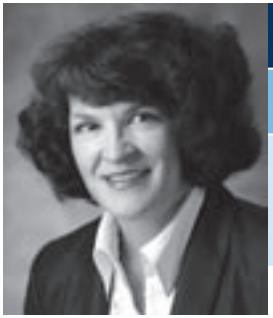

INTERVIEW

Carol Ann Huff, MD

Dr Huff is Director of the Myeloma Program and Associate Professor of Oncology and Medicine at Johns Hopkins University in Baltimore, Maryland.

Tracks 1-18

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the recent study by Mateos and colleagues on lenalidomide in high-risk smoldering multiple myeloma (MM)?

DR HUFF: The question under evaluation in this study was, is it possible to change the natural history of smoldering myeloma? Until now we have not been able to consider that with any agents because of their side-effect profiles. However, with the immunomodulatory agents and, in particular, lenalidomide — which is well tolerated by most patients — we can begin to address this question.

Mateos and colleagues reported a decreased risk of progression to symptomatic disease in the patients who received lenalidomide versus those who did not (Mateos 2010).

This isn't completely unexpected because patients are receiving treatment, so their disease markers are changing. We do not yet have long-term data or know if we've affected overall survival. A currently ongoing study is randomly assigning patients with smoldering myeloma who meet high-risk criteria to single-agent treatment with lenalidomide or observation.

DR LOVE: Outside of a clinical trial, if a patient with smoldering myeloma requested treatment with lenalidomide, would you administer it?

DR HUFF: No. Even with this decreased risk of progression we still do not know how it would affect long-term overall survival. I would encourage interested patients to participate in the clinical trial.

Track 7

DR LOVE: Would you comment on the ASH 2010 presentation, which has now been published in *Lancet Oncology*, on subcutaneous administration of bortezomib in relapsed MM?

DR HUFF: A Phase III trial was presented on subcutaneous versus intravenous bortezomib on the same standard schedule of twice weekly. Investigators reported a significantly lower incidence of neurotoxicity from subcutaneous versus intravenous bortezomib, and it seemed to be associated with lower peak levels of the drug, with equal efficacy (Moreau 2011; [4.1]). Subcutaneous administration of bortezomib is appealing, and I hope it will move forward, perhaps even administered on a once-weekly basis.

In general, with bortezomib I use once-weekly IV dosing for patients with underlying neuropathy due to their disease, diabetes or a comorbid illness. In the absence of that, I initiate treatment at the full dose and administer it twice weekly. If warranted, the first dose reduction is typically to once-weekly administration versus changing the dose and maintaining it on a twice-weekly basis.

It's a more patient-friendly schedule in terms of traveling to the office once a week versus twice a week, and it works nicely in ameliorating the severity of the neuropathy. I have used it enough that clinically it syncs up with what I've read in the literature.

4.1

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

	Bortezomib SC (n = 145)	Bortezomib IV (n = 73)
Overall response rate[1]	42%	42%
Complete response	6%	8%
Partial response	36%	34%
≥Very good partial response	17%	16%

[1] Relative risk of overall response rate is 0.99 with 95% confidence interval of 0.71-1.37

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

Track 9

DR LOVE: What are your thoughts on the third-generation IMiD pomalidomide?

DR HUFF: Pomalidomide is highly active in patients for whom lenalidomide is not. In the data from Lacy and colleagues, more than 40 percent of patients with disease progression on lenalidomide responded to pomalidomide (Lacy 2011; [4.2]), similar to how patients who experience disease progression while receiving thalidomide respond to lenalidomide. We don't have data on the converse — if the patients whose disease didn't respond to pomalidomide will respond to the other agents — but this agent is active and promising.

The toxicity seems to be predominantly hematologic but it does not appear to cause neuropathy and the other toxicities we've observed with thalidomide and, to some degree, lenalidomide. So if pomalidomide were available, I would consider it.

4.2

Pomalidomide in Myeloma Refractory to Bortezomib and Lenalidomide

	Pomalidomide 2 mg (n = 35)	Pomalidomide 4 mg (n = 35)
Objective response rate	49%	43%
Confirmed response (≥partial response)	26%	28%
Time to response (median)	1 month	1.7 months
Survival rate at six months	78%	67%

≥Minimal response rate for patients from both subgroups considered to be at high risk (N = 62) was 33%.

Lacy MQ et al. *Blood* 2011;[Epub ahead of print].

Track 10

DR LOVE: What do we know about the second-generation proteasome inhibitor carfilzomib?

DR HUFF: Carfilzomib has a slightly different mechanism of action and is administered a little differently than bortezomib. Carfilzomib is administered two days in a row intravenously. It's an hour-long infusion, and it seems to have a slightly different side-effect profile with perhaps less neuropathy, more asthenia and more fatigue. I believe it's an active agent that will likely become available for patients with myeloma, but I'm not convinced it will replace bortezomib.

DR LOVE: What are your thoughts on the presentation from ASH 2010 on carfilzomib/lenalidomide/dexamethasone (CRd) for patients with newly diagnosed MM?

DR HUFF: Andrzej Jakubowiak presented data on CRd at ASH showing high response rates and complete response rates (Jakubowiak 2010; [4.3]). It's a tantalizing combination. All of the new triple regimens are demonstrating such high response rates that it will be difficult to compare one to the other. Unfortunately, we have no head-to-head comparisons in terms of survival differences, and they would be difficult to conduct because many patients proceed to transplant or maintenance therapy. ■

4.3

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

Clinical response	CRd (n = 19)
≥Partial response (PR)	100%
≥Very good PR	63%
Complete response (CR) or near CR	37%

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

SELECT PUBLICATIONS

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**.

Lacy MQ et al. **Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease.** *Blood* 2011;[Epub ahead of print].

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* 2010;**Abstract 1935**.

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.