INTERVIEW

Nikhil C Munshi, MD

Dr Munshi is Associate Professor of Medicine at Harvard Medical School and Associate Director at Dana-Farber Cancer Institute's Jerome Lipper Multiple Myeloma Center in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 5, 12

DR LOVE: Would you discuss the existing data on the use of carfilzomib or pomalidomide up front and any thoughts you have about ongoing trials evaluating these agents?

DR MUNSHI: Data with the combination of carfilzomib, lenalidomide and low-dose dexamethasone for newly diagnosed multiple myeloma are excellent. Patients experience rapid responses with this 3-drug combination (Jakubowiak 2012; [2.1, 2.2]). I

2.1

Phase I/II Trial of Carfilzomib in Combination with Lenalidomide and Low-Dose Dexamethasone as Front-Line Therapy for Transplant-Eligible and Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma

Parameter	≥PR	≥VGPR	≥nCR	sCR
All patients (n = 53)	98%	81%	62%	42%
Treatment duration				
≥4 cycles (n = 49)	100%	88%	67%	45%
≥8 cycles (n = 36)	100%	92%	78%	61%
≥12 cycles (n = 29)	100%	86%	72%	62%
Cytogenetics*				
Normal/favorable (n = 34)	100%	76%	59%	38%
Unfavorable (n = 17)	94%	76%	65%	53%

* Unfavorable: Del(13) by metaphase, hypodiploidy, t(4;14), t(14;16) or del(17p); normal/favorable: All others
PR = partial response; VGPR = very good PR; nCR = near complete response; sCR = stringent complete response

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

2.2

Select Adverse Events During Induction with Carfilzomib/Lenalidomide/ Low-Dose Dexamethasone in Patients with Multiple Myeloma

Adverse events (n = 53)	Any grade	Grade 3 or 4
Nonhematologic		
Hyperglycemia	72%	23%
Hypophosphatemia	45%	25%
Fatigue	38%	2%
Muscle cramping	32%	0%
Peripheral neuropathy	23%	0%
Hematologic		
Thrombocytopenia	68%	17%
Anemia	60%	21%
Neutropenia	30%	17%

Jakubowiak AJ et al. *Blood* 2012;120(9):1801-9.

would especially consider administering carfilzomib up front for a patient with significant preexisting neuropathy of an extent prohibiting bortezomib.

Pomalidomide is also a powerful and active agent, but we have fewer data with that agent in the newly diagnosed setting. We do not yet have enough data for me to say that I would administer it in the front-line setting. The fact that pomalidomide works when lenalidomide has stopped working (San Miguel 2013; [2.3]) tells us that it has different, if not better, activity compared to lenalidomide. In terms of the chemical structure, pomalidomide is like a combination of thalidomide and lenalidomide. I would predict that at some point studies will be conducted and pomalidomide will be used in the newly diagnosed setting.

DR LOVE: How do you choose between carfilzomib and pomalidomide in the relapsed or refractory setting?

DR MUNSHI: For patients with mild neuropathy carfilzomib is not much of a problem, but because it's a proteasome inhibitor I lean more toward pomalidomide in that

setting. For disease initially responsive to lenalidomide, I would administer pomalidomide if lenalidomide had been stopped without disease progression for about 6 months, although that's arbitrary. If the patient experienced relapse while receiving lenalidomide maintenance therapy, I would administer carfilzomib and save pomalidomide for the next relapse.

2.3

MM-003 Study: Pomalidomide (POM) and Low-Dose Dexamethasone (LoDEX) in Patients with Relapsed/Refractory Multiple Myeloma (MM)

Outcome	POM + LoDEX (n = 302)	HiDEX (n = 153)	HR	*p*-value
Intent-to-treat population				
Median PFS	4.0 mo	1.9 mo	0.48	<0.001
Median OS	12.7 mo	8.1 mo	0.74	0.028

	HR	
Subgroup (POM + LoDEX vs HiDEX)	**PFS**	**OS**
Lenalidomide- and bortezomib-refractory MM (n = 225, 113)	0.52	0.77
Lenalidomide as last prior treatment (n = 85, 49)	0.38	0.53
Bortezomib as last prior treatment (n = 132, 66)	0.52	0.87

HR <1.0 favors POM + LoDEX
HiDEX = high-dose dexamethasone; HR = hazard ratio; PFS = progression-free survival; OS = overall survival

San Miguel JF et al. *Proc ASCO* 2013;**Abstract 8510**.

Track 6

DR LOVE: What kind of cytogenetic findings affect your treatment approach in the up-front setting? Do you change the type of induction therapy you use?

DR MUNSHI: Up front, cytogenetics change little. RVD works in either setting. Bortezomib can overcome t(4;14), and lenalidomide has similar activity. However, consolidation and maintenance therapy may be affected.

For example, for a patient with a 17p deletion who would otherwise have a poor prognosis, and to some extent for patients with t(4;14) or t(4;16), we need more intensive treatment. They would benefit from consolidation therapy and potentially a 2-drug maintenance regimen such as lenalidomide and bortezomib for a longer period. More importantly, younger patients should be considered for possible allogeneic transplant because their outcome could be quite poor. Another complicating issue is that the 17p deletion in a few cells may not mean much. Data from France indicated that when 60% of cells contain 17p, a poor prognosis is connoted and one should consider a more aggressive intervention moving forward (Avet-Loiseau 2007). ■

SELECT PUBLICATIONS

Avet-Loiseau H et al. **Genetic abnormalities and survival in multiple myeloma: The experience of the Intergroupe Francophone du Myelome.** *Blood* 2007;109(8):3489-95.

San Miguel JF et al. **MM-003: A phase III, multicenter, randomized, open-label study of pomalidomide (POM) plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).** *Proc ASCO* 2013;**Abstract 8510**.