INTERVIEW

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Tracks 1-14

Track 1 Lack of peripheral neuropathy with the newly FDA-approved irreversible proteasome inhibitor carfilzomib in multiple myeloma (MM)

Track 2 Impact of cytogenetics on approach to induction and post-transplant consolidation and maintenance therapy

Track 3 Key high-risk cytogenetic abnormalities: t(4;14) and 17p deletion

Track 4 Influence of depth of response on post-transplant consolidation and maintenance therapy

Track 5 Incorporating carfilzomib into induction treatment for newly diagnosed MM

Track 6 Mechanism of action of proteasome inhibitors

Track 7 Potential future roles for the orally bioavailable proteasome inhibitor MLN9708 and the immunomodulatory drug pomalidomide under development in MM

Track 8 Cereblon: A direct protein target for immunomodulatory and antiproliferative actions of lenalidomide and pomalidomide

Track 9 Perspectives on the MRC Myeloma IX study of zoledronic acid in patients with MM with or without bone disease and duration of bisphosphonate therapy

Track 10 Responses and tolerability with the novel monoclonal antibodies elotuzumab and daratumumab in MM

Track 11 **Case discussion:** A 55-year-old woman with symptomatic, hyperdiploid ISS Stage I MM attains a partial response to Rd, and the referring physician wishes to switch to a bortezomib-containing regimen prior to ASCT

Track 12 Up-front treatment for transplant-ineligible patients with MM and those with adverse cytogenetics

Track 13 **Case discussion:** A 68-year-old man who received treatment for MM in 2003 presents with lytic bone lesions in the humerus and femur and switches from RVD therapy to RD after 2 cycles due to neuropathy

Track 14 **Case discussion:** A 62-year-old man with symptomatic ISS Stage III MM with a 17p deletion

Select Excerpts from the Interview

Tracks 1, 5

DR LOVE: Would you comment on the newly FDA-approved agent carfilzomib in multiple myeloma?

DR BERGSAGEL: Carfilzomib is a novel irreversible proteasome inhibitor that seems to have activity similar to bortezomib, but it's hard to know if it's better. It's active in some patients with relapsed or bortezomib-refractory disease, although the response rate is lower in that setting (Vij 2012a, 2012b). The side-effect profile of carfilzomib is also different. Neuropathy, which is a big concern for a lot of patients receiving bortezomib, is not significant with this agent.

Although preliminary, data with the combination of lenalidomide, dexamethasone and carfilzomib are exciting, showing exceptionally high and deep response rates in the up-front setting (Jakubowiak 2012; [2.1, 2.2]). However, more data are needed to make these results conclusive. We participated in the Phase I/II trial of carfilzomib, and since its approval, I've administered it.

DR LOVE: In your practice, can you discern less neuropathy than with bortezomib, or is this discernible more from the trial data?

DR BERGSAGEL: With the use of weekly or subcutaneous bortezomib neuropathy seems to be less of a problem than it used to be. Patients from other practices who are receiving twice-a-week intravenous bortezomib are being referred to me and I see that they're having problems with neuropathy. However, the issue of neuropathy in myeloma is diminishing. I haven't observed problems with neuropathy in patients

2.1

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

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: Del13 by metaphase, hypodiploidy, t(4;14), t(14;16) or del17p; normal/favorable: All others

PR = partial response; VGPR = very good PR; nCR = near complete response; sCR = stringent complete response

Conclusions: The CRd regimen was well tolerated and highly active as front-line therapy for patients with newly diagnosed MM. These results will require validation in the randomized controlled setting to definitively demonstrate the benefit of adding carfilzomib to Rd. A Phase III trial of CRd compared to Rd for the treatment of relapsed MM (ASPIRE) is ongoing.

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

2.2

Select Adverse Events During CRd Induction 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.

receiving carfilzomib in my practice. So it's not just the trial data. It's also reflected in my own experience.

DR LOVE: Based on what is known about carfilzomib from the clinical trials, would you consider recommending it off protocol in the up-front setting?

DR BERGSAGEL: I would eagerly participate in a trial of carfilzomib but would not use it off protocol in the up-front setting yet. I would like to see more data about its safety profile in more patients. If I had a patient who already had neuropathy and I wanted to use a proteasome inhibitor, only then would I consider administering carfilzomib up front because I would have a clear reason in that situation.

Track 10

DR LOVE: A lot of exciting developments have occurred in a number of cancers with monoclonal antibodies but not much until recently in myeloma. What is known about elotuzumab and daratumumab?

DR BERGSAGEL: Elotuzumab is an antibody to cell surface glycoprotein CS1. It didn't show significant single-agent activity in a Phase I clinical trial (Zonder 2012), but it appears promising when examined in combination with lenalidomide and dexamethasone in the relapsed setting (Lonial 2012). I believe elotuzumab is one of the most exciting antibodies under investigation in multiple myeloma.

Daratumumab is an anti-CD38 monoclonal antibody that seems to have single-agent activity. The results were recently presented at ASCO, and the dose-limiting toxicity is yet to be reached (Plesner 2012). At the higher doses of the antibody, the investigators observed partial and minor responses in the relapsed or refractory setting. So I would say that daratumumab is even more exciting because it seems to have single-agent activity. ■

SELECT PUBLICATIONS

Jagannath S et al. **An open-label single-arm pilot phase II study (PX-171-003-A0) of low-dose, single-agent carfilzomib in patients with relapsed and refractory multiple myeloma.** *Clin Lymphoma Myeloma Leuk* 2012;12(5):310-8.

Jakubowiak AJ et al. **A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.** *Blood* 2012;120(9):1801-9.

Lonial S et al. **Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma.** *J Clin Oncol* 2012;30(16):1953-9.

Plesner T et al. **Daratumumab, a CD38 mab, for the treatment of relapsed/refractory multiple myeloma patients: Preliminary efficacy data from a multicenter phase I/II study.** *Proc ASCO* 2012;**Abstract 8019**.

Richardson PG et al. **Management of treatment-emergent peripheral neuropathy in multiple myeloma.** *Leukemia* 2012;26(4):595-608.

Siegel DS et al. **A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma.** *Blood* 2012;120(4):2817-25.

Vij R et al. **An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma.** *Blood* 2012a;119(24):5661-70.

Vij R et al. **An open-label, single-arm, phase 2 study of single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma who have been previously treated with bortezomib.** *Br J Haematol* 2012b;158(6):739-48.

Zonder JA et al. **A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma.** *Blood* 2012;120(3):552-9.