INTERVIEW

S Vincent Rajkumar, MD

Dr Rajkumar is Edward W and Betty Knight Scripps Professor of Medicine in the Division of Hematology and Chair of the Myeloma Amyloidosis Dysproteinemia Group at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-15

Track 1 Choosing the optimal induction regimen for a patient with multiple myeloma (MM)

Track 2 Early versus delayed autologous transplant after induction therapy for MM

Track 3 Importance of minimal residual disease assessment in MM

Track 4 Role of proteasome inhibitors as part of post-transplant maintenance therapy

Track 5 Treatment options for patients with disease that is refractory to agents typically used as maintenance therapy

Track 6 Dosing of carfilzomib for patients with MM

Track 7 **Case discussion:** A 72-year-old patient with previously treated MM who achieved a minimal response to pomalidomide/dexamethasone receives daratumumab

Track 8 Selecting from the recently FDA-approved therapeutic options for relapsed/refractory MM

Track 9 Phase III study results with daratumumab in combination with lenalidomide/dexamethasone (POLLUX) or with bortezomib/dexamethasone (CASTOR) for relapsed/refractory MM

Track 10 Daratumumab-associated infusion reactions

Track 11 Incorporation of daratumumab into the therapeutic algorithm for MM

Track 12 Use of panobinostat for relapsed/refractory MM

Track 13 **Case discussion:** A 75-year-old patient with MM initially treated with 3 years of lenalidomide/dexamethasone (Rd) who experienced disease relapse while off active therapy now receives elotuzumab/lenalidomide

Track 14 **Case discussion:** A 69-year-old patient with previously treated t(4;14) MM receives Rd with ixazomib

Track 15 Incorporation of ibrutinib into the therapeutic algorithm for Waldenström macroglobulinemia

Select Excerpts from the Interview

Tracks 1-2, 4-5

DR LOVE: What is your perspective on the optimal up-front induction treatment for patients with multiple myeloma (MM)?

DR RAJKUMAR: Physicians in the United States have access to a wide variety of regimens to treat newly diagnosed disease, but at ASH 2015 we heard a report on the Phase III SWOG-S0777 trial, which demonstrated that bortezomib/lenalidomide/dexamethasone (RVd) yielded not only better response rates and PFS but also significantly better overall survival in comparison to lenalidomide/dexamethasone (Durie 2015; [3.1]). These are the best data we have. We have all switched to RVd as standard

3.1

SWOG-S0777 Trial: Bortezomib/Lenalidomide/Dexamethasone (RVd) versus Rd for Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant

Efficacy	RVd (n = 242)	Rd (n = 232)	Hazard ratio	*p*-value
Median PFS	43 mo	30 mo	0.712	0.0018
Median overall survival	75 mo	64 mo	0.709	0.0250
Overall response rate	81.5%	71.5%	—	—
Select Grade ≥3 adverse events	**RVd**		**Rd**	
Sensory neuropathy	23%		3%	
Lymphopenia	23%		18%	
Neutropenia	19%		21%	
Thrombocytopenia	18%		14%	
Fatigue	16%		14%	
Diarrhea	8%		2%	
Hyperglycemia	7%		11%	

PFS = progression-free survival

Durie B et al. *Proc ASH* 2015;**Abstract 25**.

front-line therapy for elderly patients and patients who are eligible for autologous stem cell transplant (ASCT).

For patients with high-risk disease I believe RVd would still be a great choice, but some of us are starting to consider carfilzomib/lenalidomide/dexamethasone (KRd) instead. Bortezomib can be difficult to administer to elderly patients who have multiple comorbidities and poor performance status, in which case lenalidomide/dexamethasone alone is a reasonable alternative. If you do use lenalidomide/dexamethasone alone, however, you must administer it until disease progression.

I am reluctant to recommend KRd for standard-risk disease, with which patients traditionally fare well, because KRd has not been compared directly to RVd in a randomized trial. Such a trial is ongoing, and in nonrandomized comparisons KRd seems to yield better CR rates and minimal residual disease negativity. However, it can cause more toxicity and raises concerns about cardiac side effects. I believe that with high-risk disease, those chances are worth taking.

The other big news at ASH was from the IFM/DFCI 2009 trial, which evaluated RVd followed by either continued RVd or early transplant (Attal 2015). That trial demonstrated a 3-year postrandomization PFS rate of 61% on the early-transplant arm versus 48% on the RVd arm.

We also discovered that whether transplant is early or delayed, the outcomes are excellent. The 3-year postrandomization overall survival rate was extremely high at 88% and similar between the 2 study groups, which is outstanding in newly diagnosed MM. The survival results may be too early to interpret, but it appears that we still need to incorporate transplantation into our treatment strategy.

DR LOVE: What are your thoughts on the use of ixazomib as opposed to bortezomib? When do you consider using it in maintenance therapy?

DR RAJKUMAR: If it's difficult for a patient to receive bortezomib, I'm comfortable with administering ixazomib, with a couple of caveats. One is the huge cost. When generic bortezomib becomes available next year, it will be much less expensive than ixazomib, and it is more tried and tested than ixazomib. However, ixazomib is a once-weekly oral therapy, which is convenient. A Phase III randomized trial is comparing ixazomib to placebo as maintenance therapy, and the results should be available soon — I would rather wait. If exceptions exist, such as a patient who is truly not able to take bortezomib and the alternative is not receiving maintenance therapy at all, then yes, we should certainly consider ixazomib in that setting.

A meta-analysis at ASCO demonstrated a survival benefit with pooled data from 3 randomized trials of maintenance lenalidomide, so our group believes that we should offer routine maintenance (McCarthy 2016).

Track 9

DR LOVE: Would you discuss the results recently presented on the use of daratumumab-based therapies for relapsed/refractory MM?

DR RAJKUMAR: At the EHA meeting, Dr Dimopoulos presented the results of the POLLUX trial, which compared lenalidomide/dexamethasone to daratumumab/lenalidomide/dexamethasone. The hazard ratio for PFS was 0.37, which is the best we have seen in relapsed disease (Dimopoulos 2016; [3.2]). The other triplet therapies we have available — elotuzumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone, carfilzomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone and ixazomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone — all have hazard ratios of 0.7 to 0.75.

Daratumumab was also relatively well tolerated on this study. If I had to choose, I would probably go with daratumumab/lenalidomide/dexamethasone at first relapse. I would not use daratumumab as a single agent because that results in a PFS of only 4 months.

3.2

POLLUX: Results of a Phase III Study of Daratumumab, Lenalidomide and Dexamethasone (DRd) Compared to Rd for Relapsed or Refractory Multiple Myeloma

Efficacy	DRd (n = 286)	Rd (n = 283)	Hazard ratio	*p*-value
Median PFS	NR	18.4 mo	0.37	<0.0001
Overall response rate	93%	76%	—	<0.0001
VGPR or better	76%	44%	—	<0.0001
Complete response or better	43%	19%	—	<0.0001
Median DoR	NR	17.4 mo	—	—
Select Grade 3 or 4 adverse events	**DRd**		**Rd**	
Neutropenia	52%		37%	
Thrombocytopenia	13%		14%	
Anemia	12%		20%	

PFS = progression-free survival; NR = not reached; VGPR = very good partial response; DoR = duration of response

Dimopoulos M et al. *Proc EHA* 2016;**Abstract LB2238**.

A plenary presentation at ASCO of the CASTOR study evaluating bortezomib/dexamethasone versus daratumumab/bortezomib/dexamethasone also demonstrated an astounding hazard ratio of 0.39 (Palumbo 2016a; [3.3]). The absolute benefit was not as striking as the benefit observed in the POLLUX trial, but I believe a synergistic effect might occur with daratumumab/lenalidomide. ■

3.3

Results of the Phase III CASTOR Study of Daratumumab, Bortezomib and Dexamethasone (DVd) Compared to Vd for Relapsed or Refractory Multiple Myeloma

Efficacy	DVd (n = 251)	Vd (n = 247)	Hazard ratio	*p*-value
Median PFS	NR	7.2 mo	0.39	<0.001
Median time to progression	NR	7.3 mo	0.30	<0.001
Overall response rate	82.9%	63.2%	—	<0.001
Select Grade 3 or 4 adverse events	**DVd** (n = 243)		**Vd** (n = 237)	
Thrombocytopenia	45.3%		32.9%	
Anemia	14.4%		16.0%	
Neutropenia	12.8%		4.2%	
Pneumonia	8.2%		9.7%	
Hypertension	6.6%		0.8%	
Peripheral sensory neuropathy	4.5%		6.8%	
Fatigue	4.5%		3.4%	
Diarrhea	3.7%		1.3%	
Dyspnea	3.7%		0.8%	
Upper respiratory tract infection	1.6%		0.8%	
Asthenia	0.8%		2.1%	

PFS = progression-free survival; NR = not reached

Palumbo A et al. *N Engl J Med* 2016a;375(8):754-66.

SELECT PUBLICATIONS

Afifi S et al. **Immunotherapy: A new approach to treating multiple myeloma with daratumumab and elotuzumab.** *Ann Pharmacother* 2016;50(7):555-68.

Attal M et al. **Autologous transplantation for multiple myeloma in the era of new drugs: A phase III study of the Intergroupe Francophone du Myelome (IFM/DFCI 2009 trial).** *Proc ASH* 2015;**Abstract 391**.

Dimopoulos M et al. **An open-label, randomised Phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX.** *Proc EHA* 2016;**Abstract LB2238**.

Durie B et al. **Bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): Results of the randomized phase III trial SWOG S0777.** *Proc ASH* 2015;**Abstract 25**.

McCarthy P et al. **Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS).** *Proc ASCO* 2016;**Abstract 8001**.

Palumbo A et al. **Daratumumab, bortezomib, and dexamethasone for multiple myeloma.** *N Engl J Med* 2016a;375(8):754-66.

Palumbo A et al. **Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study.** *Proc ASCO* 2016b;**Abstract LBA4**.