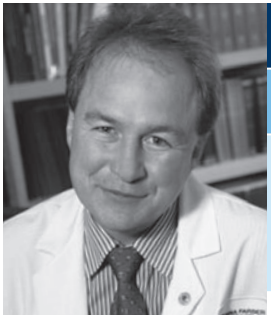

INTERVIEW

Paul G Richardson, MD

Dr Richardson is Associate Professor of Medicine at Harvard Medical School and Clinical Director of the Jerome Lipper Center for Multiple Myeloma at the Dana-Farber Cancer Institute in Boston, Massachusetts.

Tracks 1-14

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What were some of the important take-home messages from the ASH 2009 meeting related to the management of multiple myeloma?

DR RICHARDSON: Dr Mateos presented data from a large randomized trial that compared VMP to VTP as induction therapy in the older, transplant-

ineligible population, and she demonstrated equal activity but different toxicity profiles for the two regimens (Mateos 2009; [4.1]). She also showed that combined bortezomib and thalidomide maintenance therapy appeared to be superior to bortezomib maintenance with prednisone, and the take-home message is that the IMiD®/proteasome inhibitor combinations are attractive, which validates a lot of clinical and preclinical work in that context.

Another important data set presented at ASH was from the Palumbo trial, evaluating up-front melphalan/prednisone (MP) versus MP with lenalidomide (MPR) versus MPR with lenalidomide maintenance therapy.

It was no surprise that MPR with lenalidomide maintenance therapy was the winner, but it was surprising that MPR did not appear meaningfully different from MP at the 10-mg lenalidomide dose that was used, which is relatively low (Palumbo 2009). With early follow-up, the PFS differences between these two arms were superimposable.

My bet is that these results are a function of early follow-up and that with time the curves will separate, particularly because the response rates were different (4.2). Having said that, I believe the message is that lenalidomide maintenance therapy is important and should be continued.

The other message is that, frankly, we don't know whether MP is the best partner for lenalidomide. This echoes the publication of the landmark ECOG-4A03 trial, in which lenalidomide with low-dose dexamethasone was associated with better short-term overall survival and lower toxicity than lenalidomide with high-dose dexamethasone for patients with newly diagnosed myeloma (Rajkumar 2010).

4.1

Grade III/IV Adverse Events with Bortezomib/Melphalan/Prednisone (VMP) versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) versus Bortezomib/Prednisone (VP) in Elderly Patients with Untreated Multiple Myeloma

	Induction therapy		Maintenance therapy	
	VMP (n = 130)	VTP (n = 130)	VT (n = 91)	VP (n = 87)
Anemia	11%	8%	2%	2%
Neutropenia	39%	22%	3%	1%
Thrombocytopenia	27%	12%	1%	1%
Gastrointestinal toxicities	7%	2%	4%	1%
Peripheral neuropathy	5%	9%	5%	2%
Infections	7%	<1%	2%	1%
DVT/thromboembolism	<1%	2%	1%	—
Cardiologic events	—	8%	2%	1%

Mateos MV et al. *Proc ASH* 2009;**Abstract 3**.

The ECOG data clearly show that high-dose dexamethasone is the wrong partner for lenalidomide, and it's my sense, from Palumbo's presentation, that MP is not the correct partner either because myelosuppression was a problem.

I also believe these data suggest that up-front lenalidomide — but perhaps not MP — is important, if that isn't too heretical. I expect that lenalidomide will be approved on the basis of this trial.

4.2

Response Rates in a Phase III Study Evaluating Melphalan/Prednisone (MP) versus MP with Lenalidomide (MPR) versus MPR Followed by Lenalidomide Maintenance (MPR-R) for Elderly Patients with Multiple Myeloma

Best overall response[1]	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)	*p*-value (MPR-R vs MP)
Overall response rate	77%	67%	49%	<0.001
CR rate[2]	18%	13%	5%	<0.001
≥VGPR rate[3]	32%	33%	11%	<0.001
PR rate	45%	34%	37%	—

[1] As measured using EBMT criteria (Blade 1998)
[2] Immunofixation-negative with or without bone marrow confirmation
[3] VGPR: >90% reduction in M-protein

CR = complete response; VGPR = very good partial response; PR = partial response

Palumbo A et al. *Proc ASH* 2009;**Abstract 613**; Blade J et al. *Br J Haematol* 1998;102:1115-23.

Track 4

DR LOVE: Would you comment on the studies presented at ASH 2009 on maintenance therapy after transplant?

DR RICHARDSON: We participated in the CALGB-100104 trial, which randomly assigned patients to lenalidomide versus placebo maintenance therapy after single autologous stem cell transplant (ASCT). At ASH we were able to report that it was feasible from a safety perspective (McCarthy 2009), but shortly after the meeting the CALGB announced that the interim analysis was strikingly positive in favor of lenalidomide.

Also presented were preliminary data from the French randomized study (IFM 2005 02) in which patients, after ASCT, received consolidation treatment with lenalidomide followed by maintenance therapy with placebo or lenalidomide until relapse (Attal 2009).

In January 2010 the investigators announced that with a median follow-up of three years, PFS for lenalidomide maintenance therapy was 70 percent and in the control arm it was substantially lower at 35 percent. I believe this will be updated further at ASCO and presented in full form.

DR LOVE: What did you take away from the pretransplant induction therapy data presented at ASH?

DR RICHARDSON: The EVOLUTION trial showed the four-drug regimen of bortezomib, dexamethasone, cyclophosphamide and lenalidomide to be extremely active, and it validated the three-drug platform, but treatment-related mortality occurred with the four-drug combination (Kumar 2009). The pretransplant three-drug platform seems to be standard, and the use of a proteasome inhibitor before transplant also appears to be standard.

In addition, the role of the IMiDs continues to be strong both in the pretransplant setting and in the post-transplant setting as maintenance therapy. For the older population, Dr Mateos showed striking evidence that bortezomib maintenance therapy is feasible and, at least in combination with the IMiD, apparently important (Mateos 2009).

For patients who are transplant candidates, our institutional standard is a three-drug regimen, and our favorite is RVD — lenalidomide/bortezomib/dexamethasone — because we find that the neurotoxicity associated with this regimen is rarely severe. ■

SELECT PUBLICATIONS

Attal M et al. **Lenalidomide after autologous transplantation for myeloma: First analysis of a prospective, randomized study of the Intergroupe Francophone du Myelome (IFM 2005 02).** *Proc ASH* 2009;**Abstract 529**.

Dimopoulos MA et al. **VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: Cohort analysis of the Phase III VISTA study.** *J Clin Oncol* 2009;27(36):6086-93.

Kumar S et al. **Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: Encouraging results from the multi-center, randomized, Phase 2 EVOLUTION study.** *Proc ASH* 2009;**Abstract 127**.

Mateos MV et al. **Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the phase III VISTA trial.** *J Clin Oncol* 2010;28(13):2259-66.

Mateos MV et al. **A prospective, multicenter, randomized trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years.** *Proc ASH* 2009;**Abstract 3**.

McCarthy PL et al. **Phase III Intergroup study of lenalidomide (CC-5013) versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma (CALGB 100104): Initial report of patient accrual and adverse events.** *Proc ASH* 2009;**Abstract 3416**.

Palumbo A et al. **A Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma.** *Proc ASH* 2009;**Abstract 613**.

Rajkumar SV et al. **Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial.** *Lancet Oncol* 2010;11(1):29-37.