INTERVIEW

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Track 12 Carfilzomib-associated cardiopulmonary adverse events and use of carfilzomib in patients with a history of heart disease

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Track 14 Activity of daratumumab alone or in combination regimens for relapsed/refractory MM

Track 15 **Case discussion:** A 44-year-old man with high-risk, ISS Stage III MM receives triplet induction therapy followed by autologous stem cell transplant (ASCT) and RVD maintenance and remains in CR 3 years later

Select Excerpts from the Interview

Tracks 1, 12

DR LOVE: Would you discuss the results of the Phase III ASPIRE trial evaluating the addition of carfilzomib to lenalidomide/dexamethasone for relapsed multiple myeloma (MM) that were presented at ASH 2014 and subsequently published in *The New England Journal of Medicine*?

DR KAUFMAN: ASPIRE was a randomized trial for patients with relapsed MM who had received 1 to 3 prior lines of therapy. Response rates and deep responses were much higher with the addition of carfilzomib and ultimately translated into a significant improvement in progression-free survival (Stewart 2015; [2.1]). We observed the

2.1

ASPIRE: Interim Results of a Phase III Trial of Carfilzomib/Lenalidomide/ Dexamethasone (CRd) versus Rd for Relapsed Multiple Myeloma

Efficacy	CRd (n = 396)	Rd (n = 396)	Hazard ratio	*p*-value
Median progression-free survival	26.3 mo	17.6 mo	0.69	0.0001
Median overall survival	Not estimable	Not estimable		
2-year overall survival rates	73.3%	65.0%	0.79	0.04
Overall response rate	87.1%	66.7%	—	<0.001
Complete response or better	31.8%	9.3%	—	<0.001
Very good partial response or better	69.9%	40.4%	—	<0.001
Clinical benefit rate	90.9%	76.3%	—	<0.001
	CRd (n = 392)		Rd (n = 389)	
Select adverse events	All grades	Grade ≥3	All grades	Grade ≥3
Dyspnea	19.4%	2.8%	14.9%	1.8%
Hypertension	14.3%	4.3%	6.9%	1.8%
Acute renal failure	8.4%	3.3%	7.2%	3.1%
Cardiac failure	6.4%	3.8%	4.1%	1.8%
Ischemic heart disease	5.9%	3.3%	4.6%	2.1%

Stewart AK et al; ASPIRE Investigators. *N Engl J Med* 2015;372(2):142-52.

beginning of what appeared to be an improvement in overall survival. Because it's not a final analysis, they're not calling it statistically significant yet.

We've known for a long time in the up-front setting that combination therapy is the way to go, but this is the first confirmation that the same approach is also preferable in the relapsed setting.

DR LOVE: What are your thoughts on the issue of carfilzomib and patients experiencing dyspnea? How much of this do you think has to do with hydration?

DR KAUFMAN: It is rare, but I'd say that the cardiac toxicity rate is somewhere on the order of 3% to 5% in the several hundred patients to whom I've administered carfilzomib. Most of the time, if a patient has a decrease in their ejection fraction you can stop the drug and the patient will recover with time. On the ASPIRE study, we saw a 2% to 5% increase in cardiac toxicity such as heart failure and ischemic events in the carfilzomib/lenalidomide/dexamethasone arm compared to the lenalidomide/dexamethasone arm (2.1).

I don't believe fluid is the entire answer. In large part, we've minimized fluid administration for patients who are not at risk for tumor lysis. A real dyspnea signal is observed, and I believe it's drug related. When patients do experience dyspnea it usually lasts a day or two, but that's not heart failure.

DR LOVE: How would you think through using carfilzomib in a patient with heart disease or heart failure? And do you perform cardiac screening in patients about to receive carfilzomib?

DR KAUFMAN: If a patient had a history of heart disease and had coronary disease but received appropriate treatment, it would not deter me from treating, but if someone came in and had an ejection fraction of 40% and symptomatic heart failure, I probably would avoid carfilzomib in that situation. Conversely, we do not monitor ejection

fraction in younger patients. When we've run into problems with issues like heart failure, it's almost uniformly been in the older patient population.

Track 5

DR LOVE: Would you review the data that led to the recent FDA approval of panobinostat in relapsed or refractory MM?

DR KAUFMAN: It's important to first review the Phase II study. It provided proof of principle that we can overcome bortezomib resistance. In this relatively small study for patients with relapsed and bortezomib-refractory myeloma who received bortezomib/dexamethasone and panobinostat, a 35% response rate was reported (Richardson 2013).

The Phase III trial was not conducted in the bortezomib-refractory setting, however. Patients were relatively early in the course of therapy — 1 to 3 prior lines — and they may or may not have been exposed to bortezomib and IMiDs previously. We reported a numerical but not statistical improvement in overall response rate, a statistical improvement in deep responses and an improvement in progression-free survival from 8 months on the bortezomib/dexamethasone arm compared to approximately 12 months with the combination of bortezomib/dexamethasone and panobinostat (San-Miguel 2014; [2.2]). No significant increase in overall survival was observed at the time of analysis.

One of the challenges with all pan-deacetylase inhibitors is toxicity. The biggest issues I have encountered with these agents are diarrhea, nausea, fatigue and thrombocytopenia (2.3). Typically, thrombocytopenia does not cause us to stop treatment. We use dose delays or reductions. A 25% incidence of Grade 3 or 4 diarrhea was observed in the Phase III trial. If we recognize it early and it's managed aggressively, we can prevent patients coming off study. The biggest problem that I've observed that causes patients to come off study is fatigue or asthenia. It can be quite debilitating. We don't have tools to overcome that as we do for diarrhea.

2.2

PANORAMA 1: Efficacy Results of a Phase III Trial of Panobinostat with Bortezomib/Dexamethasone (VD) versus Placebo/VD in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma

Overall analysis	Panobinostat + VD (n = 387)	Placebo + VD (n = 381)	Hazard ratio	*p*-value
Median progression-free survival (PFS)	11.99 mo	8.08 mo	0.63	<0.0001
Median overall survival*	33.64 mo	30.39 mo	0.87	0.26
Overall response rate	60.7%	54.6%	—	0.09
CR/nCR	27.6%	15.7%	—	0.00006
PFS subgroup analysis (hazard ratio <1.0 favors panobinostat + VD)			Hazard ratio	
Prior exposure to bortezomib (n = 336)			0.58	
Prior exposure to immunomodulatory drugs (IMiDs) (n = 485)			0.54	
Prior exposure to bortezomib and IMiDs (n = 198)			0.53	

* Data not yet mature

CR/nCR = complete response/near complete response

San-Miguel JF et al. *Lancet Oncol* 2014;15(11):1195-206.

2.3

PANORAMA 1: Select Adverse Events with Panobinostat and Bortezomib/Dexamethasone (VD) versus Placebo/VD

	Panobinostat + VD (n = 381)		**Placebo + VD** (n = 377)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	68%	25%	42%	8%
Peripheral neuropathy	61%	18%	67%	15%
Asthenia or fatigue	57%	24%	41%	13%
Nausea	36%	6%	21%	<1%
Thrombocytopenia	98%	68%	84%	31%

San-Miguel JF et al. *Lancet Oncol* 2014;15(11):1195-206.

Consequently, when ODAC reviewed these Phase III data, they were concerned about the risk-benefit ratio. The FDA then evaluated the patient subpopulations with a specific focus on those patients who'd been exposed to both IMiDs and bortezomib. In this group of patients a much stronger risk-benefit ratio was observed (2.2), and that's ultimately where the approval was granted. I believe that's appropriate.

Track 8

DR LOVE: Would you review some of the research you've been involved with evaluating the oral proteasome inhibitor ixazomib in MM?

DR KAUFMAN: We previously reported that ixazomib is effective in combination with dexamethasone for patients with relapsed disease. We've also studied this agent in combination with lenalidomide/dexamethasone for patients with newly diagnosed MM and demonstrated a response rate of more than 90% (Kumar 2014b). What was interesting about this study was that after up to a year's worth of induction therapy, we administered maintenance ixazomib and showed that we could increase response depth in 48% of patients (Kumar 2014a).

Common toxicities associated with ixazomib are rash, nausea and diarrhea. We observe less peripheral neuropathy than with bortezomib, and, importantly, even if peripheral neuropathy occurs, it's rarely the typical painful sort we observe with bortezomib and few patients have to discontinue ixazomib because of it. ■

SELECT PUBLICATIONS

Kumar S et al. **Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients (pts) with previously untreated multiple myeloma (MM): Phase 2 study results.** *Proc ASH* 2014a;**Abstract 82**.

Kumar SK et al. **Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: An open-label phase 1/2 study.** *Lancet Oncol* 2014b;15(13):1503-12.

Richardson PG et al. **PANORAMA 2: Panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma.** *Blood* 2013;122(14):2331-7.

Stewart AK et al. **Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.** *N Engl J Med* 2015;372(2):142-52.