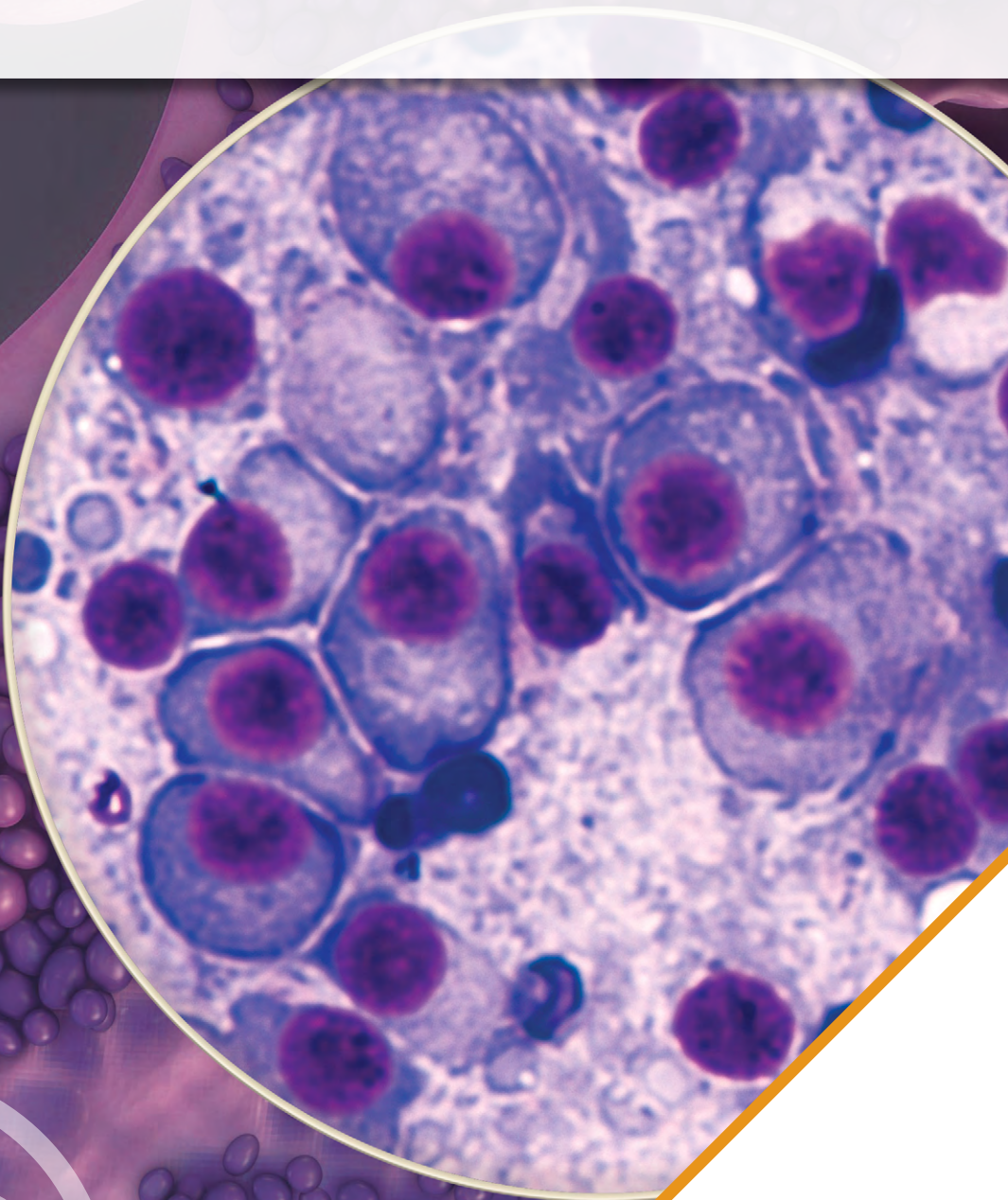


Clinical Debates in Multiple Myeloma: Putting Evidence Into Context

This transcript has been edited for style and clarity and includes all slides from the presentation.



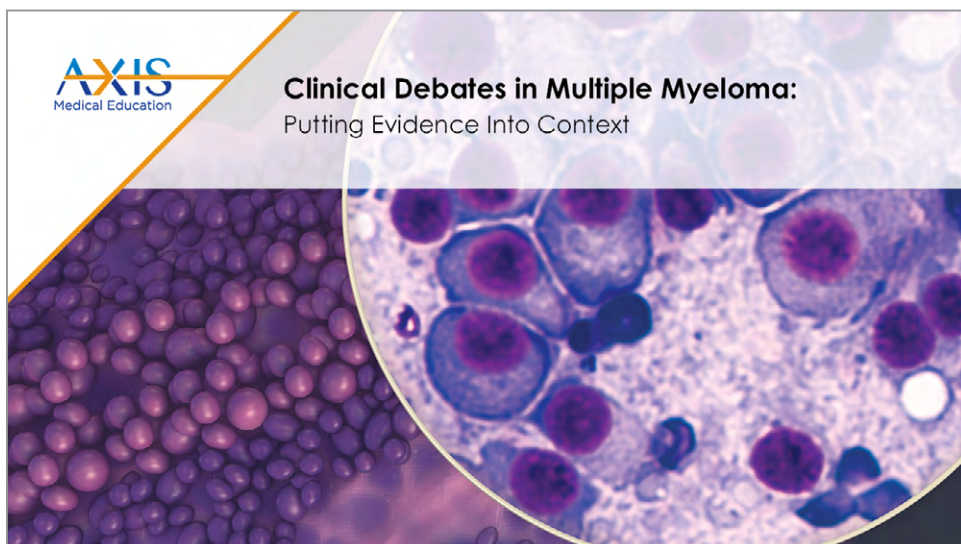
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Clinical Debates in Multiple Myeloma: Putting Evidence Into Context

Sagar Lonial, MD, FACP



- **Sagar Lonial, MD, FACP:**
Welcome to this program, Clinical Debates in Multiple Myeloma: Putting Evidence into Context. I'm Dr. Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta, Georgia. We are going to spend the next few moments talking a little bit about some very interesting and important topics that come up in the moment-to-moment management of multiple myeloma.



DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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- So, as we follow through these slides, there are the disclosure of unlabeled uses and disclaimers, as well as my conflict of interest disclosures. Please take a moment to review that.

Disclosure of Conflicts of Interest

Sagar Lonial, MD, FACP

Sagar Lonial, MD, FACP, reported a financial interest/relationship or affiliation in the form of *Consultant*, Takeda Oncology, Celgene Corporation, Novartis Pharmaceuticals Corporation, Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Inc., GlaxoSmithKline, Amgen, Inc.



Activity Agenda

- MM background: Diagnosis, staging, and risk assessment
- Debate #1: When do we observe versus initiate treatment?
- Debate #2: How do we determine transplant eligibility with age?
- Debate #3: How do we define and treat high-risk disease?
- Debate #4: What is the optimal duration of maintenance therapy?
- Debate #5: How do we best sequence newly approved drugs?
- Debate #6: How do we choose the appropriate combination at relapse?



▶ As you can see on the agenda, we've got six debate topics, and we've also got some basic background on staging, diagnosis, and risk assessment in the context of multiple myeloma.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Apply appropriate diagnostic criteria to discern when to initiate treatment for multiple myeloma versus watch and wait
- Assess patient- and disease-related characteristics using the frailty index and consensus guidelines to identify elderly patients with multiple myeloma who are eligible for autologous stem cell transplantation
- Assess patients' risk group using patient characteristics and genetic criteria and select appropriate treatment
- Identify the appropriate type and duration of maintenance therapy for patients with multiple myeloma according to consensus guidelines
- Evaluate current efficacy and safety data to appropriately select and sequence newly approved and emerging therapies for multiple myeloma
- Outline considerations that inform optimal treatment decision-making for relapsed/refractory multiple myeloma



- The learning objectives for this program are listed on this slide, and really focus on the ability to tease through a lot of the available evidence-based data as well as guidelines on recommendations to know how best to approach treatment for your patient with multiple myeloma.



MM Background: Diagnosis, Staging, and Risk Assessment

- So, let's begin with myeloma background, diagnosis, staging, and risk assessment.

Multiple Myeloma

- MM is a plasma cell disorder; features include CRAB
 - CRAB: calcium elevation, renal dysfunction, anemia, and bone destruction
- Estimated 30,770 cases and 12,770 deaths in 2018
- Median age at diagnosis: 69 yr
- 5-yr survival has improved substantially
 - 45% in 2004-2010 vs 28% in 1987-1989 due to novel agents
- Sensitive to treatment, but not curable
 - Progression inevitable
- The future: risk-adapted therapy, individualized treatment

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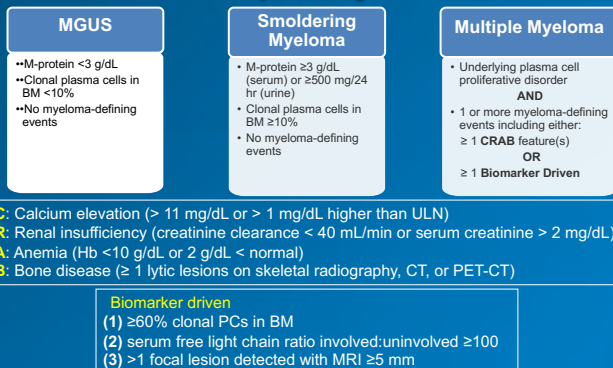
American Cancer Society, 2018; Costa et al. *Blood Adv.* 2017;1:282-287; National Cancer Institute, 2011.

▶ Myeloma is a plasma cell disorder that is often presenting with patients who have hypercalcemia, renal insufficiency, anemia, and/or bone lesions. There are about 30,000 new cases in the US and about 12,000 deaths in 2018 associated with multiple myeloma.

What we also know about myeloma is that the median age of presentation tends to be around 69 and the 5-year survival has significantly improved to 45% in 2004-2010 versus only 28% in the late 1980s in likely due part to the use of novel agents in the management of patients.

Many patients can in fact have very long durable responses. And I would argue that there is a subset of patients who may in fact be curable, about 10% to 15% of patients with aggressive early therapy, who have long progression-free survival (PFS) and overall survival (OS), but a majority of patients will ultimately experience disease relapse. And again, the future is thinking more about individualized therapy based on their presenting genetics and clinical features.

Updated IMWG Criteria for Diagnosis of Multiple Myeloma



BM, bone marrow; Hb, hemoglobin; IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; M-protein, monoclonal protein; PCs, plasma cells; ULN, upper limit of normal.
 Rajkumar et al. *Lancet Oncol*. 2014;15:e338-e348.

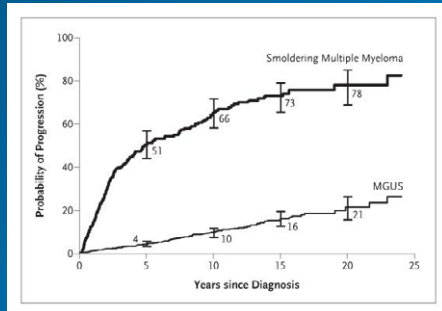
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► Let's talk a little bit about the updated IMWG criteria for the diagnosis of multiple myeloma. And this is important, because what's really changed in the past 5 years is not just the presence or absence of CRAB criteria, hypercalcemia, renal insufficiency, anemia, and bone disease, for patients who have symptomatic myeloma, but also the addition of 3 biomarker-driven criteria, which include greater than 60% plasma cells in the marrow, a serum-free light chain ratio of greater than 100, or more than one focal lesion as seen by bone marrow or as seen by MRI or PET CT scan at the time of initial presentation.

These 3 criteria are at high risk for developing symptomatic myeloma in a short time, and as such, are now categorized as symptomatic myeloma. So, this is a change in the definition of what it means to have symptomatic myeloma.

Smoldering Multiple Myeloma

Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS)



Kyle et al. N Engl J Med. 2007;356:2582-2590.

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► Now, what do we know about smoldering myeloma? Well, smoldering myeloma is a disease that is probably not one disease. And if you begin to look at the curve of patients with smoldering myeloma, what you see early on is that the curve progresses relatively quickly, about 10% per year, transformed to myeloma in the first 5 years, then the slope of that curve changes to about 5% per year, for the next 5 to 10 years, and then the curve goes down to about 2% per year. Similar to what we see in MGUS, which is at the bottom of that curve. And so, this difference really speaks to the 3 different types of patients with smoldering myeloma.

Frequency of FISH Abnormalities in IFM Experience

Genomic Aberrations	Incidence (number of patients analyzed for the aberration)
Del(13)	48% (936)
t(11;14)(q13;q32)	21% (746)
t(4;14)(p16;q32)	14% (716)
Hyperdiploidy	39% (657)
MYC translocations	13% (571)
Del(17p)	11% (532)

Missing t(14;16), approximately 10% of MM

IFM, Intergroupe Francophone du Myelome; FISH, fluorescence in situ hybridization. Adapted from Avel-Loiseau et al. Blood 2007;109:3489-3495.

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► Now, we also know that in addition to biology, there are some baseline genetic abnormalities that can predict for good risk or poor risk myeloma. This was an analysis done by the IFM of over 500 patients that were evaluated at the time of newly diagnosed myeloma. And, I think does give you a good spectrum of the frequency of genetic abnormalities.

What we see is that deletion 13 with fluorescent in situ hybridization (FISH) occurs about 50% of the time, the 11;14 translocation occurs about 20% of the time, the 4;14 translation occurs about 14% of the time and 17p deletion, a known poor risk feature, occurs about 11% of the time at diagnosis.

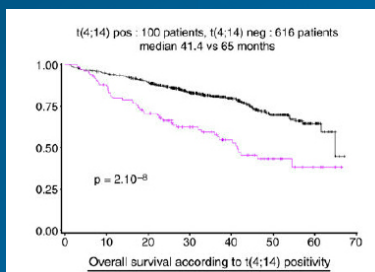
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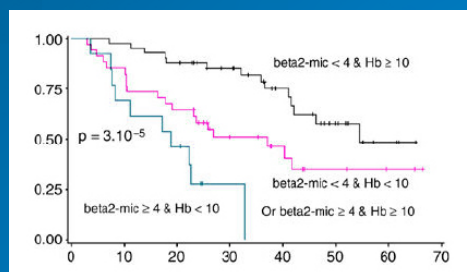
Hyperdiploidy thought to be a good risk subset of patients occurs fortunately the most frequently at about 40% of the time. Finally, a group that was not done in that initial analysis by the French group but has been reported on in subsequent series is the group of patients with MAF translocations or 14;16 that represents about 10% of all patients with myeloma at the time of diagnosis.

t(4;14) Is a Poor Risk Factor, But Not All Translocations Are the Same...

Overall survival of patients included in the IFM99 trials according to t(4;14) positivity



Overall survival of patients with t(4;14) according to hemoglobin and $\beta 2$ -microglobulin values at diagnosis



Adapted from Moreau et al. *Leukemia* 2007;21:2020-2024.

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► Now, while genetics does give us a little bit of insight in terms of the risk of relapse in the context of newly diagnosed myeloma, we know that genetics alone are not sufficient to be able to identify which patients are going to do well versus which patients are not going to do poorly. That's really nicely illustrated on this slide, where we see that some patients with 4;14 actually do significantly better than other patients with 4;14.

What that really creates is an amalgamation of the International Staging System (ISS) with the genetic abnormalities. Because if you look at that curve on the right, what you'll see is that low beta-2 and 4;14 does quite well, whereas high beta-2 and 4;14 does quite poorly, suggesting that while 4;14 is a surrogate for poor risk, not all 4;14s necessarily are the same.

Revised ISS Staging

Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS Stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification of MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.
Adapted from Palumbo et al, J Clin Oncol. 2015;33:2863-2869.

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► That has led to the revised ISS (R-ISS) that was published in the Journal of Clinical Oncology a few years ago, where it incorporates the routine ISS staging with beta-2 and albumin, but also includes genetic abnormalities and LDH. And when you put all of those together, you then create the new R-ISS staging, which begins to give us a better discrimination between different types of myeloma, which allows you to have good conversations with patients about their long-term outcomes with standard therapy and who perhaps should be considered for early clinical intervention.

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Debate #1: When Do We Observe Versus Initiate Treatment?

► So, why don't we begin with our first debate. When do we observe versus initiate therapy? And, this really does speak back to some of the discussion I had previously on the new definitions of patients with symptomatic myeloma.

The Dilemma

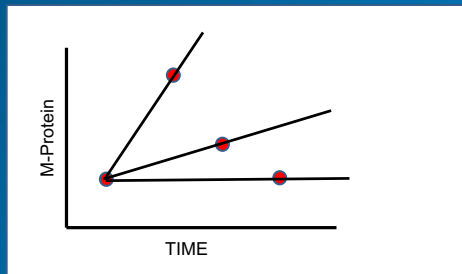
- 62-year-old healthy man presents to his primary care physician for routine care
 - Noted to have elevated total protein, 1.2 g/dL of IgG kappa protein in the blood, negative UPEP
 - Free light chain ratio is 6:1
 - Skeletal survey is normal
 - Bone marrow specimen shows 15% clonal plasma cells, FISH is hyperdiploid

FISH, fluorescence in situ hybridization; UPEP, urine protein electrophoresis.

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► So, let's start this off with a case. This is a 62-year-old man who presented for routine care. He had an elevated total protein, and then 1.2 g/dL of an IgG kappa protein with a negative urine protein electrophoresis. Free light chain ratio was 6:1, skeletal survey was unremarkable, and the bone marrow showed about 15% clonal plasma cells and by FISH this patient was hyperdiploid.

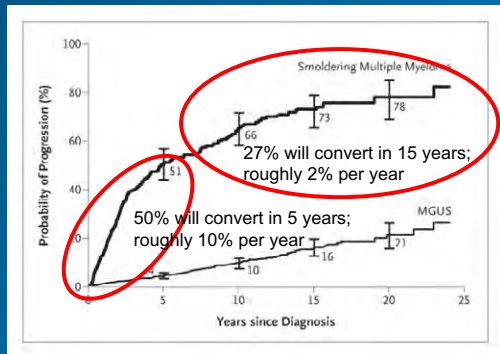
Which Scenario Is This Patient?



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► So, the real question is which scenario is this patient? Is this the scenario where a patient is flat for several years, slow increase over several years, or a rapid increase over several years? And, that really represents the challenge in dealing with patients with smoldering myeloma.

Smoldering Multiple Myeloma



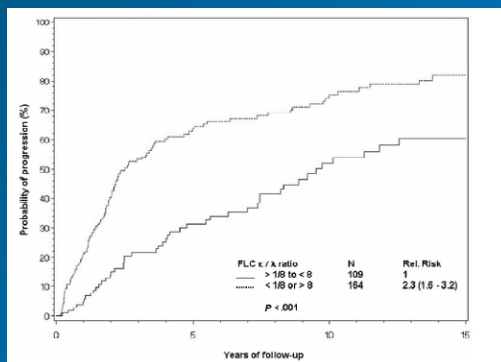
Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma or Monoclonal Gammopathy of Undetermined Significance (MGUS)

Kyle R et al. *N Engl J Med*. 2007;356:2582-2590.

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- As we saw previously, smoldering myeloma is not one group of patients. There's one group of patients who have clearly a very high risk of progression, 50% will convert in 5 years, roughly 10% per year, and then another group or 27% will convert over 15 years, roughly 2% per year. And, trying to discriminate which of these two groups represents your patient, is the real challenge at this timepoint, and we don't necessarily have good ways to do that.

Free Light Chain Ratio Is Useful for Risk Assessment in SMM



Risk of progression to myeloma or related disorder in 273 patients with SMM

SMM, smoldering multiple myeloma.
Dispenzieri et al. *Blood* 2008;111:785-789. © American Society of Hematology.

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- One of the markers that we can use to try and identify risk of progression is the serum free light chain assay. What's really nice about this slide is that it demonstrates that patients with an abnormal free light chain ratio clearly have a higher risk of progression than patients who don't have an abnormal free light chain ratio. What this allows us to do is then begin to try and identify which patients may be at higher risk of progression and using free light chain is a tool by which we can do that.

Free Light Chain Ratio Is Useful for Risk Assessment in SMM

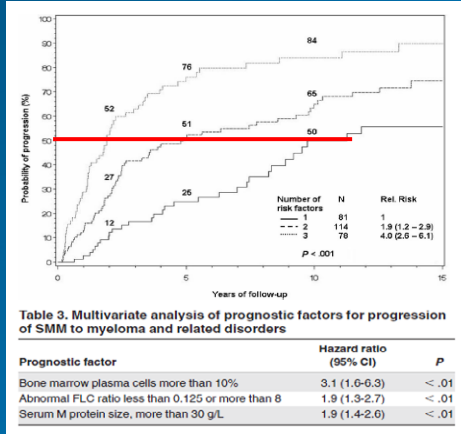


Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

Prognostic factor	Hazard ratio (95% CI)	P
Bone marrow plasma cells more than 10%	3.1 (1.6-6.3)	< .01
Abnormal FLC ratio less than 0.125 or more than 8	1.9 (1.3-2.7)	< .01
Serum M protein size, more than 30 g/L	1.9 (1.4-2.6)	< .01

SMM, smoldering multiple myeloma.
Dispenzieri et al. *Blood* 2008;111:785-789. © 2018 American Society of Hematology.

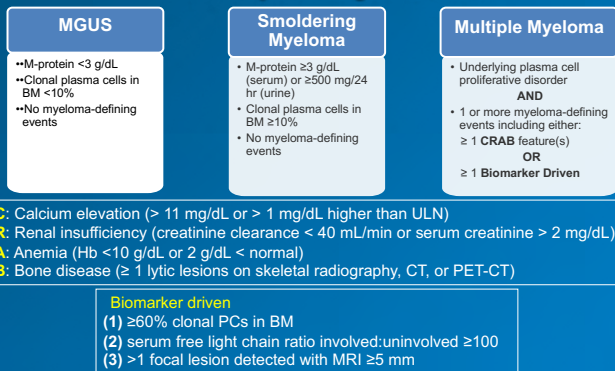
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► If you then take that one step further into what I call the ECOG criteria for risk stratification in the context of smoldering myeloma, or asymptomatic myeloma, what you see very nicely is that there are 3 groups of patients based on 3 very similar criteria.

The first is, does the patient have more than 10% plasma cells? If the answer is yes, then they get a point. Does the patient have an abnormal free light chain ratio? If the answer is yes, then they get another point. And is the serum protein, M-protein greater than 3 g/dL? If the answer is yes, then they get a third point.

And you can see the 3 curves, where they either have 1, 2, or 3 criteria and that helps determine their risk for progression. A low-risk patient is not one that I would consider enrolling in a clinical trial, because their median time to developing myeloma is well over 10 years. On the other hand, a high-risk person is somebody whose median time to developing myeloma is right at 2 years. And this is somebody I would strongly consider for a clinical trial. And the intermediate risk group then falls into the third.

Updated IMWG Criteria for Diagnosis of Multiple Myeloma



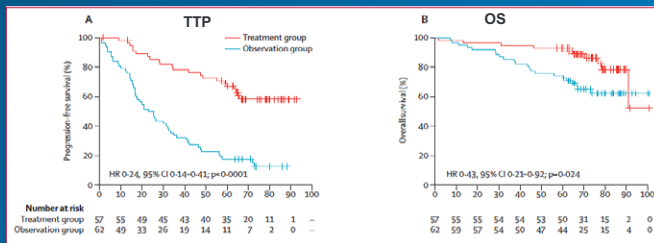
BM, bone marrow; Hb, hemoglobin; IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; M-protein, monoclonal protein; PCs, plasma cells; ULN, upper limit of normal.
Rajkumar et al. *Lancet Oncol*. 2014;15:e538-e548.

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► It's also important to understand that the new criteria have basically eliminated those patients who have the highest risk for progression, the ultra-high-risk group, which represents the biomarker-driven group of patients at the very bottom of this slide, where they no longer are observed, they are treated early as if they have myeloma to prevent the development of end-organ damage. This is really critically important and should be incorporated in everybody's treatment approaches.

QuiRedex Phase 3 Trial: Len-dex vs No Treatment in High-Risk SMM (N = 119)

Median follow-up: 75 mo



Early treatment with Len-dex significantly delayed the TTP to myeloma with a benefit in OS, BUT....

Len-dex, lenalidomide-dexamethasone; OS, overall survival; SMM, smoldering multiple myeloma; TTP, time to progression.
Mateos et al. *N Engl J Med*. 2013;369:438-447; Mateos et al. *Lancet Oncol*. 2016;17:1127-1136.

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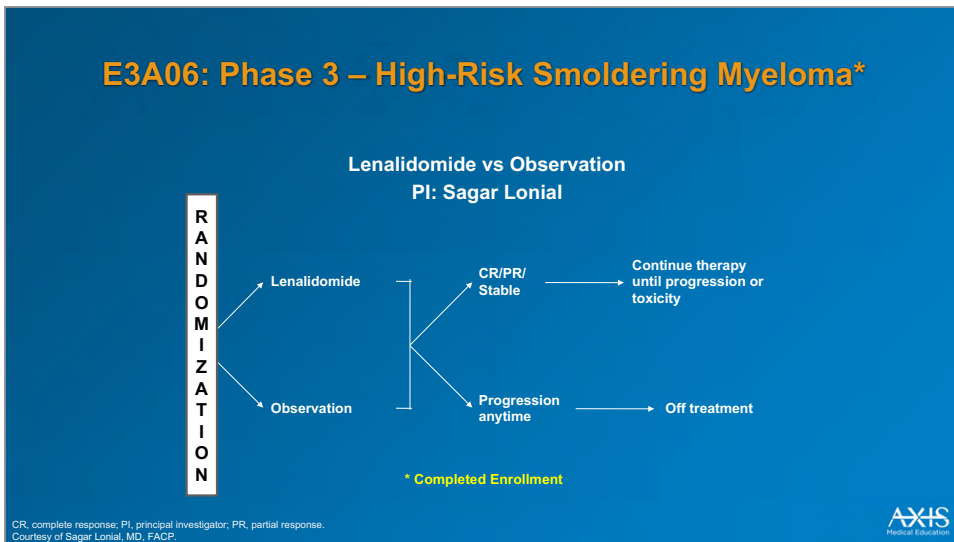
► Now what do we know about early data on treating patients with smoldering myeloma? Well, this is the Spanish study that many have used to perhaps support early treatment of patients with smoldering. This is a randomized trial of len-dex versus observation for patients with high-risk smoldering. Very small study, only 119 patients. Clearly a difference in time-to-progression favoring the group that got len-dex versus the group that received observation.

In this analysis, there was a survival difference favoring the group that received len-dex versus the group who did not. However, this trial was complicated by the fact that no patient had modern imaging. And I would argue that many of the patients on this trial did in fact have symptomatic myeloma if you use a PET scan or an MRI.

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What that functionally means is that these patients probably should not have been randomized to observation. They did in fact have symptomatic myeloma, and only a few patients on one arm or the other could have skewed the results here. So, I don't think that this is sufficient to incorporate early treatment for patients with smoldering myeloma.



► A really important trial is the ECOG trial, E3A06, and that's not just because it was the proteasome inhibitor, but because this is the largest randomized trial of patients with intermediate- and high-risk smoldering where modern bone imaging was used on all patients at study entry.

As you can see, patients were randomized to lenalidomide and observation, and we are waiting on follow-up of this study to really understand who is best to treat early versus who should be observed at this timepoint.

High-Risk SMM: Median TTP ~2 years

- ≥10% bone marrow plasma cells plus:
 - SMM with M protein ≥3 g/dL
 - Absence (<5%) of normal PCs by immunophenotyping plus immunoparesis
 - Abnormal FLC ratio 8-100
 - del(17p), t(4;14), gain(1q21)
 - M protein ≥4 g/dL
 - IgA SMM
 - Evolving pattern
 - Increased circulating plasma cells

FLC, free light chain; PCs, plasma cells; SMM, smoldering multiple myeloma; TTP, time to progression.
Rajkumar et al, Blood 2015;125:3069-3075.

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► So, what do we know about stratifying patients with smoldering myeloma? Well, this, again, are patients with a median time to progression to myeloma of about 2 years. These are patients who have an abnormal free light chain ratio, abnormal genetic features, M protein greater than 4, IgA smoldering myeloma, increased circulating plasma cells, or an evolving pattern.

These patients, as well, do not automatically need to have treatment at the time they present. But, in my view, should be considered for high-risk smoldering clinical trials. I think that the standard of care does continue to remain observation for this patient.

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Conclusion to Debate #1: When Do We Observe Versus Initiate Treatment?

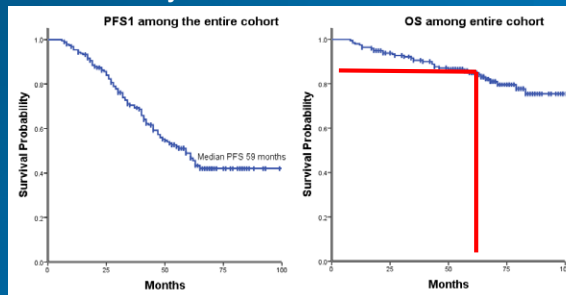
► So, in our conclusion for debate 1, again, when do we observe versus initiate treatment? I think the standard of care for smoldering continues to remain observation. Patients who are symptomatic by virtue of the new definition of myeloma, probably should proceed on to early therapy as now defined by the International Myeloma Working Group. And if you have a patient that is uncomfortable with observation, enrollment on a clinical trial does always remain an option, but I would not treat a patient with smoldering off of a clinical trial at this timepoint.

Debate #2: How Do We Determine Transplant Eligibility With Age?

- So, let's move on to debate 2. How do we determine transplant eligibility with age? This is really an important question, because there are a number of different approaches to this depending upon which continent in the world you live on.

RVD Induction in All Ages

Survival outcomes in patients with newly diagnosed myeloma with RVD induction

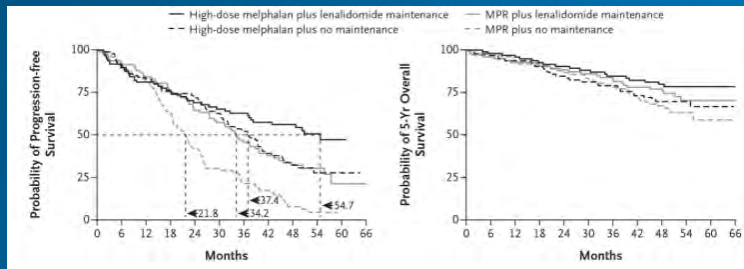


S, overall survival; PFS, progression free survival; RVD, lenalidomide, bortezomib, and dexamethasone. Joseph et al. Blood 2017;130:3139.

- I show you this data set from our group, which was presented at ASCO this past year, which really talks about RVD induction in patients regardless of age. The 2 things I want you to get a sense for is that the median PFS for all ages among patients who received RVD and then went on to high-dose therapy and transplant was about 5 years. That's the median PFS for the entire cohort.

It's also important to realize that the 10-year expected survival for this group is about 70%. The reason I bring that up also is that the use of high-dose therapy regardless of age, or eligibility is really an important strategy for improving the long-term, not just PFS, but OS of patients with newly diagnosed myeloma.

Transplant in Era of Novel Agents



- o PFS and 5-year OS from the time of diagnosis among patients who received:
 - high-dose melphalan followed by lenalidomide maintenance therapy,
 - high-dose melphalan with no subsequent maintenance therapy,
 - MPR followed by lenalidomide maintenance therapy, and
 - MPR with no subsequent maintenance therapy

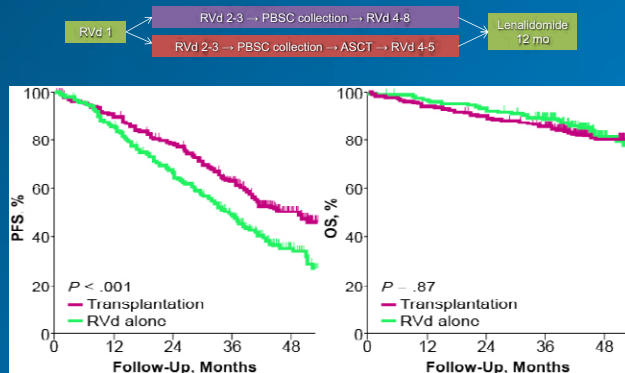
MPR, melphalan, prednisone, lenalidomide; OS, overall survival; PFS, progression-free survival.
Palumbo et al. *N Engl J Med*. 2014;371:895-905.

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► So, what do we know about the role of transplant, even in the era of novel agents? How do we continue to incorporate it? Well you can see very nicely from this analysis done by the Italian group that patients that had a transplant clearly stayed in remission longer than patients who didn't. And if you had a transplant and you had maintenance lenalidomide, your PFS and OS were the best of any of the 4 groups that were represented in this trial.

This again, to me, despite the fact that patients received novel agents in this induction, clearly demonstrates the ongoing benefit of high-dose therapy in autologous transplant.

IFM2009: RVd Alone vs RVd + ASCT



ASCT, autologous stem cell transplant; PBSC, peripheral blood stem cells; PFS, progression free survival; RVd, lenalidomide, bortezomib, dexamethasone.
Adapted from Attal et al. *N Engl J Med*. 2017;376:1311-1320.

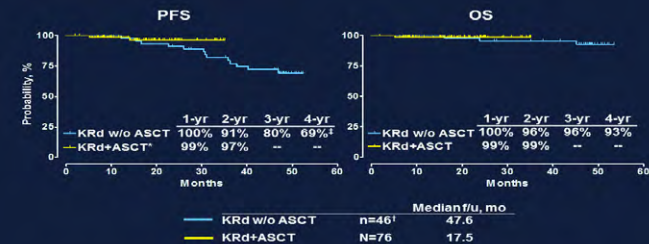
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► Now, the French presented a randomized data of lenalidomide, bortezomib, dexamethasone (RVd) plus transplant versus RVd followed by maintenance. And what we know is that the duration of remission was clearly longer for the group that received RVd and a transplant. But at the early follow-up time of 3 years, there was no difference in OS.

I'll tell you, I think that in an era where we have many, many new drugs to use, PFS is one of our goals for prolonging in the context of newly diagnosed myeloma. Because patients can have so many different treatments in the post-relapse setting, I think trying to shoot for big OS differences early on is really an unrealistic goal because I think it's going to be too hard to really reach those benchmarks. But, PFS clearly is quite different and, I think, does represent the benefit of high-dose therapy even when RVd is used as the initial therapy.

KRd Outcomes by Transplant Status

Treatment Outcomes



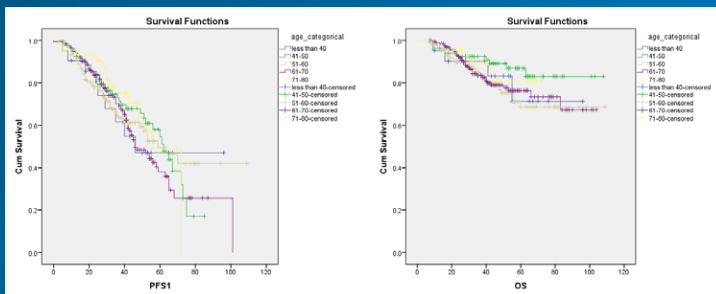
[‡]2 patients progressed (1 during pre-ASCT period; 1 after discontinued from the study after ASCT)
[‡]Excludes 7 pts who discontinued to pursue ASCT
[‡]Intent-to-treat (N=53). 4-year PFS 64%
 At cut-off date 1/1/16

ASCT, autologous stem cell transplant; PFS, progression free survival; KRd, carfilzomib, lenalidomide, dexamethasone.
 Jakubowiak et al., EHA 2016.

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► Now, what about newer treatments in induction. These are data about KRd—carfilzomib combined with lenalidomide and dexamethasone—with outcomes by transplant status. And, as you can see, the patients that had a transplant in yellow, had a much longer PFS and their OS with early follow-up at least looks as good, if not slightly better than patients who didn't have a transplant. So, I don't think the benefit of transplant is unique to RVd-based induction.

Benefit of HDT Is Independent of Age



Emory data, unpublished

um, cumulative; HDT, high-dose therapy.
 courtesy of Sagar Lonial, MD, FACP.

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► These are data from Ajay Nooka and our group that we presented at ASH a few years ago, showing that the benefit of high-dose therapy is independent of age. What I want you to notice here is that the age here goes up to 75. So, we don't use the cut-off of 65 as they do in Europe, but clearly, we use the age of up to 78 as a potential transplant-eligible patient.

In fact, if you choose patients over the age of 70 to consider for transplant, their benefit may be such that their survival begins to look like the survival of patients who did not have myeloma. That again, is a significant improvement and speaks to the idea of functional cure for patients across the board.

Considerations

- Frailty index¹
 - Additive scoring system (range 0-5), based on age, comorbidities, and cognitive and physical conditions, developed to identify 3 groups:

Additive Total Score	Patient Status	No. of Patients (%)	% (95% CI)		Cumulative Incidence at 12 mo, %	
			OS at 3 years	PFS at 3 years	Treatment discontinuation	Grade 3-4 nonhematologic AEs
0	Fit	340 (39)	84 (78-89)	48 (41-56)	16	22
1	Intermediate fitness	269 (31)	76 (67-82)	41 (32-49)	21	26
≥2	Frail	260 (30)	57 (45-68)	33 (25-41)	31	34

- Revised ASBMT guidelines indicate age alone should not be used as determining factor for transplant eligibility²
 - Instead, a score of >2 on hematopoietic cell transplantation-specific comorbidity index or a Karnofsky performance status of <90 should warrant additional caution before proceeding with ASCT in elderly patients

AEs, adverse events; ASBMT, America Society for Blood and Marrow Transplantation; ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival.
 1. Palumbo et al. *Blood* 2015;125:2068-2074.
 2. Shah et al. *Biol Blood Marrow Transplant*. 2015;21:1155-1168.



► So, rather than using age as a potential predictor of whether a patient should have a transplant, I would likely recommend the use of the Frailty index. The reason I say that is, when I look and see a new patient, I don't look at their age and decide yes or no to transplant, I look at their overall function. As I've said before, I will say no to 50 year olds and yes to 75 year olds, purely based on their Frailty index and their functional guidelines.

So, this slide actually gives you a sense of ways to assess frailty and there are guidelines from the ASBMT as well that could be used to determine transplant eligibility. Comorbid index alone and Karnofsky performance status is not sufficient really to choose whether or not a patient is potentially a transplant-eligible candidate.

Transplant in Multiple Myeloma

- Continues to offer benefit to all
- PS not age is the best predictor of benefit
- Frailty index may play a role, but more often than not, this is about the 'eye' test

► So, I think that transplant does in fact continue to offer significant benefit to all. Performance status and functional status and Frailty index are probably the best way to determine eligibility, not age.

And again, there is a lot about the eye test. When you look at a patient, when you walk in the room, you can usually get a good sense for what their functional status is, and whether they can get through the rigors of transplant.

PS, performance status.



Conclusion to Debate #2: How Do We Determine Transplant Eligibility With Age?

- ▶ Remember that patients over the age of 70 typically receive reduced dose melphalan and that again makes the tolerance of the transplant approach significantly better.

Debate #3: How Do We Define and Treat High-Risk Disease?

- ▶ So, with that, I think we'll begin to move on then to debate 3. How do we define and treat high-risk myeloma?

Put the Question Into Perspective

- “In order to manage risk we must first understand risk. How do you spot risk? How do you avoid risk and what makes it so risky?”
- “To understand risk, we must first define risk.”

Our goal is to understand
how risk and therapy are
intertwined



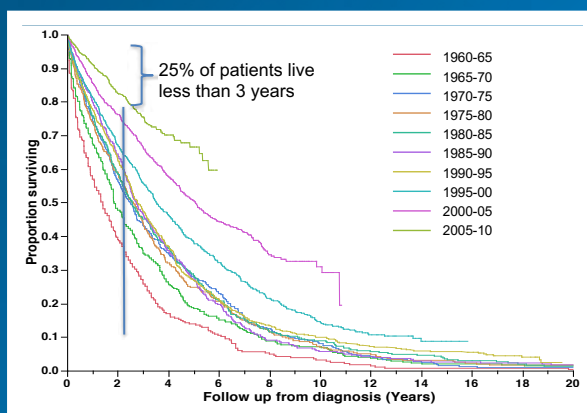
George Costanza, Seinfeld, 1994

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► So, we talked a little bit earlier on about the genetics of risk stratification including FISH analyses. And I always like to put this slide in there, because it's from one of my favorite sitcoms, where there was a quote in the middle of the show, to manage risk, we must first understand risk, how do you spot risk, how do you avoid risk, and what makes it so risky.

To understand risk, we must first define risk. And so, George Costanza had very prescient words way back in the 1980s or the 1990s in terms of what we need to think about when we think about risk stratification in the context of myeloma.

Improving Survival in MM



Courtesy of Sagar Lonial, MD, FACP.

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► So, who are the patients that we're talking about? When you get to the next slide, what you'll see very nicely is, while the survival curves for patients have significantly improved over the past 40 years in myeloma, there continues to be a drop off in the first 2 years of about 25%. And that 25% represents the true high-risk patients that have very short durations of remission and die relatively quickly compared to everybody else.

What Constitutes High-Risk Myeloma?

Summary of determinants of high-risk myeloma

Risk Factor	Measurement	High Risk
Disease Burden	β_2 -microglobulin	ISS III (β_2 M > ≥ 5.5 mg/mL)
	Serum albumin	
Tumor Biology	Extramedullary disease	PCL Plasmacytoma
	Proliferation	
Genetics	Cytogenetics	del(17p), 1q21 amplification
	FISH	t(4;14), t(14;16), del(17p), 1q21 amplification, 1p deletions
ISS/Genetics	β_2 M/serum albumin Cytogenetics/FISH	ISS II/III At least 1 genetic abnormality
Gene Expression	Expression microarray	UAMS 70 gene signature
		IFM 15 gene signature
		Proliferation Index
		EMC 92 gene signature

FISH, fluorescent in situ hybridization; ISS, International Staging System; PCL, plasma cell leukemia.
Adapted from Lonial et al, *Blood* 2015;126:1536-1543.

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► So, what are some of the factors that we can use to identify high-risk myeloma. Well, disease burden, beta-2 microglobulin clearly are the ISS ways of doing it. Tumor biology and things such as extramedullary disease is another way. Patients with plasma cell leukemia or extramedullary plasmacytomas or high proliferation with an LDH is another way to potentially identify high-risk patients.

Genetics such as FISH or cytogenetics, the presence or absence of known poor-risk features such as 4;14, 14;16, 17p deletion, or 1q amplification—these are all important.

Then again, gene expression profiling and more recently the use of mutational analysis is helpful in trying to identify high-risk patients.

Considerations

- In 2016, the IMWG released updated guidelines for the treatment of patients with high-risk cytogenetics, such as t(4;14), del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, and gain(1q), with the use of agents such as bortezomib, carfilzomib, and lenalidomide

IMWG, International Myeloma Working Group.
Sonneveld et al, *Blood* 2016;127:2955-2962.

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► Now, it is important, I think, to also realize that in 2016 the International Myeloma Working Group released updated guidelines for the treatment of patients with high-risk genetics. These include 4;14, 17p deletion, nonhyperdiploidy, and recommended the use of agents such as bortezomib, carfilzomib, and lenalidomide. This is a key point, I think, in terms of how to consider managing patients.

Revised ISS Staging

Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS Stage	
I	Serum β_2 -microglobulin < 3.5 mg/L, serum albumin \geq 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2 -microglobulin \geq 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification of MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

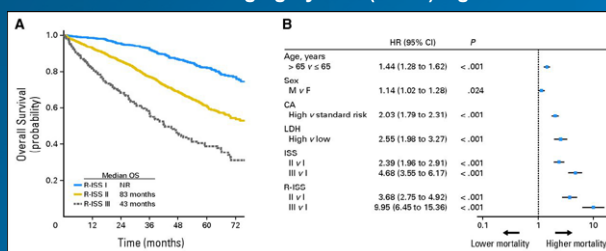
CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.
Adapted from Palumbo et al. *J Clin Oncol*. 2015;33:2863-2869.

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- And, as I suggested earlier, the R-ISS is critically important to beginning to incorporate not only just FISH and genetics, but also LDH, which is probably one of the most powerful predictors of poor outcomes for newly diagnosed myeloma. And the previously existing ISS across the board.

Overall Survival Based on R-ISS

OS in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm



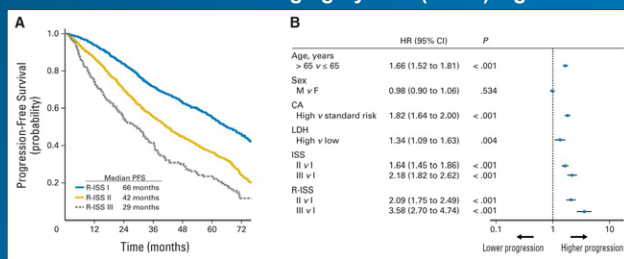
- If you begin to look at OS based on revised ISS staging, you can see stage 1, 2, and 3, really discriminate quite nicely in terms of outcomes, independent of age. And, that is, actually I think an important piece to keep in mind as well.

CA, chromosomal abnormalities; F, female; ISS, International Staging System; LDH, lactate dehydrogenase; M, male; NR, not reached; OS, overall survival.
Palumbo et al. *J Clin Oncol*. 2015;33:2863-2869.

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Progression-Free Survival Based on R-ISS

PFS in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm



Median 46 months follow-up

CA, chromosomal abnormalities; F, female; ISS, International Staging System; LDH, lactate dehydrogenase; M, male; NR, not reached; PFS, progression-free survival. Palumbo et al. *J Clin Oncol*. 2015;33:2863-2869.

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► We also know that PFS can very nicely be distinguished in using the R-ISS, also independent of age, and this does take into account, to a certain degree, what patients are using for treatment.

The reason I say that is, the use of risk-adapted maintenance therapy may potentially change that. And we're going to get into some of the tools of risk-adapted maintenance therapy in the next few slides.

Bortezomib Use in High-Risk Newly Diagnosed MM

Benefit of Bortezomib Induction and Maintenance for High-Risk

FISH	n	PFS at 60 mo, %		OS at 60 mo, %			
		Bortezomib Arm	P	Standard	Bortezomib Arm	P	Standard
t(4;14) yes/no	50/295	16% vs 27%	.04	8% vs 24%	52% vs 75%	.01	33% vs 64%
add(1q) yes/no	113/231	16% vs 32%	.005	10% vs 28%	57% vs 79%	.001	43% vs 70%
del(17p) yes/no	39/312	22% vs 27%	.47	5% vs 24%	65% vs 72%	.48	18% vs 66%

Renal insufficiency	VAD	PAD
OS at 96 months; yes/no	12 vs 42%	47 vs 48%

add, addition; del, deletion; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression free survival; t, translocation; VAD, vincristine, doxorubicin, dexamethasone. Adapted from Sonneveld et al. *Blood*. 2015;126:27.

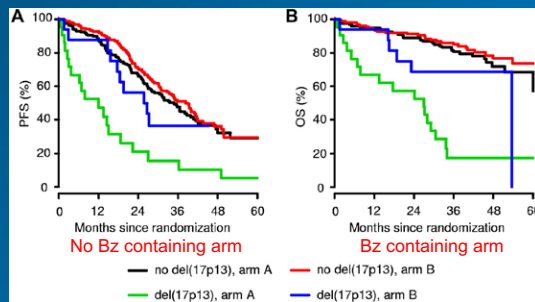
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► So, the first few slides really speaks to the use of bortezomib in patients with high-risk newly diagnosed myeloma.

These are data from the Dutch HOVON trial where patients received vincristine, doxorubicin, dexamethasone induction followed by thalidomide maintenance versus bortezomib, doxorubicin, dexamethasone (PAD) induction followed by bortezomib maintenance.

What you can see very nicely highlighted in red is that patients with 17p deletion actually did remarkably well with the PAD followed by bortezomib and a bulk of that benefit is likely related to the use of bortezomib early on.

Bortezomib and del17p



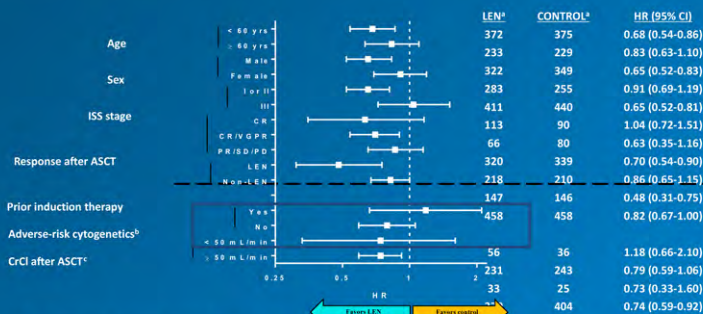
HOVON-65/GMMG-HD4 trial:
VAD induction, tandem SCT, and thalidomide maintenance
vs. PAD induction, tandem SCT, and bortezomib maintenance

Bz, bortezomib; del, deletion; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone; PFS, progression free survival; SCT, stem cell transplant; VAD, vincristine, doxorubicin, dexamethasone; Neben et al. Blood 2012;119:340-348.

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► Now what about bortezomib specifically in 17p, well again, these are PFS data from that slide, again, suggesting that if you received bortezomib and you had 17p deletion, that's arm B, the purple curve, your PFS and OS was significantly better than the group that did not receive bortezomib in either one of their treatments. And, I think, that is, in fact, critically important.

Overall Survival: Subgroup Analysis Lenalidomide Maintenance Post-ASCT



Meta-analysis of 3 RCTs: IFM 2005-02, CALGB 100104 (Alliance), GIMEMA RV-209.
^anumber of patients; ^bcytogenetic data were available only for the IFM and GIMEMA studies; ^cCrCl post-ASCT data were available only for the CALGB and IFM studies.
ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; HR, hazard ratio; ISS, International Staging System; Len, lenalidomide; OS, overall survival; PO, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
McCarthy et al. J Clin Oncol. 2017;35:3279-3289.

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► What about lenalidomide in the context of high risk? This is a forest plot looking at the meta-analysis of different phase 3 trials using lenalidomide in the maintenance setting, and what I think you see quite nicely, is that there is no real benefit for lenalidomide in the context of high-risk disease.

This is a meta-analysis of 1,000 patients and is to be contrasted with the recent MRC data, where they randomized over 1,000 patients as well to lenalidomide versus observation and did show some benefit of lenalidomide maintenance over observation.

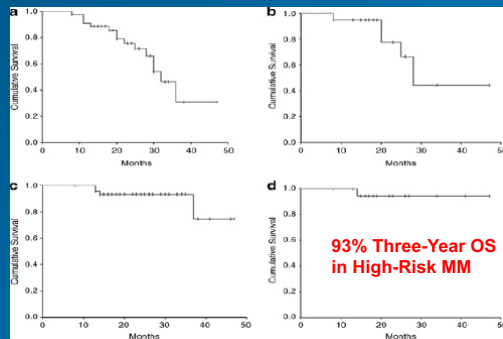
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It's important to realize that the benefit of lenalidomide, even in the MRC trial, was pretty modest—less than a year. So, I don't consider that to be sufficient magnitude to warrant the use of lenalidomide alone in the context of maintenance therapy for patients with multiple myeloma.

RVD Maintenance in High-Risk MM Post-ASCT

Survival outcomes of patients with high-risk disease

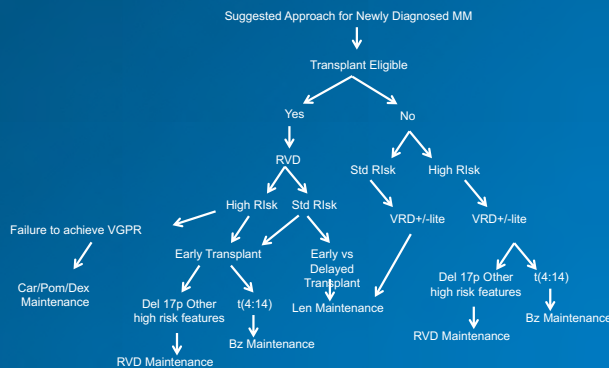


ASCT, autologous stem cell transplant; MM, multiple myeloma; OS, overall survival; RVD, lenalidomide, bortezomib, dexamethasone. Adapted from Nooka et al. *Leukemia*. 2014;28:690-693.

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- ▶ What I think is becoming an accepted standard is the use of RVD maintenance in high-risk myeloma. This is based on data from Ajay Nooka and our group demonstrating PFS and OS are clearly higher in the high-risk subset of patients that were treated with RVD maintenance and consolidation.

Suggested Approach for Newly Diagnosed MM



Courtesy of Sagar Lonial, MD, FACP.

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► And, in fact, as you can see on this algorithm, this is our approach for managing patients with newly diagnosed myeloma. Where you can see the risk-adapted approach, patients with 4;14 translocation received bortezomib maintenance, patients with 17p or other high-risk features receive RVD maintenance, and patients who failed to achieve a very good partial response or better received car/pom/dex maintenance. That is our current investigational approach for patients with high-risk disease.

Immune-Based Therapy

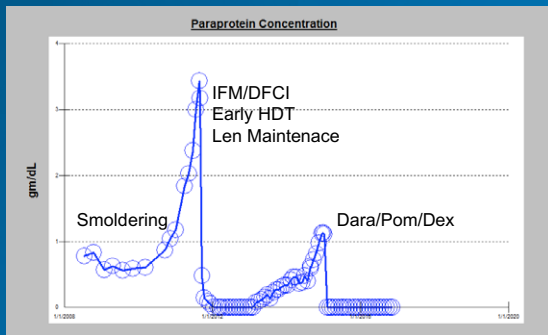
- Hopes with additional new immune-based therapy are that they will work independently of intracellular signaling
- These include targeting the PD-1/PD-L1 axis
- Other activators of immune function or immune mediated approaches such as BiTEs or CAR T-cells represent alternatives, and will be tested in the future

BiTEs, bi-specific T-cell engagers; CAR chimeric antigen receptor; PD-1, programmed cell death protein1; PD-L1, programmed cell death ligand 1.

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► Now, it is our future hope that immune-based therapies will be more effective. The reason that we hope that this will be the case is that much of the challenge of high-risk myeloma is dysregulated intracellular signaling and that by using drugs that target immune function, whether they are PD-1 or PD-L1, bispecifics, BiTEs, CAR T cells, or antibodies, we may be able to overcome that dysregulated intracellular signaling through extracellular immune-mediated killing.

Patient Treated With Dara/Pom/Dex and del 17p



Dara/Pom/Dex, daratumumab, pomalidomide, dexamethasone; HDT, high-dose treatment; IFM/DFCI, Intergroupe Francophone Du Myelome. Courtesy of Sagar Lonial, MD, FACP.

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- ▶ This is a great example—this patient, who had 17p deletion, was treated on the IFM trial, and disease progressed very, very quickly after transplant, within a year, and so he was put on pomalidomide in combination with daratumumab and dexamethasone and has been in a sustained minimal residual disease (MRD)-negative complete remission for over 3 years now. I think this really does speak to the power potentially of high-risk disease.

AXIS

Conclusion to Debate #3: How Do We Define and Treat High-Risk Disease?

- ▶ So, how do we conclude this debate? Well, I think it's important to define and treat high-risk disease differently. Risk-adapted maintenance as I outlined in our current algorithm I think is in fact quite important. I would also recommend the use of standard genetics and FISH panels to make sure you identify who those patients are. And, that you identify the patients with high-risk disease and treat them in a more aggressive fashion in the post-transplant setting, but the induction therapy for everybody should be somewhat uniform.

Debate #4: What Is the Optimal Duration of Maintenance Therapy?

- ▶ Next, we'll switch to debate 4. What is the optimal duration of maintenance therapy?

Guideline Recommendations: Maintenance Therapy

- Preferred: lenalidomide (category 1)¹
 - FDA approved as maintenance therapy for patients with multiple myeloma following autologous stem cell transplant in February 2017
 - CALGB 100104²
 - IFM 2005-02^{3,4}
- Other recommended regimen: bortezomib¹
 - HOVON⁵

¹Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.4.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

²McCarthy et al. *N Engl J Med*. 2012;366:1770-1781.

³Khalil et al. *N Engl J Med*. 2012;366:1770-1781.

⁴Holstein et al. *Lancet Haematol*. 2017;4:e431-e442.

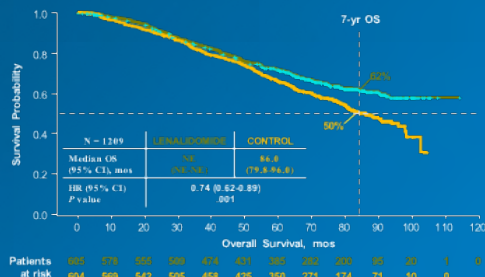
⁵Sonneveld et al. *J Clin Oncol*. 2012;30:2946-2955.

- ▶ To really speak to this, it's important to look at guideline recommendations on maintenance therapy. So, if you look at the NCCN Guidelines®, they recommend the use of lenalidomide, which is FDA approved for maintenance for patients with myeloma. Following autologous stem cell transplant based on two datasets, the CALGB and IFM dataset, as well as data for bortezomib supported by the HOVON paper that we talked about just a few moments ago.

I think it's important to realize that the era of transplant and no maintenance is hopefully passed now for all of us.

Maintenance Therapy Does Matter

- Overall Survival: Median Follow-up of 80 mo
 - There is a 26% reduction in risk for death, representing an estimated 2.5-year increase in median survival



NE, not estimable; OS, overall survival.
McCarthy et al. J Clin Oncol. 2017;35:3279-3289.

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- This meta-analysis presented by Dr. McCarthy and colleagues demonstrates a clear improvement in OS with a median follow-up of 80 months, suggesting that lenalidomide maintenance clearly offers benefit compared to patients who were treated or observed at that time point.

Issues

- Two clinical trials with maintenance until PD, 1 trial with limited duration maintenance
- OS benefit in the one with treatment until PD
- MRD not a real guide for duration
- We have no way to know how much maintenance is enough maintenance
- MRD is not a surrogate for cure in the current model

MRD, minimal residual disease; OS, overall survival; PD, progressive disease.

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- Now, the issues really in determining duration of maintenance speak a lot to the available evidence. There are 2 clinical trials with maintenance until progression and 1 trial with maintenance just for 1 year. That was the French trial. The OS benefit is only seen in the group that have maintenance until progression.

The MRD availability of that data is not currently present for any of those trials.

And we don't have a lot of data to identify how much maintenance is sufficient based on existing MRD or existing clinical trial data.

And, MRD is not a surrogate for cure in the current model, because even in the MRD-negative subsets of patients from the current IFM study, patients are continuing to relapse. So, simply saying, I'm going to treat them to MRD negativity and then stop, doesn't really represent an important step forward.

Response Criteria: Minimal Residual Disease

IMWG Criteria for Response Assessment Including Criteria for MRD	
Response Category	Response Criteria
IMWG MRD Criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF, NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD negative at 5 yr).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as <2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool standardized uptake value or decrease to less than that of surrounding normal tissue.

MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; PET/CT, positron emission tomography/computed tomography. Adapted from Kumar et al. *Lancet Oncol*. 2016;17:e328-e346.



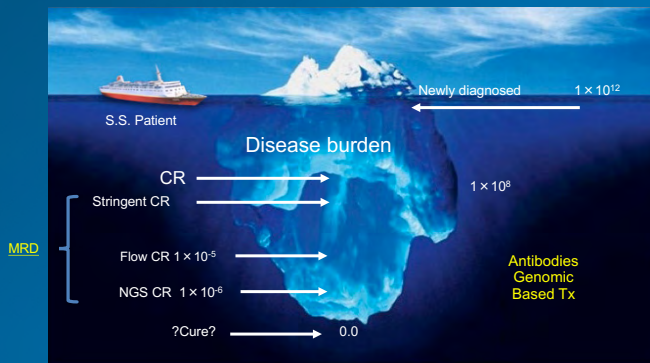
► Now what does represent an important step forward is the new IMWG criteria, the response criteria that now have different categories of deeper responses. So, one is flow MRD-negativity, typically at a sensitivity of 10^{-5} .

One is sequencing MRD-negativity. That's typically sensitivity of 10^{-6} .

Imaging with positron emission tomography, computed tomography, or magnetic resonance imaging is critically important now. And then what I think is probably the most important way to incorporate all of this, is sustained MRD negativity. And what that means is MRD negative with next-generation sequencing twice 1 year apart.

Those are patients that I think really have very durable and substantial and sustained MRD-negativity and may be considered for potential strategies at minimizing duration of therapy or stopping maintenance.

Combinations Can Achieve Better Depth and Duration of Response

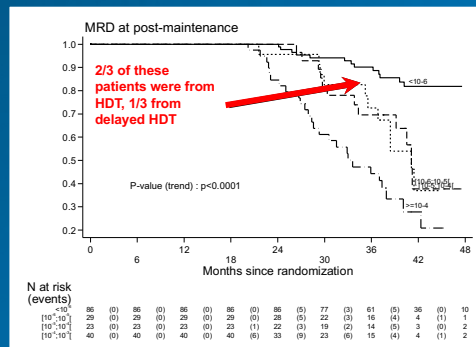


CR, complete response; NGS, next-generation sequencing; Tx, treatment. Courtesy of Sagar Lonial, MD, FACP.



► And, if you're a visual person, this will give you some sense of the iceberg. This is a slide that I created about 5 years ago that many will see quite often in terms of different talks. And it really speaks of the importance of trying to get down, even lower than 10^{-6} as a benchmark for MRD-negativity. And that it's going to be antibodies and genomics-based therapy that will hopefully get us to that cure at 10^{-0} or no myeloma cells remaining at all.

Outcomes for Patients Are the Same if They Achieved MRD Negativity



HDT, high-dose treatment; MRD, minimal residual disease.
 Aital et al. Blood 2015;126:391; Avel-Loiseau et al. Blood 2015;126:191; Blood 2017;130:435.

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► As we begin to talk about outcomes for patients, if they are MRD-negative, these are data from the IFM trial that demonstrates that if you are MRD-negative at 10^{-6} , it doesn't matter how you got to that 10^{-6} , what matters is whether you achieve that depth.

That's true, but it does also clearly identify that two-thirds of these patients underwent transplantation, speaking to the importance of transplant to achieve MRD-negativity. This is a point that's often overlooked and when people say, well it doesn't matter where you get, as long as you get deep. Well I think it's important you get deep and you stay deep for a long time, because without that, it's unlikely that you're going to have significant benefit.

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Conclusion to Debate #4: What Is the Optimal Duration of Maintenance Therapy?

► So, to wrap this one up, what is the optimal duration of maintenance therapy?

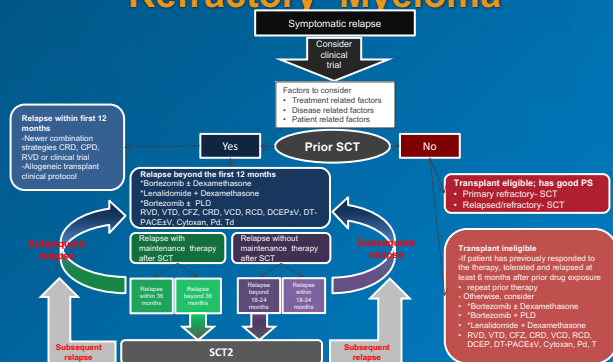
Well, I think in the United States, our approach is to treat until progression, particularly with lenalidomide. If you look at the difference between the IFM study that gave 1 year of maintenance with a median PFS of 48 months, versus our current data at our center with 1,000 patients in follow-up where the median PFS is closer to 5 years, it suggests that additional treatment until progression adds another year to the PFS overall.

There is a randomized trial from the US version of the IFM trial that gives maintenance until progression and will hopefully give us an answer to this question about duration. But for now, we don't have enough data or MRD information to guide when to discontinue maintenance therapy. The current recommendations will be treatment until progression.

Debate #5: How Do We Best Sequence Newly Approved Drugs?

► Debate number 5. How do we best sequence newly approved drugs?

Treatment Options for Relapsed and Refractory Myeloma



NCCN category 1 recommendations

CFZ, carfilzomib; CRD, carfilzomib; lenalidomide and dexamethasone; CPD, carfilzomib, pomalidomide and dexamethasone; RVD, lenalidomide, bortezomib and dexamethasone; DCEP±V, dexamethasone, cyclophosphamide, etoposide, and cisplatin ± bortezomib; DT-PACE±V, dexamethasone, thalidomide, doxorubicin, cyclophosphamide, and etoposide ± bortezomib; Pd, pomalidomide and dexamethasone; PLD, liposomal doxorubicin; PFS, progression-free survival; PS, performance status; RCD, lenalidomide, cyclophosphamide and dexamethasone; SCT, autologous stem cell transplant; SCT2, second SCT; Td, thalidomide and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone; VTD, bortezomib, thalidomide and dexamethasone.

Nooka et al. Blood 2015;125:3085-3099.

► This is really an important question because as you can see from this cartoon, there are lots and lots of different treatment approaches for the management of patients with relapsed myeloma. So, trying to figure out how to sequence them, how to use them all, really does represent an important question.

FDA Approvals of Novel Agents for Patients With R/R MM

Novel Agent or Regimen	FDA Approval Date	Patient Population
Panobinostat + bortezomib/dexamethasone	February 23, 2015	Patients with ≥2 prior standard therapies, including bortezomib and an IMiD agent
Carfilzomib + lenalidomide/dexamethasone	July 24, 2015	Patients with relapsed disease who had received 1-3 prior lines of therapy
Daratumumab	November 16, 2015	Patients with at least 3 prior treatments
Ixazomib + lenalidomide/dexamethasone	November 20, 2015	Patients who had received at least 1 prior therapy
Elotuzumab + lenalidomide/dexamethasone	November 30, 2015	Patients with 1-3 prior therapies
Carfilzomib + dexamethasone	January 21, 2016	Patients with relapsed disease and 1-3 prior therapies
Daratumumab + bortezomib/dexamethasone	November 21, 2016	Patients who had received at least 1 prior therapy
Daratumumab + lenalidomide/dexamethasone	November 21, 2016	Patients who had received at least 1 prior therapy
Daratumumab + pomalidomide/dexamethasone	June 16, 2017	Patients who had received ≥2 prior standard therapies, including bortezomib and an IMiD agent

IMiD, immunomodulatory drug; MM, multiple myeloma; R/R, relapsed/refractory.
Orlowski and Lonial. *Clin Cancer Res*. 2016;22:5443-5452; FDA.gov.



► So, if you think about FDA approvals, just in the past 5 to 10 years, you can see panobinostat, carfilzomib, daratumumab, ixazomib, elotuzumab, carfilzomib-dexamethasone alone, daratumumab with bortezomib, daratumumab with lenalidomide, and daratumumab with pomalidomide. So, how do we put all of these together in a coherent rational way?

Available Regimens in Early Relapse: NCCN Guidelines

Preferred Regimens	
Level 1 Regimens	Other Regimens
<ul style="list-style-type: none"> •Carfilzomib/dexamethasone •Carfilzomib/lenalidomide/dexamethasone •Daratumumab/bortezomib/dexamethasone •Daratumumab/lenalidomide/dexamethasone •Elotuzumab/lenalidomide/dexamethasone •Ixazomib/lenalidomide/dexamethasone 	<ul style="list-style-type: none"> •Repeat primary induction therapy (if relapse at >6 months) •Bortezomib/lenalidomide/dexamethasone
Other Regimens	
Level 1 Regimens	Other (Alkylator-Based)
<ul style="list-style-type: none"> •Bortezomib/ipsofomal doxorubicin/dexamethasone •Bortezomib/dexamethasone •Lenalidomide/dexamethasone •Panobinostat/bortezomib/dexamethasone •Pomalidomide/dexamethasone 	<ul style="list-style-type: none"> •Bendamustine •Bendamustine/bortezomib/dexamethasone •Bendamustine/lenalidomide/dexamethasone •Cyclophosphamide/lenalidomide/dexamethasone •DCEP (dex/cyclophosphamide/etoposide/cisplatin) •DT-PACE (dex/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide) ± bortezomib (VTD-PACE) •High-dose cyclophosphamide
	Other (PI-Based)
	<ul style="list-style-type: none"> •Bortezomib/cyclophosphamide/dexamethasone •Carfilzomib/cyclophosphamide/dexamethasone •Carfilzomib/dexamethasone •Daratumumab •Daratumumab/pomalidomide/dexamethasone •Elotuzumab/bortezomib/dexamethasone •Ixazomib/dexamethasone •Ixazomib/pomalidomide/dexamethasone •Panobinostat/carfilzomib •Panobinostat/lenalidomide/dexamethasone •Pomalidomide/cyclophosphamide/dexamethasone •Pomalidomide/bortezomib/dexamethasone •Pomalidomide/carfilzomib/dexamethasone

Note: NCCN Guidelines do not break out regimens into separate categories of early and late relapse.
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► Well, here are the NCCN Guidelines, which basically are what I would consider to be the sort of laundry list of potential different options. They don't necessarily give you any guidance, and most of these approaches do have level 1 evidence as being seen in randomized phase 3 trials.

Who Are the Players?

- Still have 'older' novel agents
 - Bortezomib, lenalidomide
 - Carfilzomib, dose/schedule
 - Pomalidomide
- 'New' novel agents
 - Ixazomib, panobinostat
 - Elotuzumab, daratumumab

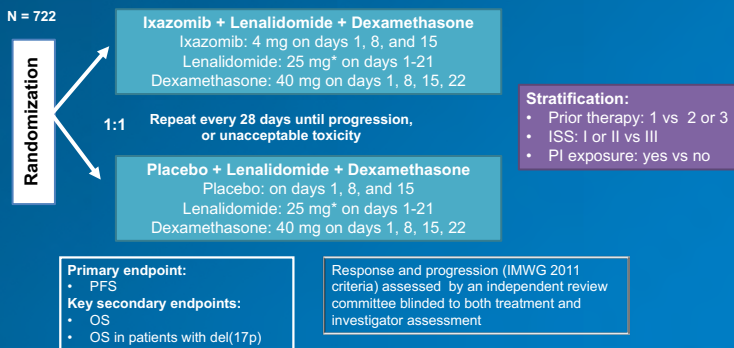
earlier lines or
induction, partner for
newer agents

► So, what are the drugs we have to think about when we see patients in the context of relapsed myeloma? Well, we've got what I call the older novel agents, bortezomib, lenalidomide, carfilzomib, and pomalidomide. And, then we have the new novel agents, of ixazomib, panobinostat, elotuzumab, and daratumumab.

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TOURMALINE-MM1 Study Design

Global, double-blind, randomized, placebo-controlled study design



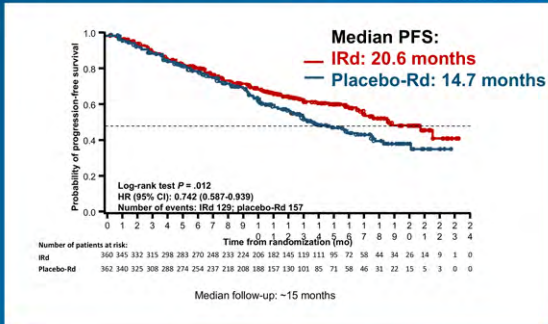
*10 mg for patients with creatinine clearance ≤ 60 or ≤ 50 mL/min, depending on local label/practice.
ISS, International Staging System; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor.
Moreau et al. *N Engl J Med*. 2016;374:1621-1634.

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► So, let's go through some of that data. These are data from the TOURMALINE-1 trial of ixazomib, lenalidomide, and dexamethasone (IRd) versus lenalidomide and dexamethasone.

TOURMALINE-MM1 Final PFS Analysis

A Significant, 35% Improvement in PFS with IRd vs placebo-Rd



IRd, ixazomib, lenalidomide, dexamethasone; PFS, progression-free survival
Moreau et al. *N Engl J Med*. 2016;374:1621-1634.

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Ixazomib: Outcomes by Cytogenetic Risk Group

	ORR, %		≥VGPR, %		≥CR, %		Median PFS, mo		
	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

- Median OS could not be estimated
- 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

* $P < .05$ 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)

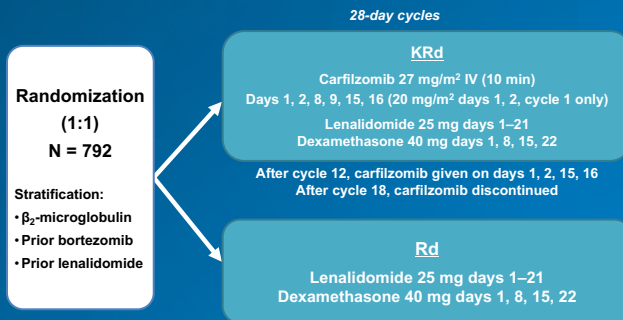
CR, complete response; IRd, ixazomib, lenalidomide, dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response. Avet-Loiseau et al. *Blood* 2017;130:2610-2618.

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- ▶ Big difference in PFS. To date, no difference in OS.

▶ But, what's really striking about ixazomib is this high-risk signal. This suggests here that if you have high-risk myeloma, your PFS is exactly the same as if you have standard-risk myeloma. This has been noted with bortezomib or other proteasome inhibitors such as carfilzomib, but it's never clearly been validated in a randomized trial like this. It'd be nice to see other trials confirm these data, but this certainly represents a major important step forward for ixazomib.

ASPIRE Study Design



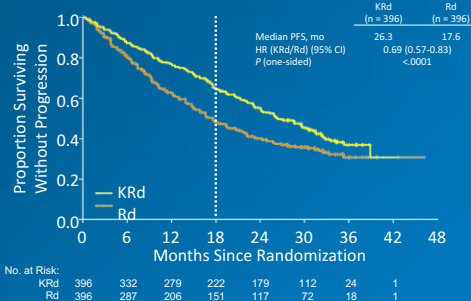
IV, intravenous; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.
Stewart et al. *N Engl J Med*. 2015;372:142-152.

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- What about carfilzomib? This is the ASPIRE trial; KRd versus lenalidomide and dexamethasone (Rd).

ASPIRE Results

Primary Endpoint: Progression-Free Survival
ITT Population (N = 792)

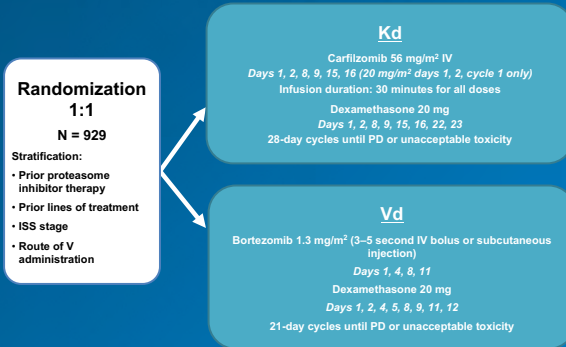


ITT, intention to treat; KRd, carfilzomib, lenalidomide, and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.
Stewart et al. *N Engl J Med*. 2015;372:142-152.

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- Again, big difference in PFS. And we now know that there's a big difference in OS as well, favoring the use of KRd versus Rd.

ENDEAVOR Study Design

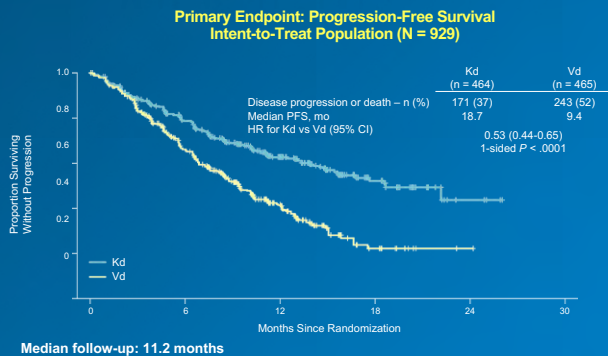


► This is to be compared with the ENDEAVOR trial, which looked at doublet versus doublet, Kd versus Vd.

ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.
Dimopoulos et al. *Lancet Oncol.* 2016;17:27-38.

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ENDEAVOR Results

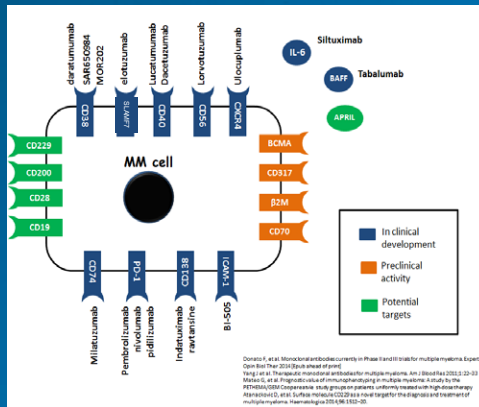


► Again, big difference in PFS, and there's a big difference in OS here as well.

ITT, intention to treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.
Dimopoulos et al. *Lancet Oncol.* 2016;17:27-38.

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Targets for Monoclonal Antibodies in Multiple Myeloma



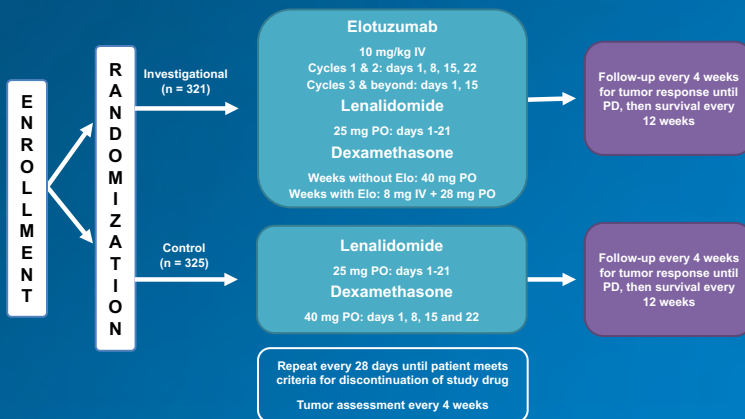
Loriot et al. *Leukemia*. 2015;30:526-535.

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► But the area that I think most of us are really excited and enthusiastic about is the availability of monoclonal antibodies. And this, I think, has really changed the way we approach patients with relapsed myeloma.

As you can see there are a number of important targets in myeloma that have been identified and developed.

ELOQUENT-2 Study Design

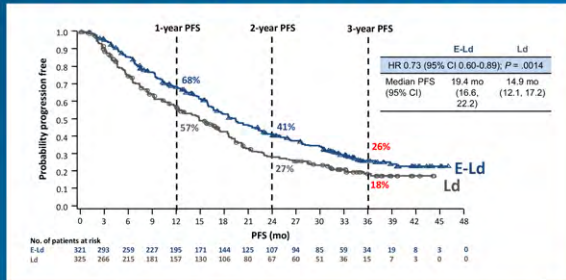


Loriot et al. *N Engl J Med*. 2015;373:621-631.

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► Let's talk first, about the ELOQUENT-2 study, which looked at elotuzumab plus lenalidomide-dexamethasone versus lenalidomide and dexamethasone.

ELOQUENT-2 Extended Progression-Free Survival



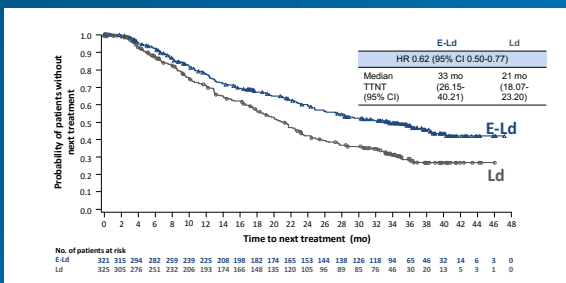
- PFS benefit with E-Ld was maintained over time (vs Ld):
 - Overall 27% reduction in the risk of disease progression or death
 - Relative improvement in PFS of 44% at 3 years

E-Ld, elotuzumab, lenalidomide, dexamethasone; PFS, progression-free survival.
Lonial et al. *N Engl J Med* 2015;373:621-631; *J Clin Oncol*. 2017;35:8028-8028.

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- Clear improvement in PFS, which is now holding up with a median follow-up of more than 4 years and continues to be about a 30% improvement in PFS.

ELOQUENT-2 Time to Next Treatment



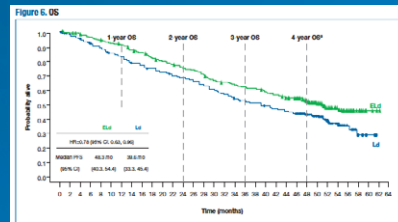
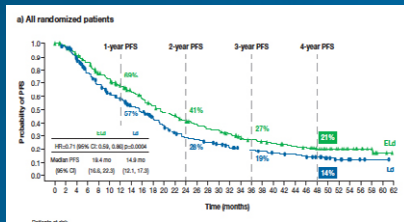
- E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients

E-Ld, elotuzumab, lenalidomide, dexamethasone; TTNT, time to next treatment.
Dimopoulos et al. *Br J Haematol*. 2017;178:896-905.

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- And, time to next treatment is also longer in the group that received elotuzumab.

ELOQUENT-2 Update



ELd, elotuzumab, lenalidomide, dexamethasone; OS, overall survival; PFS, progression-free survival.
Lonial et al. *J Clin Oncol*. 2017;35:8028-8038.

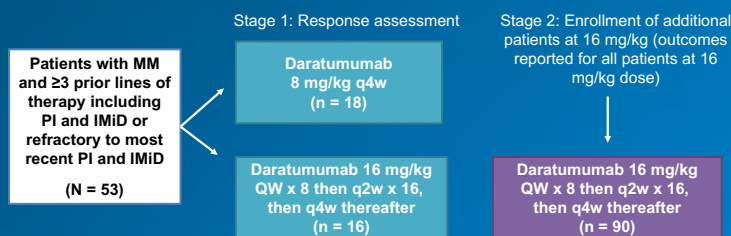
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- If you look at the most recent update of elotuzumab, there is now a survival benefit for patients who received elotuzumab plus Rd versus Rd alone.

This I think is critically important because survival benefits are, I think, an important benchmark of how we approach next steps in the management of patients.

SIRIUS Trial Design

- Open-label, international, multicenter, 2-stage study



- Primary objective: ORR

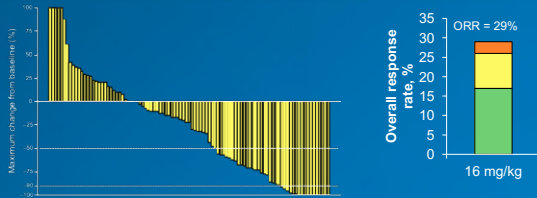
IMiD, immunomodulatory drug; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; q2w, every 2 weeks; q4w, every 4 weeks; QW, once weekly; RMM, relapsed/refractory multiple myeloma.
Lonial et al. *Lancet* 2016;387:1551-1560.

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- What about daratumumab? Well the trial that led to the approval of daratumumab was the SIRIUS trial. It was a multi-institution, multi-country study of over 100 patients with symptomatic multiple myeloma who received single agent daratumumab.

SIRIUS Trial

Phase 2 study of daratumumab in patients with ≥ 3 lines of prior therapy or double refractory MM

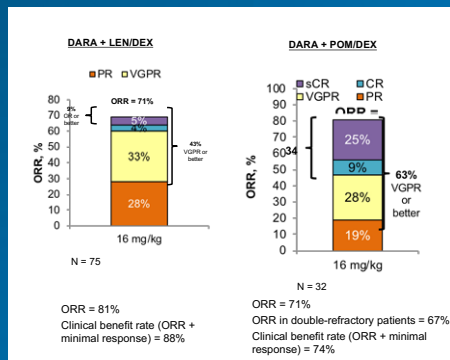


MM, multiple myeloma; ORR, overall response rate.
Lonial et al. Lancet 2016;387:1551-1560.

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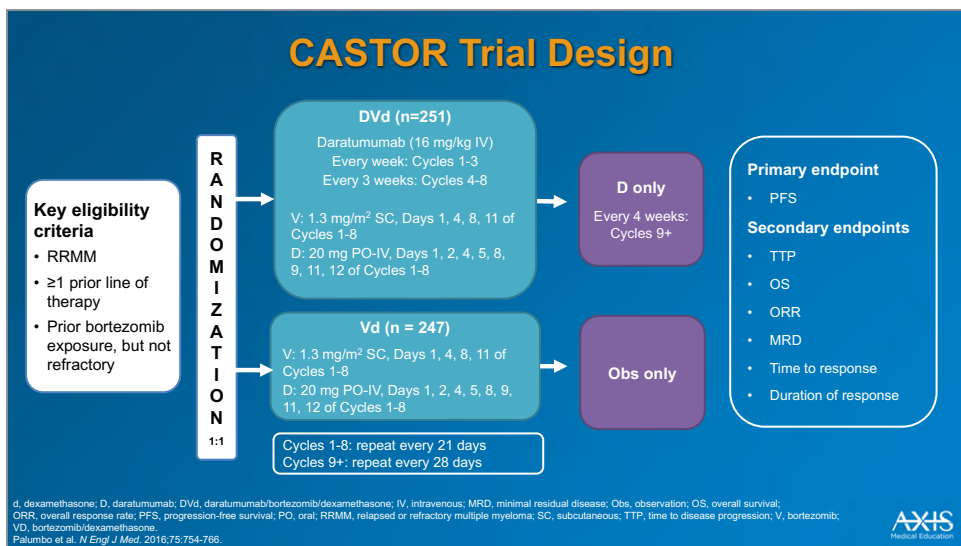
- ▶ As you can see in this waterfall plot as well as response rate, clearly there was benefit favoring the use of daratumumab in a single-arm phase 2 study.

Overall Response Rate

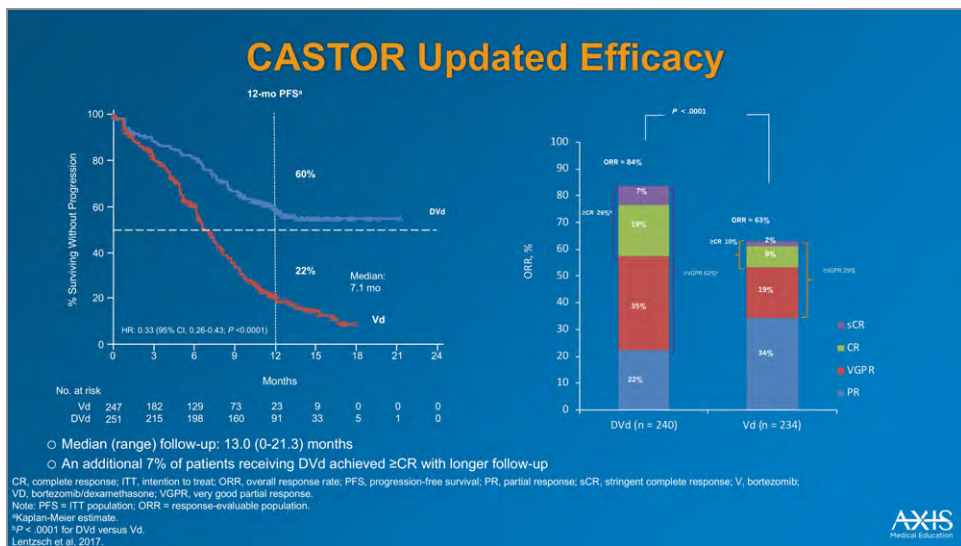


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- ▶ And again, if you look at preliminary data in combinations, you see significant improvement in response rate when combined with Rd as well as with pomalidomide and dexamethasone.

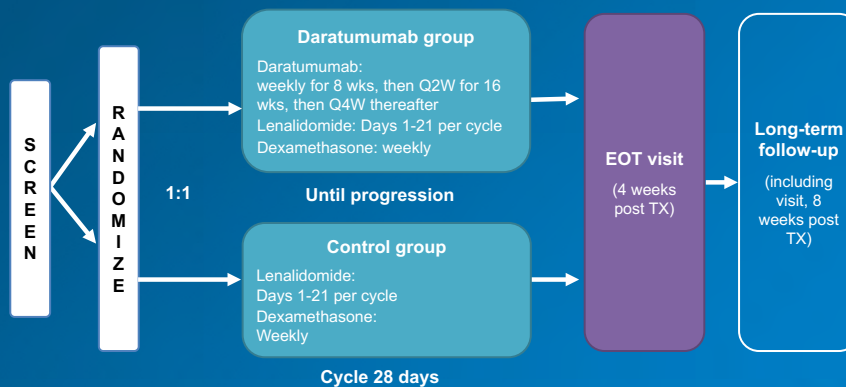


► This in turn led to 2 important large phase 3 trials—the first was the CASTOR trial; daratumumab with bortezomib-dexamethasone, versus bortezomib-dexamethasone.



► Where we saw a clear improvement in PFS, and a clear improvement in response rate. Overall survival has not been reached yet.

POLLUX Trial Design

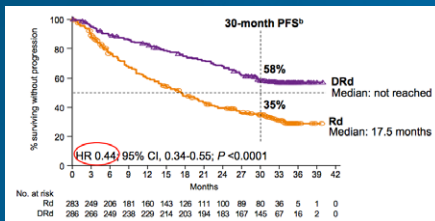


EOT, end of treatment; Q2W, every 2 weeks; TX, treatment.
Dimopoulos et al. *N Engl J Med*. 2016;375:1319-1331.

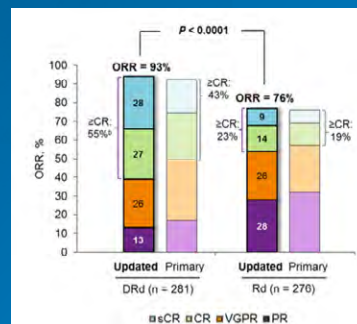
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- That's to be compared with the POLLUX trial, which looked at daratumumab combined with lenalidomide-dexamethasone versus lenalidomide-dexamethasone, also a randomized phase 3 trial.

POLLUX Updated Efficacy



Median follow-up: 32.9 months (range, 0 – 40.0 months)



- Big, big differences in PFS and overall response rate. And again, survival is not quite ready yet.

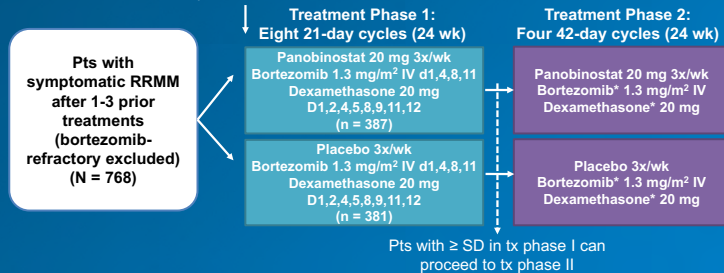
Exploratory analyses based on clinical cut-off date of October 23, 2017.
PR, partial response; sCR, stringent complete response.
*Kaplan-Meier estimate.
Dimopoulos et al. *Blood* 2017;130:739.

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PANORAMA-1 Study Design

- Randomized, double-blind trial
- Primary endpoint reached: median PFS ↑ by 3.9 mo

Stratified by prior lines of therapy
and prior bortezomib



Bortidex, bortezomib, dexamethasone; D, day; PFS, progression-free survival; Pts, patients; RRMM, relapsed/refractory multiple myeloma;
SD, stable disease; tx, treatment.
*Reduced frequency
San-Miguel et al. *Lancet Oncol*. 2014;15:1195-1206.

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► Let's wrap up then with panobinostat or the PANORAMA trial. This was a randomized trial of panobinostat/bortezomib/dexamethasone, versus bortezomib-dexamethasone.

PANORAMA-1 Results

- 387 patients randomly assigned to panobinostat, bortezomib, and dexamethasone
- 381 patients randomly assigned to placebo, bortezomib, and dexamethasone
- Median follow-up: 6.47 mo in the panobinostat group and 5.59 mo in the placebo group
- Median PFS significantly longer in panobinostat group than in placebo group
 - 11.99 vs 8.08 mo
 - HR 0.63
 - 95% CI 0.52-0.76
 - $P < .0001$

PFS, progression-free survival.
San-Miguel et al. *Lancet Oncol*. 2014;15:1195-1206.

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► And again, big difference in PFS, particularly among patients who had resistant disease. So, if you'd seen more than 2 prior lines of therapy, the benefit was even larger for panobinostat/bortezomib/dexamethasone, compared to patients who received just bortezomib-dexamethasone.

Conclusion to Debate #5: How Do We Best Sequence Newly Approved Drugs?

► So, how do we sequence newly approved drugs? Well, I'm going to show you some approaches in our center in the next debate, specifically that answer that question. It is important to realize which drugs can work where. For instance, if you're resistant to bortezomib, the likelihood of benefit of ixazomib is pretty low, and the likelihood of benefit to low-dose carfilzomib is probably pretty low as well.

On the other hand, if you're resistant to lenalidomide, then pomalidomide probably becomes the important immunomodulatory drug to partner with antibodies or with proteasome inhibitors.

Again, the antibodies clearly, daratumumab has single agent activity, partners well with almost every drug and right now, in terms of elotuzumab, the only drug we really know it partners well with is lenalidomide, and hopefully we'll have additional data very soon.

Debate #6: How Do We Choose the Appropriate Combination at Relapse?

► So, finally debate 6. How do we choose the appropriate combination at relapse? This is an important question, building on the last debate that we had as well. There are 3 sets of criteria that we look at to make this decision.

Disease-Related Factors to Consider for Treatment Selection at Relapse

- Nature of relapse
 - Indolent vs aggressive
- Risk stratification
 - Genetics of initial and relapsed marrow
- Disease burden
 - High vs low
- R-ISS staging
 - 1 vs 2-3

Nooka et al. *Blood* 2015;125:3085-3099; Orlowski and Lonial. *Clin Cancer Res*. 2016;22:5443; Palumbo et al. *N Engl J Med*. 2011;364:1046-1060; Palumbo et al. *Blood* 2011;118:4519-4529.



- ▶ The first is disease-related factors that may consider or guide our treatment in the management of relapse. That is, the nature of relapse, the genetics, disease burden, and R-ISS staging. All of those can influence how we choose what we choose, when we treat patients.

Treatment-Related Factors to Consider for Treatment Selection at Relapse

- Previous therapy
 - Patients with PD receiving IMiDs, PIs, or cytotoxic doublet/triplet therapies can benefit from next-generation regimens
 - Avoid agents of previous regimen-related toxicity
 - Maintenance therapy
- Regimen-related toxicity
 - Toxicity profile should be considered in light of pt comorbidities
 - Neuropathy: consider neuropathy sparing drugs (avoid bortezomib, thalidomide)
 - Cardiac issues (uncontrolled HTN, CHF): careful consideration of carfilzomib
 - COPD: monoclonal antibodies with caution (daratumumab)
 - DVT/PE: use anticoagulation with IMiDs
- Depth and duration of previous response, tumor burden at relapse
- Retreatment with previous therapies an option if patient had previous response to the treatment, acceptable tolerance, and relapse occurred at least 6 mo after previous exposure

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; HTN, hypertension; IMiDs, immunomodulatory drugs; PE, pulmonary embolism; PD, progressive disease; PIs, proteasome inhibitors.
Nooka et al. *Blood* 2015;125:3085-3099; Palumbo et al. *N Engl J Med*. 2011;364:1046-1060; *Blood* 2011;118:4519-4529.



- ▶ What about treatment-related factors? Well, what was the previous line of therapy? What were the side effects? Did they receive a doublet or a triplet? Did they have maintenance therapy? What toxicity did they receive? Did they have cardiac issues, neuropathy? Did they have bad chronic obstructive pulmonary disease or pulmonary embolism? What was the depth of response and how long did it last in terms of previous therapy?

Patient-Related Factors to Consider for Treatment Selection at Relapse

- Renal insufficiency: disease related or due to comorbidities (hypertension, vascular disease, diabetes, nephrotoxicity)¹
- Hepatic impairment common in patients with R/R MM¹
- Comorbidities and frailty¹
 - Treatment decisions complicated in elderly
 - ↑ toxicity due to ↓ organ function, physiologic reserve
 - European Myeloma Network vulnerability assessment algorithm anticipates regimen-related toxicities and assists individualizing therapy with least potential for interruption^{2,3}
- Patient preferences
 - Convenience, ease of travel, insurance and other social factors

MM, multiple myeloma; R/R, relapsed/refractory.
 1. Nooka et al. *Blood* 2015;125:3085-3099.
 2. Palumbo et al. *N Engl J Med*. 2011;364:1046-1060.
 3. Palumbo et al. *Blood* 2011;118:4519-4529.



► Finally, patient-related factors to consider in the context of relapse as well. Renal insufficiency, hepatic dysfunction, comorbidities and frailty, and finally, patient preferences.

If a patient lives 3 1/2 hours away, having them come twice a week for subcutaneous or injection therapy is not likely to be very practical.

On the other hand, if their copay for oral meds is very high, then they may prefer to try IV medications as first choice. Those are all factors that weigh in to early relapse management.

Emory Approach to Early Relapse

Clinical Trial
 Check if patient is t(11;14)

Slow indolent relapse

+ Len maintenance

Consider
Dara/Pom/Dex

Consider
adding
Ixazomib/Dex*

Consider
Adding Elo/Dex*

* Increase len
dose

- Len maintenance

Consider
Dara/Len/Dex

Consider
Elo/Len/Dex

Consider
Car/Len/Dex

Aggressive relapse

+ Len maintenance

Consider
Dara/Pom/Dex

Consider
Car/Pom/Dex

- Len maintenance

Consider
Dara/Len/Dex

Consider
Dara/Bor/Dex

Consider
Car/Pom/Dex

Car/Pan as second salvage if IMiD used

Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; IMiD, immunomodulatory drug; Len, lenalidomide; Pom, pomalidomide.
 Courtesy of Sagar Lonial, MD, FACP.



► What I'm showing you on the next slide is our current approach for management of relapsed disease. What I think you'll see is that in early relapse we have an antibody-based approach, almost across the board for management of these patients; whether it's pomalidomide or lenalidomide as the partner. And one could consider the use of ixazomib or other approaches in as secondary choices in that, whether or not patients have slow indolent relapse or aggressive relapses.

Obviously, we consider clinical trials early on and then we check to see if the patient is 4;14-positive. Then, for us, carfilzomib becomes salvage after antibody-based therapy, in an effort to try and maximize use of all of the drug classes.

Conclusion to Debate #6: How Do We Choose the Appropriate Combination at Relapse?

► So, to conclude debate 6, how do we choose the appropriate combination at relapse? I think it's really key here to use antibodies early on in the relapse setting. Antibodies tend to partner quite nicely with immunomodulatory drugs but can also partner with proteasome inhibitors as well.

I think it's also important to think about your strategy. How are you going to best utilize each of the drugs if a patient has seen bortezomib and has not seen a proteasome inhibitor again, can you use ixazomib? Can you use carfilzomib? Will you use an antibody in that line of therapy?

These are all important questions that I think we need to think about and have an approach, or as I like to say, have a long-term plan. When I meet a patient with newly diagnosed myeloma, I tell them, "you're on a 10-plus year journey with me, and together we're going to figure how to do what's best for you."

So, as we work through that journey, it's important that we all have the same goals, we all understand what each other is striving for, and ultimately understand the limitations and benefits of therapy and use this information together to make decisions about the best treatment approach for patients.

**Thank you for participating
in this activity!**

- ▶ So, with that I will again, thank you for your participation in this activity and hope you enjoyed this debate and got some important information. Thank you for your time.

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