INTERVIEW

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Tracks 1-13

Track 1 Redefining treatment parameters in smoldering multiple myeloma (MM)

Track 2 Survival advantage with lenalidomide in combination with low-dose dexamethasone compared to observation for patients with high-risk smoldering MM

Track 3 ECOG-E3A06: A Phase III trial of lenalidomide versus observation for asymptomatic high-risk smoldering MM

Track 4 Initial results of the Phase III FIRST trial of lenalidomide/dexamethasone (Rd) versus melphalan/prednisone/thalidomide (MPT) for transplant-ineligible patients with newly diagnosed MM

Track 5 Therapeutic options and duration of therapy for elderly patients with MM

Track 6 Activity, tolerability and ongoing trials of the oral proteasome inhibitor ixazomib (MLN9708) in MM

Track 7 Preference for subcutaneous bortezomib versus intravenous administration

Track 8 **Case discussion:** A 66-year-old patient with standard-risk MM with t(11;14) translocation achieves a complete response with RVD followed by autologous stem cell transplant

Track 9 Effect of initial response and/or adverse cytogenetics on approach to maintenance therapy for MM

Track 10 Toward prolonged survivals and potential cure for patients with MM

Track 11 Clinical experiences with and tolerability of carfilzomib and pomalidomide

Track 12 Unique clinical considerations for patients receiving carfilzomib (hydration, cardiopulmonary side effects, attenuated peripheral neuropathy)

Track 13 Promising novel monoclonal antibodies under investigation in MM

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: What were the important points of your recently published article on redefining smoldering multiple myeloma (SMM) (Dispenzieri 2013)?

DR RAJKUMAR: Some features are associated with a high risk of disease progression. The earlier therapy is initiated, the easier it is to prevent the occurrence of bone disease, acute renal failure or vertebral compression fracture. At least 3 markers indicate that therapy should be initiated for MM regardless of whether a patient has end-organ damage. These are bone marrow with greater than 60% involvement, serum free light chain (FLC) ratio of 100 or greater and MRI scan of 1 or more focal lesion.

DR LOVE: Would you discuss the interventions available for high-risk SMM?

DR RAJKUMAR: In a Spanish trial of lenalidomide and dexamethasone (len/dex) versus observation for patients with high-risk SMM, early treatment prolonged time to disease

progression and increased overall survival (OS) (Mateos 2013; [2.1]). Although this study has some caveats in the sense that the definitions used for high-risk SMM are not widely accepted, it gives us confidence that early therapy is not harmful but has the potential to save lives.

I would encourage patient participation in the ongoing US ECOG-E3A06 trial of lenalidomide versus observation. The trial is evaluating patients with high-risk SMM with 10% or greater plasma cells in the bone marrow. Patients should have measurable monoclonal protein levels and an abnormal FLC ratio. With these criteria, the risk of disease progression is about 20% per year, meaning that 50% of patients will experience disease progression within 2 years.

This cohort of patients closely resembles the Spanish trial population. However, without the US trial, we will not be able to use single-agent lenalidomide for the treatment of MM outside the United States because regulatory bodies will not accept lenalidomide/dexamethasone as proof that lenalidomide works. Also, some differences exist between the 2 trials, including age differences and questions about the eligibility criteria in the Spanish trial. Therefore, a confirmatory trial is needed to ascertain whether lenalidomide is indeed useful in high-risk SMM.

2.1

Phase III Study of Induction Therapy with Lenalidomide (Len) in Combination with Dexamethasone Followed by Maintenance Len for Patients with High-Risk Smoldering Multiple Myeloma (SMM)

Survival	Treatment (n = 57)	Observation (n = 62)	Hazard ratio	*p*-value
Median time to progression	Not reached	21 months	0.18	<0.001
Three-year overall survival (OS) rate since enrollment	94%	80%	0.31	0.03
Five-year OS rate since SMM diagnosis	94%	78%	0.28	0.02
Responses	**Induction (n = 57)**	**Maintenance (n = 50)**	**Hazard ratio**	***p*-value**
Overall response rate	79%	90%	Not reported	
	Treatment (n = 62)		Observation (n = 63)	
Adverse events (induction)	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
Neutropenia	18%	5%	0%	0%
Anemia	24%	2%	5%	0%
Infections*	41%	6%	22%	0%
Asthenia	18%	6%	10%	0%
Diarrhea	21%	2%	4%	0%

* Grade 5 infection developed in 1 patient in the treatment group.

Mateos MV et al. *N Engl J Med* 2013;369(5):438-47.

Track 4

DR LOVE: Would you discuss the initial results of the Phase III FIRST trial for transplant-ineligible patients with newly diagnosed MM?

DR RAJKUMAR: This is a large study of 1,623 patients who received melphalan/prednisone/thalidomide (MPT) or lenalidomide/low-dose dexamethasone (Rd) (Facon 2013; [2.2]). It has 2 Rd arms — treatment for 18 months or continuously until disease progression. The study demonstrated an OS improvement with Rd. It's the first time a nonmelphalan-based regimen yielded better results in elderly patients with MM. Rd represents a new standard treatment in this setting.

In the United States, melphalan has not been widely used for elderly patients in the past 5 to 10 years. Outside the United States, where melphalan-based regimens are the standard, the FIRST trial changes that. Rd is a good option because it's oral. For patients with trisomies, it's a particularly good option. Elderly patients with high-risk cytogenetic features would be more likely to be candidates for a bortezomib-based regimen such as bortezomib/cyclophosphamide/dexamethasone (CyBorD).

DR LOVE: What are your thoughts on the differences observed between the 2 Rd arms?

DR RAJKUMAR: Unlike other MM treatments, Rd is chronically suppressive. The 18-month schedule yielded a TTP of 21.9 months, suggesting that once therapy is discontinued, the disease recurs. If this regimen is chosen, it needs to be administered on a chronically suppressive schedule until disease progression.

2.2

Initial Results from the Phase III FIRST Trial of Lenalidomide in Combination with Low-Dose Dexamethasone (Rd) versus MPT in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Outcome	Rd18 (n = 541)	Continuous Rd (n = 535)	MPT (n = 547)
Median PFS*	20.7 months	25.5 months	21.2 months
p-value	0.00001		—
	—	0.00006	
Four-year OS rate*	55.7%	59.4%	51.4%
p-value	0.307		—
	—	0.0168	
ORR	73.4%	75.1%	62.3%
Grade 3/4 adverse events	(n = 540)	(n = 532)	(n = 541)
Neutropenia	26.5%	27.8%	44.9%
Infections	21.9%	28.9%	17.2%
Anemia	15.7%	18.2%	18.9%
Pneumonia	8.3%	8.1%	5.7%
Thrombocytopenia	8.0%	8.3%	11.1%

PFS = progression-free survival; OS = overall survival; ORR = overall response rate
* No significant difference between Rd18 and MPT ($p > 0.05$)

Facon T et al. *Proc ASH* 2013;**Abstract 2**.

Tracks 6, 12

DR LOVE: How do you use the currently approved proteasome inhibitors in MM, and in what situations do you envision using novel agents in this class?

DR RAJKUMAR: With regard to carfilzomib, I believe it's a well-tolerated agent. Many of the initial renal problems with administration of this agent have been solved with dosing and fluid administration. Concern exists about cardiac or pulmonary side effects, which I pay attention to, but we need to better understand the frequency and exact mechanism of these issues.

Another point I want to make with regard to carfilzomib is the neuropathy rate. It does seem to be lower, but one caveat is that many of the carfilzomib trials excluded patients with preexisting neuropathy. So you have to be fair to bortezomib, in the sense that gauging the true rate of this neuropathy risk will require more studies in which carfilzomib is administered ahead of bortezomib. A Phase III Intergroup trial comparing bortezomib/lenalidomide/dexamethasone to carfilzomib/lenalidomide/dexamethasone is available across the United States. This kind of trial is necessary before we conclude that one regimen is better than the other.

These proteasome inhibitors are also useful as maintenance therapy. Each has a different side-effect profile and mode of administration (2.3). Based on the differences, these agents are suitable for different patients. Also, some noncross resistance occurs. For instance, carfilzomib works in patients for whom bortezomib has failed and vice versa.

Ixazomib is of particular interest because it's a once-weekly pill. This makes it a good drug for compliance, especially for elderly patients, and a more attractive maintenance approach. It's well tolerated at the right doses. ■

2.3 Key Features of the Proteasome Inhibitors Bortezomib, Carfilzomib and Ixazomib

Feature	Bortezomib	Carfilzomib	Ixazomib (MLN9708)
Generation	First in class	Second generation	Second generation
Inhibition type	Reversible inhibitor	Irreversible inhibitor	Reversible inhibitor
Half-life	110 minutes	<30 minutes	18 minutes
Mode of administration	Intravenous, subcutaneous	Intravenous	Oral
Most common associated side effects	Peripheral neuropathy, diarrhea	Fatigue, hematologic toxicity	Thrombocytopenia, fatigue, rash
Clinical stage	Approved for MM	Approved for R/R MM	Phase III trials in ND and R/R MM

MM = multiple myeloma; R/R = relapsed or refractory; ND = newly diagnosed

Moreau P et al. *Blood* 2012;120(5):947-59; Dick LR, Fleming PE. *Drug Discov Today* 2010;15(5-6):243-9.

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Facon T et al. **Initial Phase 3 results of the FIRST (frontline investigation of lenalidomide + dexamethasone versus standard thalidomide) trial (MM-020/IFM 0701) in newly diagnosed multiple myeloma patients ineligible for stem cell transplantation.** *Proc ASH* 2013;**Abstract 2**.

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