INTERVIEW

Robert Z Orlowski, MD, PhD

Dr Orlowski is Director of the Myeloma Section and Professor of Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-14

Track 1 Advances in proteasome inhibition for multiple myeloma (MM)

Track 2 Hypotheses for responsiveness to carfilzomib after bortezomib treatment

Track 3 Potential for combination proteasome inhibition in the treatment of hematologic cancer

Track 4 Carfilzomib, lenalidomide and dexamethasone (CRd) in newly diagnosed MM: Initial results of a Phase I/II study

Track 5 Benefits of subcutaneous bortezomib administration

Track 6 Bendamustine as a treatment option for relapsed MM

Track 7 Role of autologous stem cell transplant (ASCT) in the era of novel agents

Track 8 Perspective on the risk of second primary cancers with post-transplant maintenance lenalidomide in MM

Track 9 "Ascertainment bias" in detection of second primary cancers with post-transplant maintenance lenalidomide

Track 10 Consideration of resistance mechanisms to IMiDs in the debate regarding maintenance lenalidomide

Track 11 **Case discussion:** An 80-year-old woman with bone pain and pathologic fracture is diagnosed with del(13) and t(11;14) IgA lambda MM with 67% bone marrow plasma cells

Track 12 **Case discussion:** A 62-year-old man with high-risk del(13) and del(17p) IgA MM with 80% involvement of plasma cells in the bone marrow and acute renal failure receives induction CyBorD followed by ASCT and maintenance bortezomib/lenalidomide

Track 13 A proposed Intergroup study of lenalidomide, bortezomib and dexamethasone (RVD) induction followed by RVD maintenance versus RVD and elotuzumab induction followed by RVD and elotuzumab maintenance for high-risk MM

Track 14 Dose-reduced lenalidomide in patients with renal failure

Select Excerpts from the Interview

Tracks 1, 4-5

DR LOVE: Would you comment on the use of proteasome inhibition in multiple myeloma (MM)?

DR ORLOWSKI: The first proteasome inhibitor, bortezomib, was approved in 2003 for relapsed and refractory MM. Carfilzomib is a newer proteasome inhibitor, but it's different than bortezomib because, whereas bortezomib binds the proteasome and then lets go, carfilzomib is irreversible, and the degree or duration of inhibition is longer. Carfilzomib was evaluated in a Phase I trial and is undergoing Phase II testing, and it demonstrates activity in relapsed and refractory disease. It has a low risk of peripheral neuropathy (PN). Carfilzomib is administered intravenously, and studies suggest that bortezomib can be administered subcutaneously.

DR LOVE: What are your thoughts on the data presented at ASH 2010 on carfilzomib, lenalidomide and dexamethasone (CRd)?

DR ORLOWSKI: CRd is one of the best up-front therapies for newly diagnosed MM. The Phase I/II study by Dr Jakubowiak took lenalidomide/dexamethasone and added carfilzomib (Jakubowiak 2010; [2.1]). It was well tolerated and the response rates were excellent, but in Dr Richardson's data RVD has a 100% response rate (Richardson 2010). That's difficult to improve on.

DR LOVE: Another option to lower the risk of neuropathy is subcutaneous (SC) bortezomib. Any thoughts?

DR ORLOWSKI: A French trial was published of intravenous (IV) bortezomib with or without dexamethasone compared to SC bortezomib with or without

2.1

Carfilzomib/Lenalidomide/Dexamethasone (CRd) in Newly Diagnosed Multiple Myeloma

Clinical response	CRd (n = 27)
≥Partial response (PR)	96%
≥Very good PR	70%
Complete response (CR) or near CR	33%

Jakubowiak AJ et al. *Proc ASH* 2010;**Abstract 862**.

2.2

MMY-3021: A Phase III Trial of Subcutaneous (SC) versus Intravenous (IV) Administration of Bortezomib in Relapsed Multiple Myeloma

Response (n = 145, 73)	**Bortezomib SC**	**Bortezomib IV**
Overall response rate	42%	42%
Complete response	6%	8%
Nonhematologic adverse events (n = 147, 74)		
Any peripheral neuropathy (any grade)	38%	53%
Any peripheral neuropathy (Grade ≥3)	6%	16%

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

dexamethasone in relapsed MM (Moreau 2011; [2.2]). The response rates and the duration of response were similar, but SC dosing yielded a lower rate of PN. The lower rate of PN seen with SC bortezomib may be associated with the lower peak concentrations of the drug with SC dosing versus IV dosing.

Clearly, more studies with SC bortezomib are needed because so far we only have published results from one randomized trial in the relapsed setting. However, I don't know of a reason why the results would be any different in other disease settings, such as up-front therapy. Many of the trials of bortezomib that are now being planned are mandating SC dosing or at least allowing SC dosing, even those in the up-front setting.

I believe SC bortezomib is an important new standard, but until we see more data, I believe we should be a little cautious. In our practice, we are beginning to use SC bortezomib. From our experience it seems that patients are able to get in and out of their appointments more rapidly because they don't need an intravenous line put in, leading to less chair time.

Track 7

DR LOVE: What is the current role of autologous stem cell transplant (ASCT) in the era of novel agents in MM?

DR ORLOWSKI: This is a hot topic, and the IFM is leading a trial in which patients are receiving induction bortezomib/lenalidomide/dexamethasone followed by a randomization to transplant as up-front therapy or an option at relapse. It's a great study that we hope will answer the question, is up-front transplant still part of standard therapy?

In addition, at ASH 2010 data were presented from the ECOG study that compared lenalidomide with low-dose dexamethasone to lenalidomide with high-dose dexamethasone. Patients who underwent transplant as part of their initial therapy fared better (Siegel 2010).

Tracks 8-9

DR LOVE: What are your thoughts on the issue of post-transplant maintenance with lenalidomide?

DR ORLOWSKI: Two randomized studies — a trial from France and a trial from the CALGB — show a progression-free survival benefit of about 18 months with lenalidomide maintenance after transplant (2.3). However, both studies also show a small increase in second primary cancers in patients who received lenalidomide maintenance.

In the Spanish study of high-risk asymptomatic MM, in the patients who received lenalidomide/dexamethasone they found 2 secondary cancers (Mateos 2011). One was prostate cancer, and that patient in retrospect had an elevated PSA when the study started. The other was a JAK2-positive myeloproliferative

2.3

Post-Transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	Placebo (n = 307)	Lenalidomide (n = 231)	Placebo (n = 229)
Median PFS[1] or TTP[2]	41 mo	24 mo	48 mo	31 mo
	$p < 10^{-8}$		$p < 0.0001$	
	(n = 306)	(n = 302)	(n = 231)	(n = 229)
Second primary cancers				
Hematologic	11	3	8	0
Solid tumors	10	4	10	4

PFS = progression-free survival; TTP = time to progression

[1] Attal M et al. *Proc 13th International Myeloma Workshop* 2011; [2] McCarthy PL et al. *Proc 13th International Myeloma Workshop* 2011.

disorder, and before this patient received lenalidomide he had a JAK2 mutation. Some cases of MDS have been reported in addition to acute myeloid leukemia and solid tumors, so one has to be vigilant. One possible explanation is ascertainment bias, in that patients who receive placebo experience disease progression more rapidly and then come off trial. Follow-up on those patients is not as long, whereas because the other patients stay on study longer the follow-up is longer and it's easier to detect second cancers. I believe the issue of second primary cancers is less critical than has been touted, and until more data are available we haven't changed our recommendation. Ultimately we hope the additional planned studies will clarify whether a true risk exists. ■

SELECT PUBLICATIONS

Attal M et al. **Maintenance treatment with lenalidomide after transplantation for myeloma: Analysis of secondary malignancies within the IFM 2005-02 trial.** *Proc 13th International Myeloma Workshop* 2011.

Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of Phase I/II MMRC trial.** *Proc ASH* 2010;**Abstract 862**.

Mateos MV et al. **Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: A Phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (len-dex) as induction therapy followed by maintenance therapy with len alone vs no treatment.** *Proc ASH* 2011;**Abstract 991**.

McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB ECOG BMT-CTN 100104.** *Proc 13th International Myeloma Workshop* 2011.

Moreau P et al. **Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: A randomised, phase 3, non-inferiority study.** *Lancet Oncol* 2011;12(5):431-40.

Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

Siegel DS et al. **Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in the ECOG E4A03 randomized clinical trial.** *Proc ASH* 2010;**Abstract 38**.