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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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.

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.
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.

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?
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

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

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.
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

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.
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.
Frequency of FISH Abnormalities in IFM Experience

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

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

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.

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.

(cont. on next page)
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 β2-microglobulin values at diagnosis

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.

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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.
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Revised ISS Staging
Standard Risk Factors for MM and the R-ISS

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>ISS Stage</td>
<td>Serum 𝛽₂-microglobulin &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>Not ISS stage I or II</td>
</tr>
<tr>
<td></td>
<td>Serum 𝛽₂-microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td>Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)</td>
</tr>
<tr>
<td>High risk</td>
<td>No high-risk CA</td>
</tr>
<tr>
<td>LDH</td>
<td>Serum LDH &lt; the upper limit of normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Serum LDH &gt; the upper limit of normal</td>
</tr>
</tbody>
</table>

A new model for risk stratification of MM

R-ISS stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
</tr>
<tr>
<td>II</td>
<td>Not R-ISS stage I or II</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
</tr>
</tbody>
</table>

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.

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.
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

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.
Free Light Chain Ratio Is Useful for Risk Assessment in SMM

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.

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.
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.
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updated IMWG criteria for Diagnosis of Multiple Myeloma

MGUS
- M-protein <3 g/dL
- Clonal plasma cells in BM <10%
- No myeloma-defining events

Smoldering Myeloma
- M-protein 3-10 g/dL (serum) or >1500 mg/24 hr (urine)
- Clonal plasma cells in BM ≥10%
- No myeloma-defining events

Multiple Myeloma
- Underlying plasma cell proliferative disorder
- AND
  - 1 or more myeloma-defining events including either:
    - ≥1 CRAB feature(s)
    - OR
    - ≥1 Biomarker Driven

Biomarker Driven
1. ≥60% clonal PCs in BM
2. serum free light chain ratio involved:uninvolved ≥100
3. ≥1 focal lesion detected with MRI ≥5 mm

C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or 2 g/dL < normal)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

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.

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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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.

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.

► 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.

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

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

- 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.


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.
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.

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 index\(^1\)
  - Additive scoring system (range 0-5), based on age, comorbidities, and cognitive and physical conditions, developed to identify 3 groups:

<table>
<thead>
<tr>
<th>Additive Total Score</th>
<th>Patient Status</th>
<th>No. of Patients (%)</th>
<th>% (95% CI)</th>
<th>Cumulative Incidence at 12 mo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fit</td>
<td>340 (39)</td>
<td>84 (78-89)</td>
<td>46 (41-56)</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>209 (21)</td>
<td>76 (67-82)</td>
<td>41 (32-49)</td>
</tr>
<tr>
<td>2</td>
<td>Frail</td>
<td>260 (30)</td>
<td>57 (45-68)</td>
<td>33 (25-41)</td>
</tr>
</tbody>
</table>

PS, performance status.

- Revised ASBMT guidelines indicate age alone should not be used as determining factor for transplant eligibility\(^2\)
  - Instead, a score of &gt;2 on hematopoietic cell transplantation-specific comorbidity index or a Karnofsky performance status of &lt;90 should warrant additional caution before proceeding with ASCT in elderly patients


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.

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

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.

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

Improving Survival in MM

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.

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.
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.
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.

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.
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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.

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Bortezomib Use in High-Risk Newly Diagnosed MM

Benefit of Bortezomib Induction and Maintenance for High-Risk

<table>
<thead>
<tr>
<th>FISH</th>
<th>PFS at 60 mo, %</th>
<th>OS at 60 mo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Bortezomib Arm</td>
</tr>
<tr>
<td>t(4;14) yes/no</td>
<td>50/295</td>
<td>16% vs 27%</td>
</tr>
<tr>
<td>add(1q) yes/no</td>
<td>113/231</td>
<td>16% vs 32%</td>
</tr>
<tr>
<td>del(17p) yes/no</td>
<td>39/312</td>
<td>22% vs 27%</td>
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Renal insufficiency | VAD | PAD
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</thead>
<tbody>
<tr>
<td>OS at 96 months; yes/no</td>
<td>12 vs 42%</td>
<td>47 vs 48%</td>
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</tbody>
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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.
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.

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.

(cont. on next page)
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.
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.

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

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.

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.
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 2005-02³,⁴
- Other recommended regimen: bortezomib¹
  - HOVON⁵

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

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

![Graph showing survival probability over time for different maintenance therapies.](image)

**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

![Note: Image or graph related to the discussion of issues.](image)

- NE, not estimable; OS, overall survival; PD, progressive disease.


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.

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.
Combinations Can Achieve Better Depth and Duration of Response

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained MRD-negative</td>
<td>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).</td>
</tr>
<tr>
<td>Flow MRD-negative</td>
<td>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.</td>
</tr>
<tr>
<td>Sequencing MRD-negative</td>
<td>Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as &lt;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.</td>
</tr>
<tr>
<td>Imaging plus MRD-negative</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

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

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.

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?

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.
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?

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.
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, ixazomib, panobinostat, elotuzumab, and daratumumab.

So, let’s go through some of that data. These are data from the TOURMALINE-MM1 trial of ixazomib, lenalidomide, and dexamethasone (IRd) versus lenalidomide and dexamethasone.
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.
Primary Endpoint: Progression-Free Survival

ITT Population (N = 792)

ASPIRE Study Design

- Randomization
  - (1:1)
  - N = 792

- Stratification:
  - β2-microglobulin
  - Prior bortezomib
  - Prior lenalidomide

- 28-day cycles

- **KRd**
  - Carfilzomib 27 mg/m² IV (16 min)
  - Days 1, 2, 8, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
  - Lenalidomide 25 mg days 1–21
  - Dexamethasone 40 mg days 1, 8, 15, 22

  - After cycle 12, carfilzomib given on days 1, 2, 15, 16
  - After cycle 18, carfilzomib discontinued

- **Rd**
  - Lenalidomide 25 mg days 1–21
  - Dexamethasone 40 mg days 1, 8, 15, 22

**ASPIRE Results**

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

- Median PFS, mo: 26.3 (KRd) vs. 17.6 (Rd)
- HR (KRd/Rd): 0.69 (95% CI: 0.57–0.83)
- P (one-sided) < .0001

- No. at Risk:
  - KRd: 396 332 279 222 179 112 24 1
  - Rd: 396 287 206 151 117 72 18 1

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

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

**Kd**
- **Carfilzomib 56 mg/m² IV**
  - Days 1, 2, 8, 9 (20 mg/m² Days 1, 2, cycle 1 only)
  - Infusion duration: 30 minutes for all doses

**Dexamethasone 20 mg**
- Days 1, 2, 8, 9, 15, 19, 25, 26, 27
- 28-day cycles until PD or unacceptable toxicity

**Vd**
- **Bortezomib 1.3 mg/m² (3-5 second IV bolus or subcutaneous injection)**
  - Days 1, 4, 8, 11

**Dexamethasone 20 mg**
- Days 1, 4, 8, 11
- 21-day cycles until PD or unacceptable toxicity

**Randomization**
- 1:1
- **N = 929**
- Stratification:
  - Prior proteasome inhibitor therapy
  - Prior line of treatment
  - ISS stage
  - Route of V administration

ENDEAVOR Results

**Primary Endpoint: Progression-Free Survival**

**Intent-to-Treat Population (N = 929)**

- **Kd (n = 464)**
  - 171 (37)

- **Vd (n = 465)**
  - 243 (52)

**Disease progression or death—n (%)**
- Median PFS, mo
- HR for Kd vs Vd (95% CI)

- **Kd**
  - Median: 21.7
  - HR: 0.53 (0.44-0.65)
  - 1-sided P < .0001

- **Vd**
  - Median: 18.7
  - HR: 0.44 (0.33-0.58)

**Median follow-up: 11.2 months**

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

Again, big difference in PFS, and there’s a big difference in OS here as well.
Let’s talk first, about the ELOQUENT-2 study, which looked at elotuzumab plus lenalidomide-dexamethasone versus lenalidomide and dexamethasone.

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
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

- HR 0.62 (95% CI 0.50-0.77)
- Median TTNT (95% CI)
  - E-Ld: 33 months (26.15-40.21)
  - Ld: 21 months (18.07-23.20)

E-Ld, elotuzumab, lenalidomide, dexamethasone; PFS, progression-free survival.


► 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

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

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.

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**SIRIUS Trial Design**

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

  - **Stage 1: Response assessment**
    - Patients with MM and ≥3 prior lines of therapy including PI and IMiD or refractory to most recent PI and IMiD (N = 53)
    - Daratumumab 8 mg/kg q4w (n = 18)
    - Daratumumab 16 mg/kg QW x 8 then q2w x 16, then q4w thereafter (n = 16)

  - **Stage 2: Enrollment of additional patients at 16 mg/kg (outcomes reported for all patients at 16 mg/kg dose)**
    - Daratumumab 16 mg/kg QW x 8 then q2w x 16, then q4w thereafter (n = 90)

**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; Rd, elotuzumab, lenalidomide, dexamethasone;**


Overall Response Rate

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.

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.
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.

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

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

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, finally debate 6. 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, 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.
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.

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 interruption2,3
- Patient preferences
  - Convenience, ease of travel, insurance and other social factors

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* (increase len dose)

Aggressive relapse

- Len maintenance
  - Consider Dara/Pom/Dex
  - Consider Elo/Len/Dex
  - Consider Car/Pom/Dex

Car/Pan as second salvage if IMiD used

 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, they may prefer to try IV medications as first choice. Those are all factors that weigh in to early relapse management.

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.
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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