INTERVIEW

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Track 2 Activity of the novel anti-CD38 antibody daratumumab in RR MM

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Track 13 Clinical experience with the third-generation IMiD pomalidomide in RR MM

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on the use of elotuzumab in the treatment of multiple myeloma (MM)?

DR STEWART: Elotuzumab is not that active as a single agent, but when used in combination with lenalidomide it has dramatically better results. ELOQUENT-2 was a study that compared the combination of elotuzumab with lenalidomide/dexamethasone to lenalidomide/dexamethasone in patients with MM who had received 1 to 3 prior therapies. The results showed an improvement in PFS of approximately 5 months on the elotuzumab arm (Lonial 2015a; [2.1]).

These results should lead to the approval of elotuzumab in combination with lenalidomide in the relapsed setting. A trial in patients with newly diagnosed disease and data in combination with bortezomib are expected soon. Once these data become available, one would expect to see elotuzumab used more broadly and in an earlier setting.

2.1

ELOQUENT-2: Results of a Phase III Study of Lenalidomide/ Dexamethasone (Len/Dex) with or without Elotuzumab (Elo) for Patients with Relapsed or Refractory Multiple Myeloma

Efficacy	Elo + len/dex (n = 321)	Len/dex (n = 325)	Hazard ratio	*p*-value
Median PFS	19.4 months	14.9 months	0.7	<0.001
ORR	79%	66%	NR	<0.001
	Elo + len/dex (n = 318)		Len/dex (n = 317)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Lymphocytopenia	99%	77%	98%	49%
Neutropenia	82%	34%	89%	44%
Fatigue	47%	8%	39%	8%
Infections	81%	28%	74%	24%

PFS = progression-free survival; ORR = overall response rate; NR = not reported

Lonial S et al. *N Engl J Med* 2015a;373(7):621-31; Lonial S et al. *Proc ASCO* 2015;**Abstract 8508**.

DR LOVE: What is known about the anti-CD38 monoclonal antibody daratumumab?

DR STEWART: The Phase II SIRIUS trial of daratumumab monotherapy in patients with refractory MM that was presented at ASCO 2015 reported that it had single-agent activity in approximately 30% of patients (Lonial 2015b; [2.2]). In combination with other agents, it's likely to be at least additive, if not synergistic. The results reported at ASCO will hopefully lead to approval of this agent in refractory MM. This drug is also being investigated in the Phase III setting, both in relapsed and newly diagnosed disease.

2.2

SIRIUS: Results of a Phase II Study of Daratumumab Monotherapy for Patients with 3 or More Lines of Prior Therapy or Double-Refractory Multiple Myeloma

Efficacy	Daratumumab (n = 106)	
Overall response rate	29%	
Median progression-free survival	3.7 months	
Select adverse events	**All grades**	**Grade 3 or 4**
Fatigue	40%	3%
Anemia	33%	24%
Thrombocytopenia	26%	25%
Neutropenia	23%	14%

Lonial S et al. *Proc ASCO* 2015b;**Abstract LBA8512**.

Tracks 3-8

DR LOVE: Would you discuss the results of the Phase III ASPIRE and ENDEAVOR trials evaluating carfilzomib in relapsed MM?

DR STEWART: ASPIRE was a large Phase III trial that evaluated the addition of carfilzomib to lenalidomide/dexamethasone (CRd). The PFS was 26.3 months on the carfilzomib arm — the best PFS that's been reported in this patient population — versus 17.6 months with lenalidomide/dexamethasone alone, which was impressive. The complete response rate was 3 times as high with the addition of carfilzomib (Stewart 2015; [2.3]). The overall survival trended in favor of the 3-drug regimen. But most astonishing to me was that the global quality of life was improved with the 3-drug regimen. It speaks to the power of deep responses and the well-being of knowing that the disease is well controlled.

The Phase III ENDEAVOR trial evaluated carfilzomib versus bortezomib in combination with dexamethasone in patients with relapsed MM. This was a real-life trial with most patients having received prior bortezomib therapy. The dose of carfilzomib was 56 mg/m^2, which is double the FDA-approved dose. It was surprising how positive the data were in favor of the carfilzomib arm in terms of response rate, depth of response and particularly the improvement in PFS (Dimopoulos 2015; [2.4]).

Patients have to come in 6 days a month when receiving carfilzomib. We also see a tradeoff in terms of toxicity. With carfilzomib less neuropathy occurs compared to with bortezomib, but more adverse effects in the cardiovascular and renal systems occur with carfilzomib.

Both of these studies cement the role of carfilzomib at first or second relapse and should result in more widespread approval of carfilzomib. These trials should also encourage the use of carfilzomib in an earlier setting and suggest that treatment should continue for an extended period of time. In my practice, I usually combine carfilzomib with cyclophosphamide or pomalidomide in the relapsed setting.

DR LOVE: Do you believe there is cardiac toxicity associated with carfilzomib?

DR STEWART: A small percent of patients receiving carfilzomib may experience a syndrome that resembles heart failure with fluid retention, shortness of breath and edema.

2.3

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

Efficacy	CRd (n = 396)	Rd (n = 396)	Hazard ratio	*p*-value
Median PFS	26.3 mo	17.6 mo	0.69	0.0001
ORR	87.1%	66.7%	—	<0.001
CR or better	31.8%	9.3%	—	<0.001
VGPR or better	69.9%	40.4%	—	<0.001
	CRd (n = 392)		Rd (n = 389)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
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%

PFS = progression-free survival; ORR = overall response rate; CR = complete response; VGPR = very good partial response

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

2.4

ENDEAVOR: Results of a Phase III Study Evaluating Carfilzomib/Dexamethasone (Cd) versus Bortezomib/Dexamethasone (Vd) in Relapsed Multiple Myeloma

Efficacy	Cd (n = 464)	Vd (n = 465)	Hazard ratio	*p*-value
Median PFS	18.7 mo	9.4 mo	0.53	<0.0001
ORR	77%	63%	—	<0.0001
CR or better	13%	6%	—	<0.0001
VGPR or better	54%	29%	—	<0.0001
	Cd (n = 463)		Vd (n = 456)	
Select adverse events	All grades	Grade ≥3	All grades	Grade ≥3
Dyspnea	29%	5%	13%	2.2%
Hypertension	25%	9%	9%	3%
Peripheral neuropathy	9%	1.3%	27%	5%
Acute renal failure	8%	4%	5%	3%
Cardiac failure	8%	5%	6%	1.8%

PFS = progression-free survival; ORR = overall response rate; CR = complete response; VGPR = very good partial response

Dimopoulos MA et al. *Proc ASCO* 2015;**Abstract 8509**.

In the ASPIRE trial, in which the approved dose of carfilzomib was used, the toxicity profile was favorable with the 3-drug combination. The ENDEAVOR trial demonstrated a small increase in cardiac and renal events. But in both of the Phase III trials, no effect on death or discontinuation of drug was evident.

The treating physician must be aware of the potential for hypertension and dyspnea, especially in the first couple weeks of treatment. It can be managed with dose reductions, regulating fluid administration and diuretics. Carfilzomib should preferably be avoided in patients with a history of heart failure or renal failure.

DR LOVE: What is known about carfilzomib in the front-line setting?

DR STEWART: A trial investigating the 4-drug combination of carfilzomib, cyclophosphamide, thalidomide and dexamethasone in patients with newly diagnosed MM demonstrated good efficacy. At ASCO 2015, an update was presented on the use of CRd in patients with newly diagnosed MM, and the results were impressive. The response rate was 100% if patients remained on the combination. When CRd is combined with transplant, complete response rates are in the 60% to 80% range, which is remarkable (Zimmerman 2015). Because CRd is well tolerated, patients can be kept on therapy for a longer time, resulting in deep responses and longer survival.

Tracks 9, 11

DR LOVE: Would you discuss the potential future role of the oral proteasome inhibitors ixazomib and oprozomib in MM?

DR STEWART: Ixazomib is in Phase III testing in combination with lenalidomide/dexamethasone for patients with newly diagnosed and relapsed MM and in the maintenance setting. Recent data with ixazomib have demonstrated high response rates with about 20% complete remissions. Ixazomib is well tolerated overall. Side effects include

rash, neuropathy, thrombocytopenia and gastrointestinal (GI) toxicity, but they are manageable. Carfilzomib and bortezomib delivered systemically are slightly more potent in the short term. But ixazomib may catch up with time because it can be conveniently administered for longer periods.

Oprozomib is also an active agent and is being investigated in Phase II studies. It is associated with upper GI toxicity that can be difficult to tolerate, particularly long term. The new formulation and routine administration of antiemetics have helped. Oprozomib may find its place, but I believe it won't have the impact that ixazomib will.

Track 12

DR LOVE: What are your thoughts on panobinostat, which was recently approved for MM?

DR STEWART: The Phase III PANORAMA 1 trial comparing panobinostat with bortezomib/dexamethasone to bortezomib/dexamethasone in patients with relapsed or refractory MM showed a significantly improved PFS from 8 months to 12 months. Panobinostat was ultimately approved in combination with bortezomib and dexamethasone for patients with MM who have received prior bortezomib and an immunomodulatory agent (San-Miguel 2014).

The concern has been the high frequency of adverse events, which include thrombocytopenia, fatigue and diarrhea that can sometimes be severe. At ASCO 2015, a study showed panobinostat in combination with carfilzomib was much better tolerated than the bortezomib combination previously reported (Berdeja 2015). In my practice I would reserve panobinostat for younger patients with relapsed MM who are at high risk.

Track 13

DR LOVE: Pomalidomide has been approved for more than 2 years now. How do you integrate it into your practice?

DR STEWART: Pomalidomide is a potent drug that can be combined with almost any other agent. Neutropenia is a bit more common than it is with the other 2 agents in this class. One still has to be concerned about deep venous thrombosis as well.

Many oncologists tend to use pomalidomide as an agent of last resort, but it should be considered as an option earlier in the treatment algorithm. My own bias is to use it either alone or in combination with carfilzomib early on in the treatment course, even at first relapse or for patients who cannot tolerate lenalidomide. It's well tolerated in the majority of patients. ■

SELECT PUBLICATIONS

Berdeja J et al. **A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM).** *Proc ASCO* 2015;**Abstract 8513**.

San-Miguel JF et al. **Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: A multicentre, randomised, double-blind phase 3 trial.** *Lancet Oncol* 2014;15(11):1195-206.

Zimmerman TM et al. **Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM).** *Proc ASCO* 2015;**Abstract 8510**.