INTERVIEW

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Tracks 1-15

Track 1 **Case discussion:** An 82-year-old man with newly diagnosed Stage III, IgG kappa multiple myeloma (MM) receives lenalidomide/dexamethasone

Track 2 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 3 Continuous versus fixed duration of Rd treatment

Track 4 Dosing of lenalidomide in elderly patients with MM

Track 5 Effect of adverse cytogenetics on outcomes of transplant-ineligible patients with newly diagnosed MM treated with continuous Rd

Track 6 Results of a Phase I/II trial of the newly FDA-approved oral proteasome inhibitor ixazomib in combination with Rd for previously untreated MM

Track 7 Results of the Phase III TOURMALINE-MM1 trial: Improvement in progression-free survival with the addition of ixazomib to Rd for patients with relapsed/refractory MM

Track 8 Perspective on the development and potential role of the oral proteasome inhibitor oprozomib

Track 9 **Case discussion:** A 62-year-old woman whose disease relapses 2 years after autologous stem cell transplant (ASCT) is enrolled on the ASPIRE study and achieves a complete remission with carfilzomib/Rd (CRd)

Track 10 Therapeutic options for induction and maintenance therapy in patients with MM

Track 11 Activity and tolerability of CRd

Track 12 Incidence and management of carfilzomib-associated dyspnea

Track 13 Perspective on the integration of CRd and panobinostat/bortezomib/dexamethasone into the treatment landscape for relapsed/refractory MM

Track 14 Results of ELOQUENT-2: A Phase III trial of lenalidomide/dexamethasone with or without the newly FDA-approved monoclonal antibody elotuzumab for relapsed/refractory MM

Track 15 Activity of the newly FDA-approved anti-CD38 antibody daratumumab for heavily pretreated or double-refractory MM

Select Excerpts from the Interview

Tracks 2-3, 5

DR LOVE: You were one of the investigators on the Phase III FIRST trial of lenalidomide and dexamethasone for transplant-ineligible patients with multiple myeloma (MM). Would you discuss the results of this study (Benboubker 2014)?

DR MOREAU: This trial was primarily for patients age 65 or older. It was a 3-arm study comparing melphalan/prednisone/thalidomide (MPT) for 12 cycles to lenalidomide/

low-dose dexamethasone (Rd) for 18 cycles or continuously until disease progression. A total of 1,623 patients were enrolled and randomly assigned in a 1:1:1 ratio. The primary endpoint was PFS. The study clearly demonstrated that continuous Rd was superior with a median PFS of 25.5 months versus 20.7 months with Rd for 18 cycles and 21.2 months with MPT. Continuous Rd was also associated with a clear OS benefit.

I believe that Rd should be used continuously until disease progression if patients are able to tolerate the combination. Reviewing the data carefully, approximately 35% of patients older than 75 years on the continuous Rd arm had to discontinue treatment because of adverse events such as gastrointestinal (GI) toxicity, fatigue, neutropenia or infections. The message is that continuous Rd should be tried if possible and discontinued when necessary.

DR LOVE: Would you provide some insight into the results of the subanalysis of the "FIRST" trial investigating the effects of cytogenetics on treatment outcomes that were recently presented at the ASH 2015 meeting (Avet-Loiseau 2015; [3.1])?

DR MOREAU: In the relapsed setting, it is known that Rd is less effective for patients with poor cytogenetics. This can also be true in the up-front setting. If a patient presents with disease harboring the t(4;14) translocation, a 3-drug combination such as RVd-lite is probably a good regimen to consider, with the use of once-weekly bortezomib to limit toxicity.

3.1

Effect of Cytogenetics on Treatment Outcomes for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM) Treated with Lenalidomide/Low-Dose Dexamethasone (Rd) in the Phase III FIRST Trial

Median PFS	High risk (n = 142)	Nonhigh risk (n = 620)	All patients (n = 762)
Rd continuous	8.4 mo	31.1 mo	25.3 mo
Rd18	17.5 mo	21.2 mo	20.4 mo
MPT	14.6 mo	24.9 mo	23.3 mo
Three-year OS	n = 142	n = 620	n = 762
Rd continuous	40.7%	77.1%	70.7%
Rd18	39.6%	71.0%	64.9%
MPT	46.8%	64.8%	61.5%
ORR	n = 142	n = 620	n = 762
Rd continuous	76.7%	81.0%	80.2%
Rd18	67.3%	79.9%	77.4%
MPT	68.1%	70.9%	70.4%

PFS = progression-free survival; Rd18 = Rd for 18 cycles; MPT = melphalan/prednisone/thalidomide; OS = overall survival; ORR = overall response rate

Conclusions: These data support the use of continuous Rd as a standard treatment option for patients with NDMM who are ineligible for transplant, especially those without high-risk cytogenetics. Additional PFS and OS benefits may be achieved in patients with high-risk cytogenetics when continuous Rd is used as a backbone for combination therapy with a novel agent.

Avet-Loiseau H et al. *Proc ASH* 2015;**Abstract 730**.

Tracks 7-8

DR LOVE: What are some of the key ongoing trials evaluating oral proteasome inhibitors for patients with MM?

DR MOREAU: Two Phase III TOURMALINE trials of ixazomib in combination with lenalidomide/dexamethasone in MM are ongoing. One is for patients with relapsed/refractory MM (TOURMALINE-MM1). The other is for patients with newly diagnosed MM (NCT01850524). The latter is dedicated to patients who are not eligible for stem cell transplant.

At the ASH 2015 meeting, I will present the results of the pivotal Phase III TOURMALINE-MM1 trial (Moreau 2015; [3.2]). The study will show an improvement in PFS with ixazomib. Based on the results of this study, I believe ixazomib in combination with lenalidomide/dexamethasone will soon be FDA approved as treatment for patients with MM who have received 1 prior therapy. Because this was an international study, the triplet regimen should also be approved in Europe soon.

Oprozomib is another oral proteasome inhibitor. It's currently under investigation in Phase II trials. Ixazomib was quickly developed based on the simplicity of the dosing schedule. Although ixazomib is associated with no important toxicity, oprozomib is. Oprozomib causes significant GI toxicity, so its formulation is currently under investigation. As yet, the optimal dose of oprozomib is unknown, and a lot of work must be done for its clinical development.

Editor's note: Subsequent to this interview, on November 20, 2015 the FDA granted approval to ixazomib in combination with lenalidomide/dexamethasone as treatment for patients with MM who have received 1 prior therapy.

3.2

TOURMALINE-MM1: Efficacy and Safety Results of a Phase III Trial of Lenalidomide (R) and Dexamethasone (d) with or without Ixazomib (I) for Patients with Relapsed or Refractory Multiple Myeloma

Efficacy	**IRd** (n = 360)	**Rd** (n = 362)	Hazard ratio	*p*-value
Median progression-free survival	20.6 mo	14.7 mo	0.742	0.012
Response	**IRd**	**Rd**	Odds ratio	*p*-value
Overall response rate	78.3%	71.5%	1.44	0.035
Median duration of response	20.5 mo	15.0 mo	Not reported	Not reported
Select Grade ≥3 adverse events	**IRd**		**Rd**	
Neutropenia	19%		16%	
Thrombocytopenia	13%		5%	
Pneumonia	6%		8%	
Diarrhea	6%		2%	
Rash	4%		1%	
Renal failure	2%		3%	

Moreau P et al. *Proc ASH* 2015;**Abstract 727**.

Tracks 14-15

DR LOVE: Can you provide an overview of the monoclonal antibodies daratumumab and elotuzumab in the management of MM and where you think these agents are headed?

DR MOREAU: These monoclonal antibodies are one of the most important steps forward in the treatment of MM. In my opinion, the most fascinating agent in this class is daratumumab, an anti-CD38 monoclonal antibody. Daratumumab is not toxic, and it has single-agent activity in patients who have received 3 or more lines of prior therapy or have double-refractory MM (Lonial 2015a).

The median duration of response was approximately 8 months. I believe that the future use of daratumumab will likely be in combination with agents such as lenalidomide/dexamethasone or bortezomib/dexamethasone.

We are awaiting the results of the Phase III POLLUX trial of lenalidomide/dexamethasone with or without daratumumab in relapsed or refractory MM (NCT02076009). The trial quickly enrolled about 600 patients. The primary endpoint of the study is PFS. The secondary endpoints include OS, and we are hoping for an improvement in OS with daratumumab. I believe daratumumab will be the first monoclonal antibody to be FDA approved for MM and that it will be the most widely used one in the future.

Elotuzumab targets SLAMF7 but has no single-agent activity. In combination with lenalidomide, synergistic activity is evident. The results of the Phase III ELOQUENT-2 trial for patients with relapsed/refractory MM clearly demonstrated that lenalidomide/dexamethasone in combination with elotuzumab was superior to lenalidomide/dexamethasone alone in terms of PFS (Lonial 2015b). The results of the Phase III ELOQUENT-1 trial of lenalidomide/dexamethasone with or without elotuzumab for patients with newly diagnosed MM should also be presented soon (NCT01335399).

Editor's note: Subsequent to this interview, on November 16, 2015 the FDA granted accelerated approval to daratumumab for patients with MM who received at least 3 prior treatments, and on November 30, 2015 the FDA approved elotuzumab for use in combination with lenalidomide and dexamethasone for patients with MM following the failure of 1 to 3 prior therapies. ■

SELECT PUBLICATIONS

Benboubker L et al. **Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.** *N Engl J Med* 2014;371(10):906-17.

Lonial S et al. **Phase II study of daratumumab (DARA) monotherapy in patients with ≥ 3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius).** *Proc ASCO* 2015a;**Abstract LBA8512**.

Lonial S et al. **Elotuzumab therapy for relapsed or refractory multiple myeloma.** *N Engl J Med* 2015b;373(7):621-31.

Moreau P et al. **Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRd), significantly extends progression-free survival (PFS) for patients (pts) with relapsed and/or refractory multiple myeloma (RRMM): The phase 3 Tourmaline-MM1 study (NCT01564537).** *Proc ASH* 2015;**Abstract 727**.