment, and what are the doses that the patient is going to be able to tolerate? And obviously, the most important thing is the patient. You do have to take into account patient preferences, what the patient's goals of treatment are, and I think it is important to have all of these discussions every time one is considering treatment of relapsed disease.



We have, as I have mentioned already, a number of new drugs are now available. So, while this is a good place to start, it can also be very confusing. As you all know, we had five new drug approvals in 2015 alone. So, while we are very fortunate to have that many new agents in multiple myeloma, it also becomes challenging in terms of selecting the most appropriate therapy for our patients. As you all know, we have panobinostat, which has been approved with bortezomib and dexamethasone. Carfilzomib is now approved in combination with lenalidomide-dexamethasone. Daratumumab is approved as a single agent. We have ixazomib and we have elotuzumab, both of them approved with lenalidomide and dexamethasone. We are going to review some of the data to clarify which patients we'll be able to use with these drugs, which will hopefully allow us some insight into treatment selection.



I do want to mention pomalidomide, as well. We have data with pomalidomide when compared to dexamethasone, which has resulted in pomalidomide being approved in patients who are lenalidomide-refractory. These patients saw a progression-free survival benefit, as well as an overall survival benefit.

Pom + LoDex + Bortezomib in Relapsed MM

Cohort	ORR
Cohort 1 (n=3)	2 (67%)
Cohort 2 (n=3)	1 (33%)
Cohort 3 (n=3)	3 (100%)
Cohort 4 (n=3)	3 (100%)
Cohort 5 + Exp Cohort (n=9)	6 (67%)*

* 8 of 9 patients were evaluable for response; one patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer.
Exp=expansion; LMWH=low-molecular-weight heparin; QD=every day; RRMM=relapsed/refractory MM
Richardson PG, et al. *Blood* [ASH Annual Meeting Abstracts]. 2013;122:abstract 1969.

I am going to show you data from some of the phase II trials, which have resulted in a new phase III trial. This is pomalidomide with low-dose dexamethasone and bortezomib, so PVD, and this has been done in a phase I and II study, and now we are, in fact, doing the phase III trial as we speak with this combination. This is a perfectly reasonable combination in patients who are progressing on lenalidomide, because this is the common relapse that you are going to see. Our patients who have had RVD have had either a transplant or no transplant and then been on lenalidomide and then progressed. So, what you do in that situation? Adding on pomalidomide would be perfectly reasonable, if they have not seen a proteasome inhibitor for a long time before they relapsed on the lenalidomide. Adding in a proteosome inhibitor at this point in time is something one would consider doing in this patient population.

Phase II Trial: Carfilzomib/Pomalidomide/ Dexamethasone in Patients With RRMM

N = 79

Induction
(cycles 1-6, 28-day cycle)

- Carfilzomib 20 mg/m^2 days 1,2 of cycle 1; 27 mg/m^2 days 8,9,15,16 cycle 1, all days of following cycles
- Dexamethasone 40 mg Days 1,8,15,22
- Pomalidomide 4 mg Days 1-21

- Maintenance cycles: cycles 7+, 28-day cycle, carfilzomib 27 mg/m^2 Days 1,2,15,16; dexamethasone and pomalidomide dosing remain unchanged
- Coagulation prophylaxis with aspirin 81 mg QD or LMWH in aspirin-intolerant patients
- Antiviral therapy administered with treatment
- All patients refractory to previous lenalidomide treatment

Shah JJ, et al. *Blood* [ASH Annual Meeting Abstracts]. 2013;122(21):abstract 690.

We also have data with the other proteosome inhibitor, carfilzomib. So, pomalidomide has been combined with carfilzomib and dexamethasone in the relapsed/refractory setting.

Car-Pom-d Outcomes: ORR, DOR, PFS, and OS

Outcome	Patient Response
≥ VGPR, %	27
ORR, %	70
CBR, %	83
DOR (median), mos	17.7
PFS (median), mos	9.7
OS (median), mos	> 18

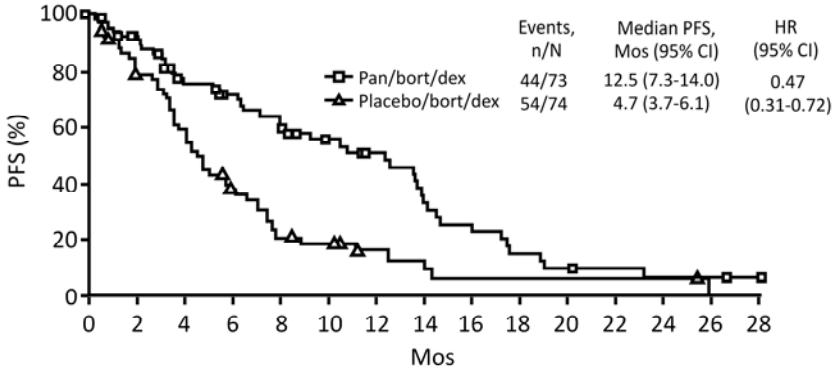
- Median number prior patient therapy lines: 5
- In patients with high-risk FISH/cytogenetic status (n = 18), the ORR was 78% (n = 14)
- 49% of patients had high- or intermediate-risk status at baseline
- PFS and OS were sustained independent of risk status

CBR=clinical benefit rate; DOR=duration of response; FISH=fluorescence in situ hybridization
Shah JJ, et al. *Blood* [ASH Annual Meeting Abstracts]. 2013;122(21):abstract 690. Reproduced with permission.

And what you see with this combination is a very high overall response rate of close to 70%, with nearly 30% of these patients achieving a VGPR or better. This is quite remarkable in patients who have otherwise failed both lenalidomide and bortezomib in the frontline setting, which is generally the patient population that we deal with in the United States, because the majority of us tend to use combinations.

PANORAMA 1: Bort/Dex ± Panobinostat in RR Myeloma, Prior Bort and IMiDs

- Subgroup analysis of patients who received ≥ 2 previous treatments, including bortezomib and an IMiD
  - FDA approved indication based on subgroup analysis



IMiD=immunomodulatory agent; Pan=panobinostat; RR=relapsed/refractory
San-Miguel JF, et al. *J Clin Oncol*. 2015;33(18): (suppl; abstract 8526).

This is data from the PANORAMA 1 trial, which was the trial that earned panobinostat its approval. As of right now, panobinostat is approved based on the sub-group analysis in patients who had two previous lines of treatment with bortezomib as well as an IMiD and then progressed. This is fairly straightforward in the majority of patients. So, the way I think about using panobinostat is, if I am thinking of using bortezomib in any of my patients and they have had two prior lines of treatment, I would rather add the bortezomib with panobinostat. There was a progression-free survival in this patient population, and I think it is important to understand that you may need to adjust the dose of panobinostat, although it is approved as 20 mg given three times a week. Depending on diarrhea and thrombocytopenia, it is important to dose adjust in patients when they are on bortezomib.

Pom + Ricolinostat: Phase 2
Maximum % Change in M-Protein

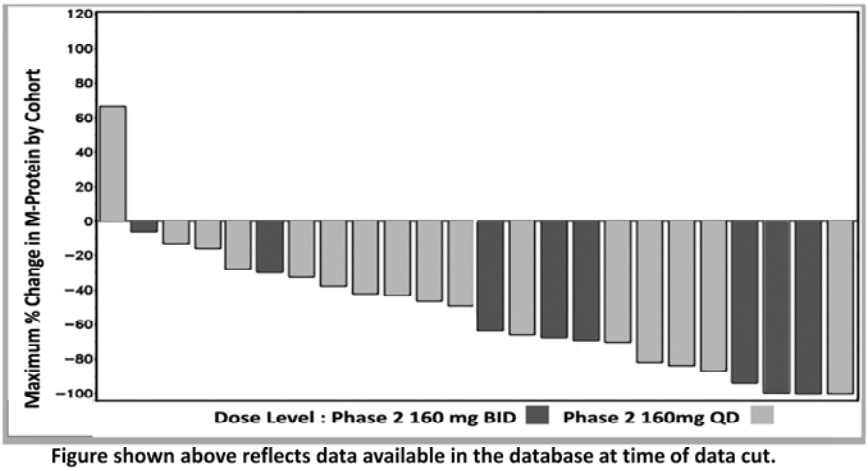
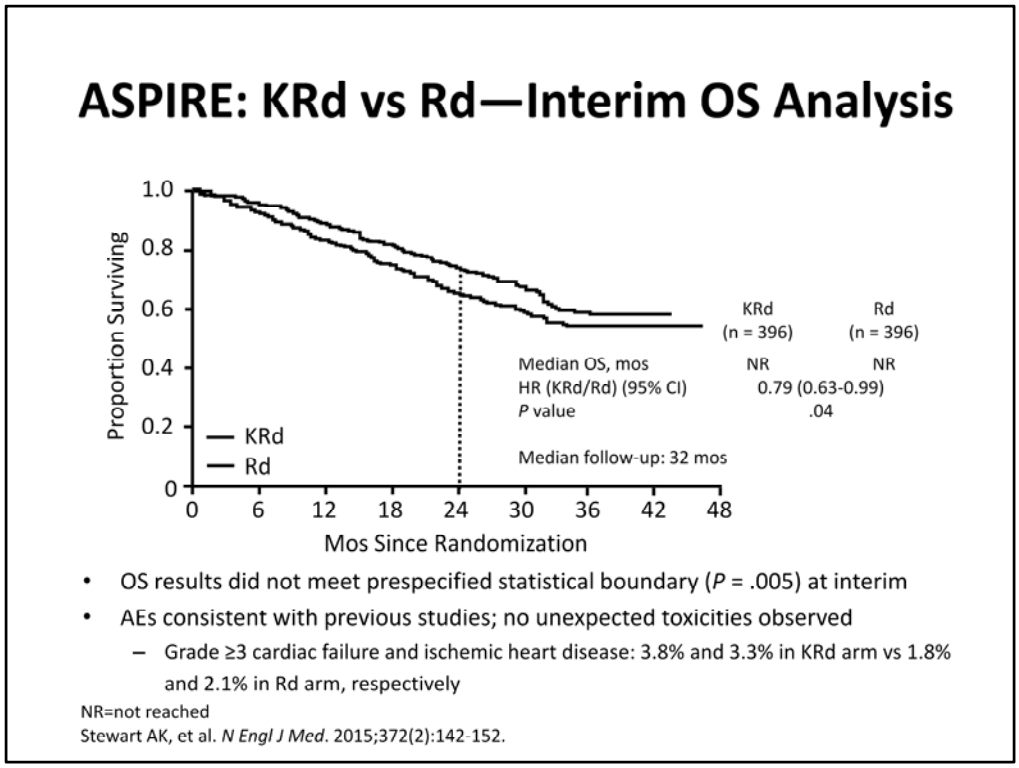


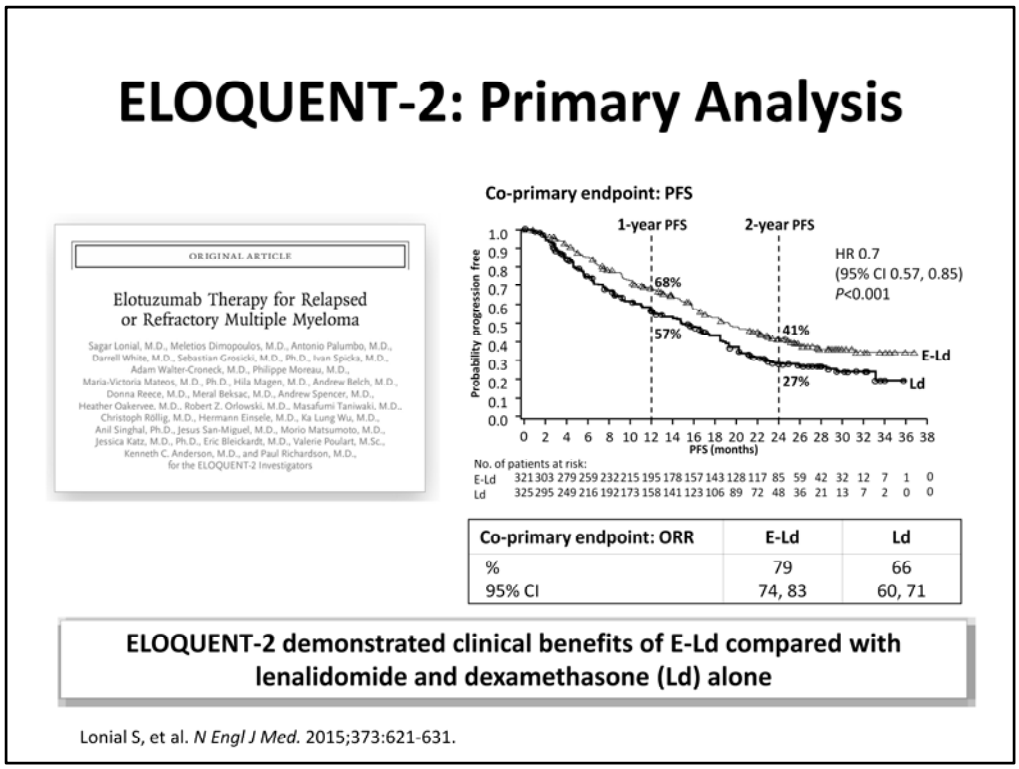
Figure shown above reflects data available in the database at time of data cut.
Additional 4 patients are represented in response tables after further query of sites.

Raje N, et al. EHA 2015 Abstract P279 Available at *http://learningcenter.ehaweb.org/eha/2015/20th/100529/noopur.raje.ricolinostat.(acy-1215).the.first.selective.hdac6.inhibitor.in.html*. Last Accessed February 17, 2016.

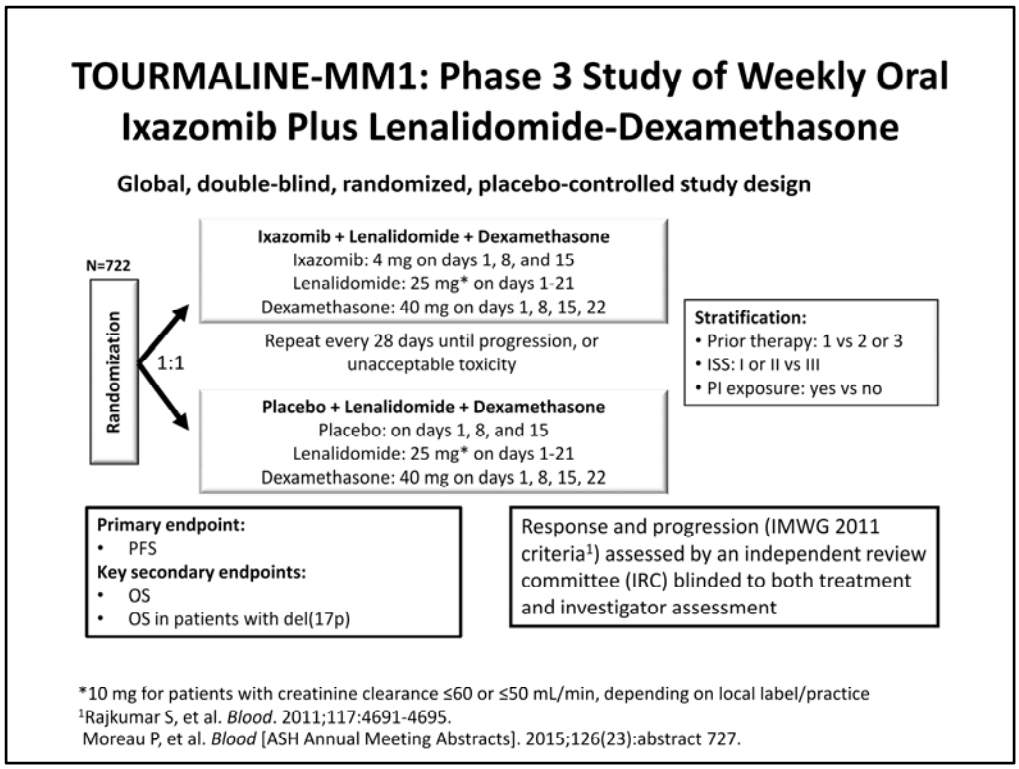
There is now more and more data in the context of HDAC inhibitors and the use of other IMiDs. So, we are using IMiDs in combination panobinostat and other HDAC inhibitors, which I will talk about.



The other drug combination which did get approved was the KRD combination which is called carfilzomib, lenalidomide, and dexamethasone. This is data which all of you are familiar with, it is the ASPIRE trial. There was a survival benefit, as well as a progression-free survival, and the PFS was close 8 to 9 months. There are other studies which are followed through which have compared carfilzomib with bortezomib in the relapsed/refractory setting and have shown an improvement in progression-free survival with the carfilzomib-containing treatment. So, carfilzomib would be a perfectly reasonable proteosome inhibitor to combine with lenalidomide, may not be so useful in our setting, as I mentioned, most of our patients are progressing on lenalidomide maintenance and that was not necessarily the patient population which was treated on the ASPIRE trial.

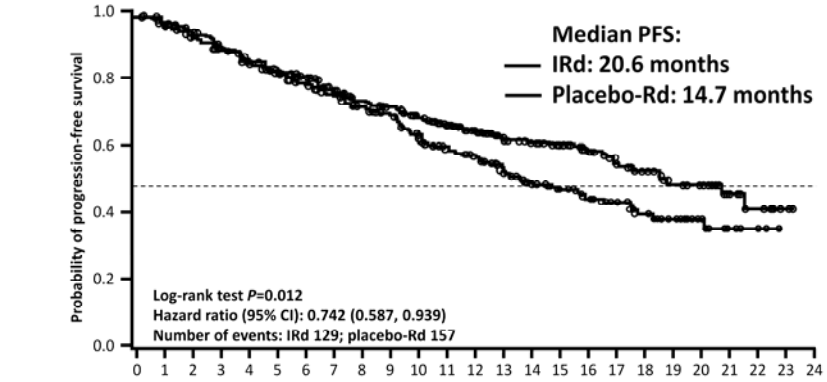


The ELOQUENT trial is the trial for which elotuzumab received approval. The data was updated at ASH this past year, and what was shown here was that the progression-free survival benefit with elotuzumab persisted for a 3-year period. Based on this and a progression-free survival difference of nearly 4 months, elotuzumab is now approved in patients who have received one to three lines of treatment in combination with lenalidomide. If you are thinking of using lenalidomide in your patient population, I would suggest adding on elotuzumab, because as you see, there is a theme out here, with the three-drug combinations always having better results than the two-drug combinations. So, if you are thinking of using lenalidomide and dexamethasone and the patient is relapsing which is not a very aggressive relapse, I would consider adding elotuzumab. Elotuzumab is an infusion initially given once a week and then subsequently once every other week. Once you have dealt with the initial infusion-related reactions, most patients do extremely well with this combination.



The other drug which has gotten approved is ixazomib. Ixazomib was approved based on the TOURMALINE data which was presented by Dr. Philippe Moreau at ASH this past year, and this again is approved in the relapsed setting after one to three lines of treatment where ixazomib is combined with lenalidomide and dexamethasone. The comparator arm was placebo with lenalidomide-dexamethasone. What is really quite nice about ixazomib is it is an oral drug, very well tolerated, given once a week, on days 1, 8, and 15 at a dose of 4 mg.

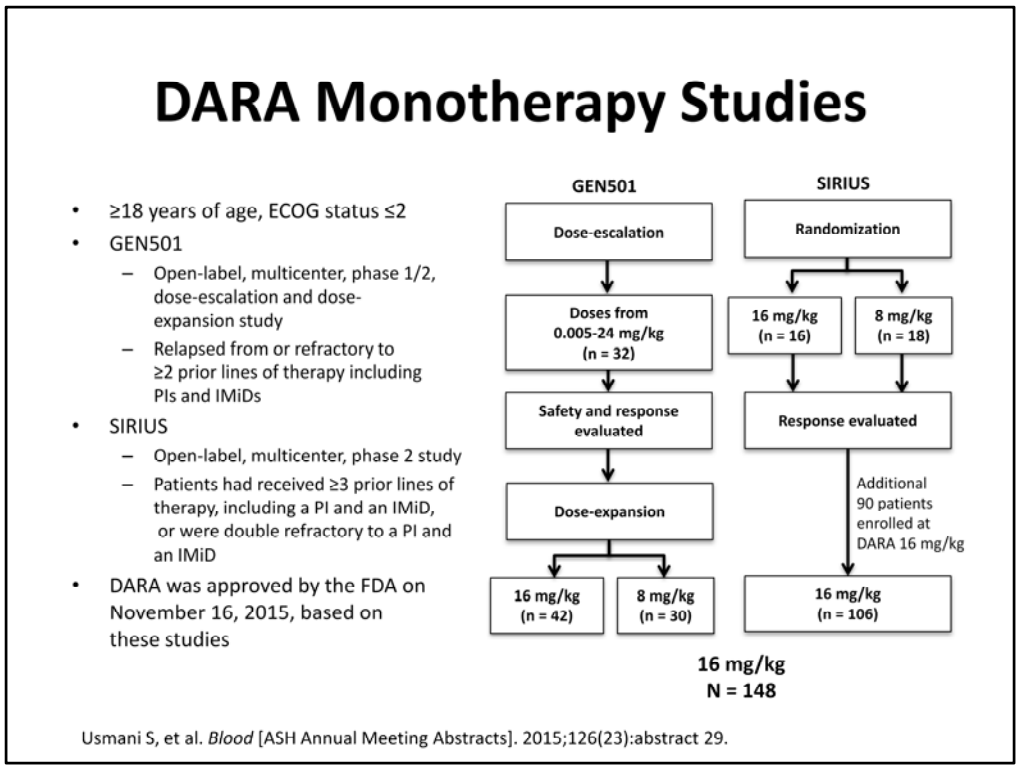
Final PFS Analysis: A Significant, 35% Improvement in PFS with IRd vs Placebo-Rd



Median follow-up: ~15 months

Moreau P, et al. *Blood* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 727.

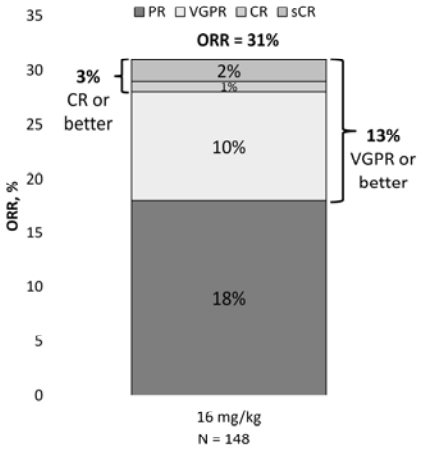
What was striking here was the difference in progression-free survival. There was a progression-free survival of almost a 5-month difference between IRd versus placebo, again suggesting that the triplet arm did better. What was really quite striking to me was the difference between toxicity of Rd versus IRd; you have to really look hard to see which was the placebo arm versus the IRd arm, again underscoring the fact that ixazomib is extremely well tolerated, very easy to give. So again, this would be an additional option, and this is where I think patient preference plays a big role. If you are going to use lenalidomide-dexamethasone in the relapsed setting, you have a choice. You have a choice of ixazomib or elotuzumab. The benefit of ixazomib is an oral drug once a week. For elotuzumab, patients will have to come into the clinic once every other week. So, this is where patient preference might play into it. As far as comorbidities are concerned, I think both are equally well tolerated. The difference is that one is IV and one is oral in this situation.



The last agent which was approved is daratumumab. Daratumumab is a monoclonal antibody against CD38. This was approved based on two trials, and both trials were combined in an updated analysis which was presented by Dr. Saad Usmani at this year's ASH. Dr. Usmani had almost 150 patients from the GEN501 study as well as SIRIUS study, and what daratumumab has shown is a very high response rate in quadruple refractory patients.

Efficacy in Combined Analysis

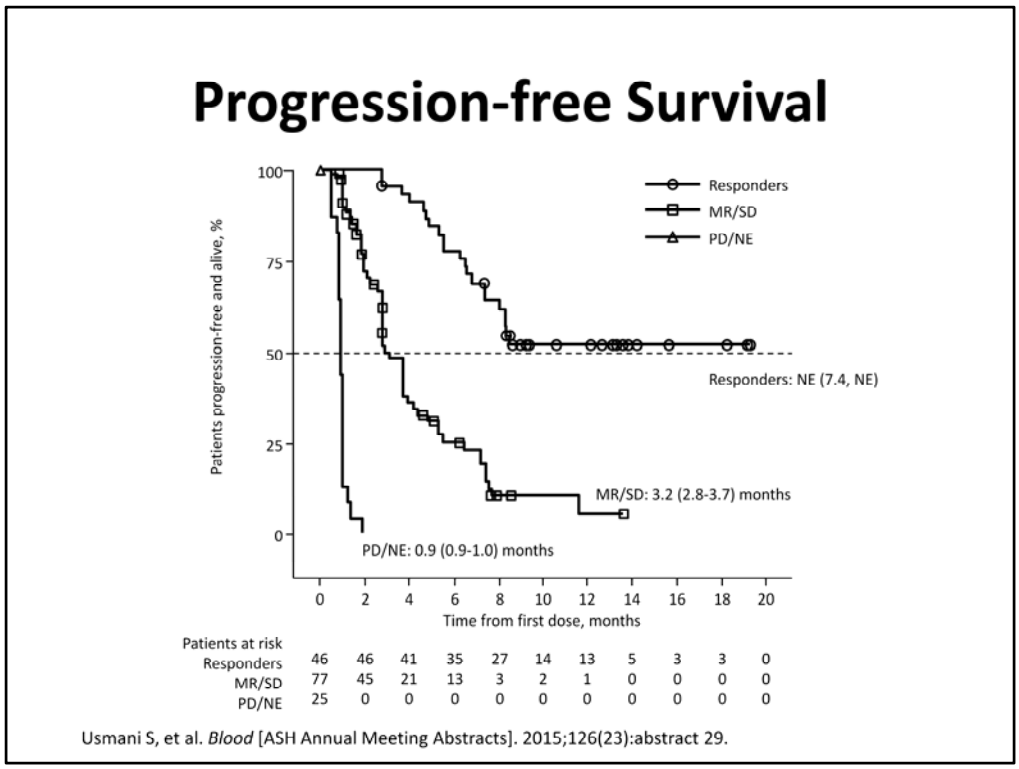
	16 mg/kg (N = 148)	
	n (%)	95% CI
Overall response rate (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7



- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Usmani S, et al. *Blood* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 29.

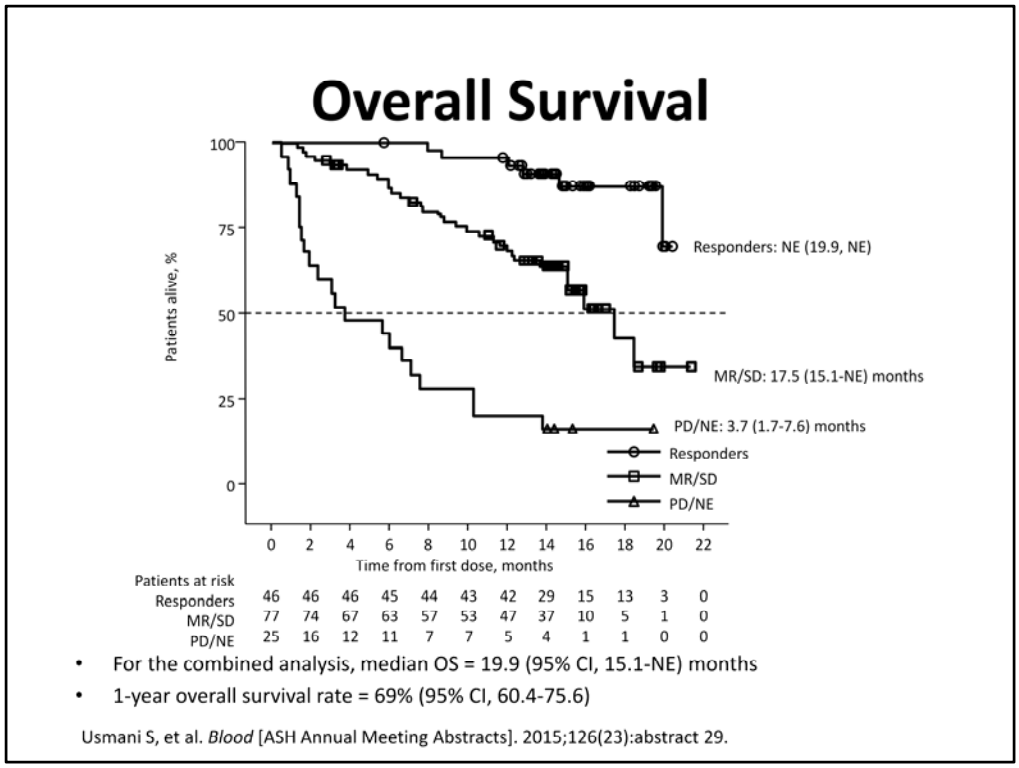
We are now beginning to see quite remarkable activity in patients in this trial. We are seeing 30% response rates in patients who have progressed on a proteosome inhibitor, as well as an IMiD, including both bortezomib and carfilzomib, and lenalidomide and pomalidomide. This is a patient population which is extremely hard to treat. Typically in the old days, the survival of these patients was very low, with a PFS of less than 5 months, and an overall survival of close to 8 or 9 months with quite dismal outcomes. Now with the incorporation of daratumumab, we have new hope and we are seeing a 30% response rate in this very refractory patient population.



Usmani S, et al. *Blood* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 29.

And more importantly, the patients who actually respond have a continued response, where patients have not quite achieved median PFS and they are continuing on the daratumumab for protracted periods of time.

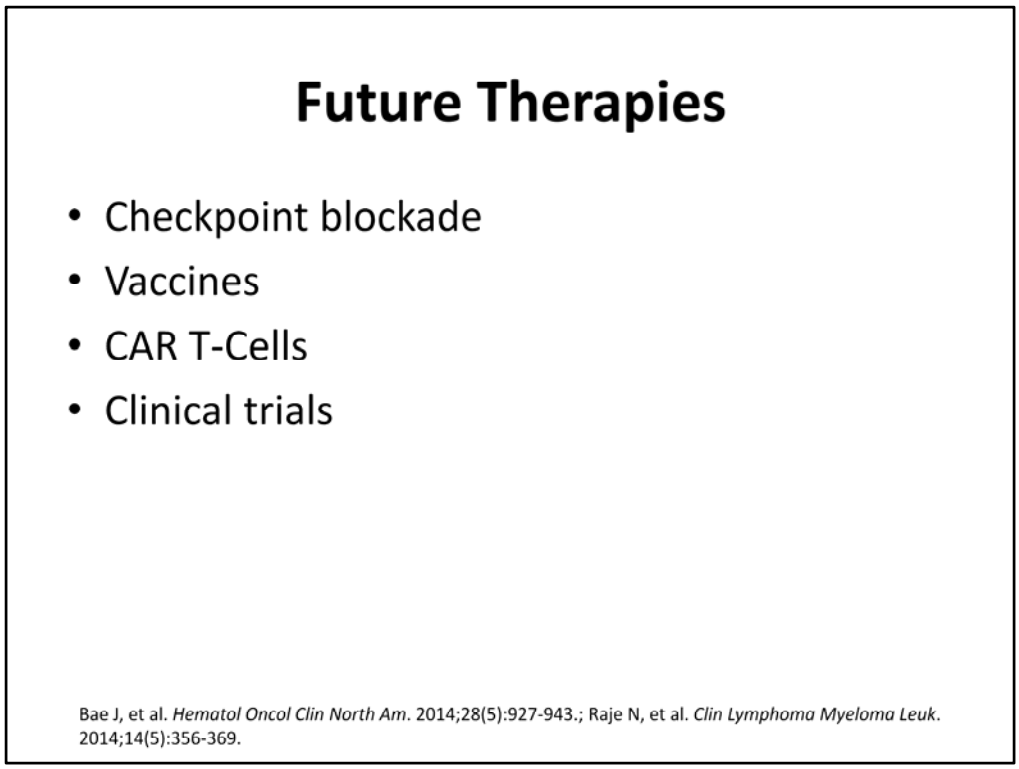
The Art and Science of Sequencing in Multiple Myeloma



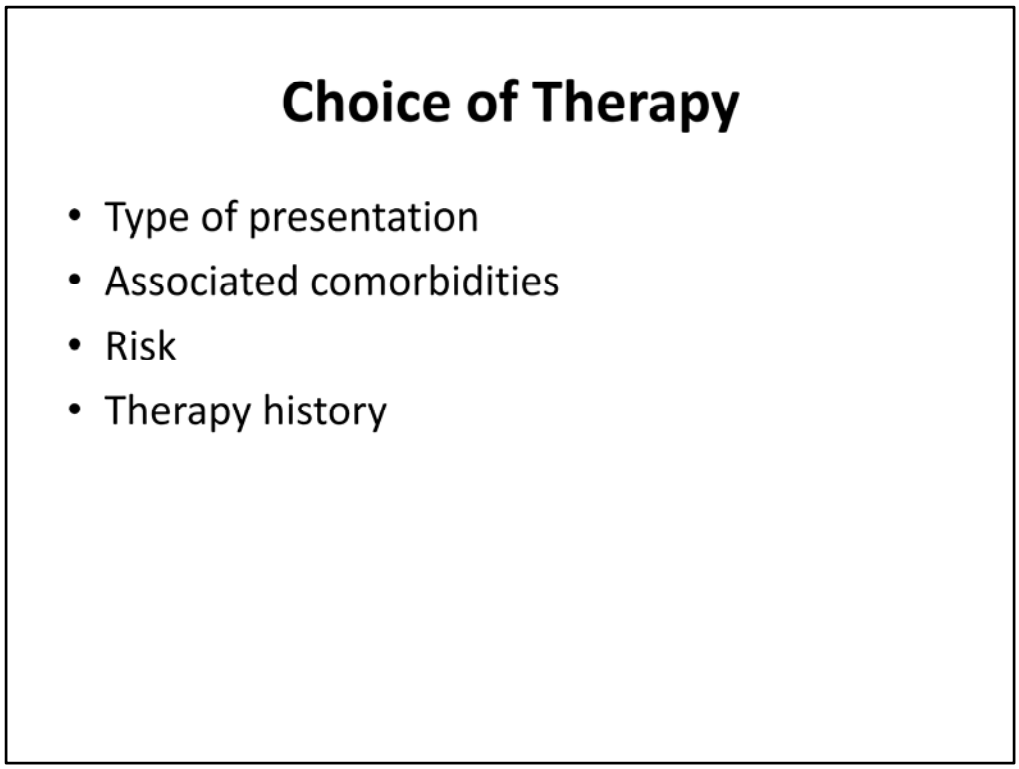
- For the combined analysis, median OS = 19.9 (95% CI, 15.1-NE) months
- 1-year overall survival rate = 69% (95% CI, 60.4-75.6)

Usmani S, et al. *Blood* [ASH Annual Meeting Abstracts]. 2015;126(23):abstract 29.

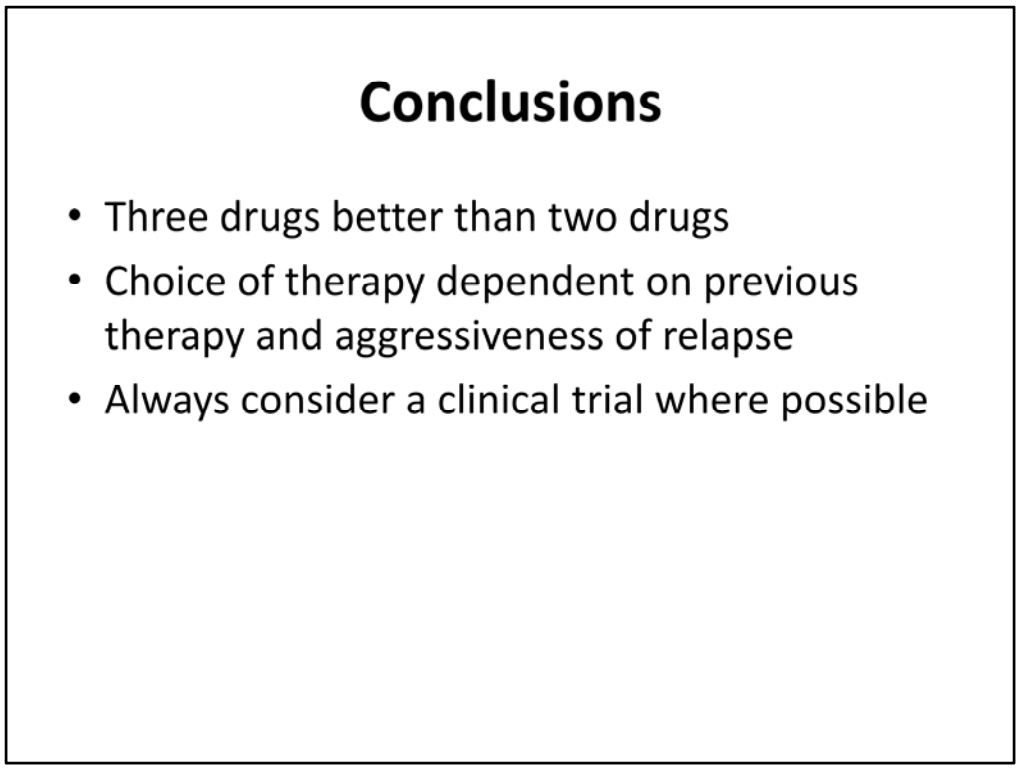
This has also translated into an improvement in their overall survival. So, responding patients are doing significantly better with single-agent daratumumab. Going forward, we have several different trials in the relapsed setting, in which daratumumab has been combined with both lenalidomide and pomalidomide. We saw some of that data at ASH, where the response rates are very high when combined with an IMiD. This is something we would be using in our relapsed/refractory patients who have seen, or who have become, quadruple refractory which, in fact, is the population we are dealing with in the refractory patient population in myeloma, as of right now.



What about the future? It may appear as if we have a lot of drugs already, but I still think that the future is very bright here. We saw some very interesting and encouraging data specifically in immuno-oncology with myeloma. We saw the use of checkpoint blockade, and in this case, we saw data with pembrolizumab. We saw that in combination with lenalidomide as well as in combination with pomalidomide. What was striking to me from this data set was the fact that about 50% of these patients in both of these small phase I/II studies were refractory to the IMiD prior to going on the checkpoint inhibitor, and just adding the checkpoint inhibitor on to the backbone IMiD was able to reinstitute response in these patients. That to me is very encouraging, because that is the patient population we will be seeing, given that we are using all of these drugs in the maintenance settings. We are using vaccination approaches. DC fusion vaccines are going to be coming down the pike in the posttransplant setting. We saw very nice data with CAR T-cells in a late-breaking abstract although again not large numbers. There were nine patients, but this was the first time where we have used CAR T-cells directed against a target known as BCMA, which we all believe is a very relevant target in multiple myeloma, and this was data which was presented from the NIH of these eight patients who are very refractory to every possible treatment. We are beginning to see complete responses and very good partial responses in this patient population with engineered CAR T-cells against BCMA. So again, I think we have to wait on data for this. We have to look at followup on this, but in my mind, this is the future of where myeloma is going. I will underscore the fact that most of these patients who are in the relapsed/refractory setting should be considered for clinical trials. We are where we are with all of these approvals because of we have been conducting these trials and our patients have been participating in them. So, there is an available clinical trial for many patients, I do think one needs to consider this while choosing the type of therapy as I have alluded to already.



One needs to look at the type of presentation at the time of relapse, look at the associated comorbidities, look at risk factors, and cytogenetic risks and also look at therapy history. Based on therapy history, you want to choose something which a patient has not necessarily seen, or use a different class of drugs, if possible.



And lastly, I think what we have learned now is not only in the upfront setting, but also in the relapsed setting, three drugs are better than two drugs. In my mind, we do know that as myeloma progresses, it becomes more genetically evolved, it acquires more genetic resistance, and I do believe that using three drugs is better than using two drugs. Again, I have talked about choice of treatment and again always consider a clinical trial, if it is possible, for your patient. Thank you for your attention.

Thank you for viewing this activity, and for additional resources, you can view other educational activities on *ManagingMyeloma.com*.

Reference:
Ali SA, Shi V, Wang M, et al. LBA-1 Remissions of Multiple Myeloma during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor. ASH 57th Annual Meeting and Exposition. 2015. https://ash.confex.com/ash/2015/webprogram/Paper87396.html