INTERVIEW

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DR LOVE: Certainly 2015 was an exciting year in myeloma with 4 new drugs approved by the FDA. The histone deacetylase inhibitor panobinostat was approved in February, and in November we saw approvals of the oral proteasome inhibitor ixazomib in addition to the 2 monoclonal antibodies elotuzumab and daratumumab.

I'd like to get your thoughts on all these recently approved agents. Let's start with panobinostat, which was approved in combination with bortezomib and dexamethasone on the basis of the PANORAMA-1 trial for the treatment of multiple myeloma (MM) after at least 2 other therapies, including bortezomib and an IMiD (San-Miguel 2014; [3.1]). How do you integrate panobinostat into your practice?

DR FONSECA: Panobinostat is arguably the first true bench-to-bedside discovery in MM. Although the Phase III PANORAMA-1 trial produced positive results, toxicity issues have prevented the widespread use of panobinostat (3.1). In particular it is associated with diarrhea and thrombocytopenia. But I still find panobinostat exciting because when it is administered at a different dose or in combination with carfilzomib or

3.1

PANORAMA-1: A Phase III Trial of Panobinostat and Bortezomib/Dexamethasone (PVd) versus Placebo and Bortezomib/Dexamethasone (PlacVd) for Relapsed or Relapsed and Refractory Multiple Myeloma

Outcome	PVd (n = 387)	PlacVd (n = 381)	Hazard ratio	*p*-value
Median PFS	11.99 mo	8.31 mo	0.63	<0.0001
Overall response rate	60.7%	54.6%	—	0.09
	PVd (n = 381)		PlacVd (n = 377)	
Select adverse events	Any	Grade ≥3	Any	Grade ≥3
Thrombocytopenia	98%	68%	84%	31%
Lymphopenia	83%	54%	74%	40%
Diarrhea	68%	25%	42%	8%
Peripheral neuropathy	61%	18%	67%	15%
Asthenia/fatigue	57%	24%	41%	13%

PFS = progression-free survival; overall survival data are not yet mature

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

IMiDs, early data show promising results with less toxicity (Berdeja 2015). This raises the question of whether panobinostat might be used in a better way.

It has not gained much traction in the relapsed or even up-front settings, simply because we have so many other treatment options. I hope and expect that in the near future, as clinical trials continue to generate results, panobinostat will acquire a greater role as a therapeutic option. However, I doubt that it will be the prime contender for use at first or second relapse.

DR LOVE: On the basis of the results of the TOURMALINE-MM1 trial, the FDA also recently approved ixazomib in combination with lenalidomide and dexamethasone for the treatment of MM after disease progression on at least 1 prior therapy (Moreau 2016; [3.2]). What are your thoughts on the utility of ixazomib in clinical practice?

DR FONSECA: In many ways you can think of ixazomib as an oral bortezomib. It has demonstrated proteasome inhibitor activity, and therefore it increases the depth of response and has the ability to control the disease.

So whenever you're considering bortezomib you could be considering ixazomib. Currently it is approved only for relapsed/refractory MM, but it will continue to move forward. I can envision that this might become part of front-line therapy, and several clinical trials are testing its efficacy in that setting. However, every agent comes with its pros and cons, and we are still learning about the best ways to administer ixazomib and manage its toxicities, especially gastrointestinal toxicity. It will take us 1 or 2 years to become more familiar with this agent.

DR LOVE: Next let's talk about the 2 recently approved monoclonal antibodies. Elotuzumab was approved in combination with lenalidomide and dexamethasone for patients with MM who have received 1 to 3 prior therapies. This approval was based on the results of the Phase III ELOQUENT-2 trial (Lonial 2015; [3.3]). How do you envision this agent being used in practice?

3.2

TOURMALINE-MM1: A Phase III Trial of Oral Ixazomib, Lenalidomide and Dexamethasone (IRd) versus Placebo, Lenalidomide and Dexamethasone (PRd) for Relapsed/Refractory Multiple Myeloma

Outcome	IRd (n = 360)	PRd (n = 362)	Hazard ratio	*p*-value
Median progression-free survival	20.6 mo	14.7 mo	0.74	0.01
Overall response rate	78.3%	71.5%	—	0.04
	IRd (n = 361)		PRd (n = 359)	
Select adverse events	Any	Grade ≥3	Any	Grade ≥3
Thrombocytopenia	31%	19%	16%	9%
Rash	36%	5%	23%	2%
Diarrhea	45%	6%	39%	3%
Constipation	35%	<1%	26%	<1%
Vomiting	23%	1%	12%	<1%
Peripheral neuropathy	27%	2%	22%	2%

Moreau P et al. *N Engl J Med* 2016;374(17):1621-34.

3.3

ELOQUENT-2: A Phase III Trial of Elotuzumab and Lenalidomide/Dexamethasone (ERd) versus Lenalidomide/ Dexamethasone (Rd) Alone for Relapsed/Refractory Multiple Myeloma

Outcome	ERd (n = 321)	Rd (n = 325)	*p*-value	
Median progression-free survival	19.4 mo	14.9 mo	<0.001; hazard ratio 0.7	
Overall response rate	79%	66%	<0.001; odds ratio 1.9	
	ERd (n = 318)		Rd (n = 317)	
Select adverse events	Any	Grade ≥3	Any	Grade ≥3
Lymphocytopenia	99%	77%	98%	49%
Thrombocytopenia	84%	19%	78%	20%
Neutropenia	82%	34%	89%	44%
Fatigue	47%	8%	39%	8%
Second primary cancer	7%	N/A	4%	N/A

N/A = not applicable

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

DR FONSECA: It is possible to administer elotuzumab to a patient who experiences a biochemical relapse while receiving lenalidomide maintenance therapy after up-front lenalidomide/bortezomib/dexamethasone. However, I believe better options exist in that situation.

I am excited about the idea of clinical trials using elotuzumab up front in the nontransplant setting for patients who are eligible to receive lenalidomide/dexamethasone — for example, an elderly patient with hyperdiploid-variant MM and multiple trisomies without high-risk factors. This constitutes a large portion of the myeloma population, and I believe this is the niche in which elotuzumab will be most used. Importantly,

elotuzumab is one of the safest options in terms of infusional toxicity, and in general monoclonal antibodies are well tolerated.

DR LOVE: Last but not least, the Phase I/II GEN501 study and the Phase II SIRIUS trial led to FDA approval of single-agent daratumumab for MM in patients who have received at least 3 other therapies (3.4). What is your clinical experience with daratumumab?

DR FONSECA: I typically use daratumumab as monotherapy, although several of my colleagues have used it in combination with pomalidomide and dexamethasone. I have administered it mostly in the setting of extensive prior therapy. We have the occasional patient with advanced disease for whom it is difficult to achieve much response. On the other hand, we've been gratified by some patients whose aggressive disease has been well controlled with daratumumab.

Daratumumab can require prolonged infusion, and we schedule our patients to start early in the morning. Infusion reactions occur in about 50% of patients, in which case we stop therapy, treat the reaction and then restart the infusion at 50% of the rate when the reaction has subsided. Most patients are able to get through the first dose. If the infusion can be continued, instead of admitting the patient we finish the day with whatever we are able to administer and then go on to day 2. In my experience the first infusion has been completed in every case. Subsequently the infusions are shorter, in the area of 4 hours. ■

3.4

Efficacy and Safety Results with Daratumumab Monotherapy (16 mg/kg) from the GEN501 Phase I/II Trial and the SIRIUS MMY2002 Phase II Trial for Patients with Heavily Pretreated Relapsed/Refractory Multiple Myeloma

Outcome	GEN501[1] (n = 42)	SIRIUS[2] (n = 106)	Combined[3] (n = 148)
Overall response rate	36%	29.2%	31.1%
Median PFS	5.6 mo	3.7 mo	4.0 mo
Median OS	NR	Not reached	20.1 mo
One-year OS	77%	64.8%	NR
Select adverse events (all grades)	n = 42	n = 106	n = 148
Infusion-related reactions	71%	42%	48%
Fatigue	40%	40%	41.9%
Anemia	NR	33%	28.4%
Back pain	NR	22%	27%
Thrombocytopenia	NR	25%	21.6%
Neutropenia	12%	23%	20.9%

PFS = progression-free survival; OS = overall survival; NR = not reported

[1] Lokhorst HM et al. *N Engl J Med* 2015;373(13):1207-19; [2] Lonial S et al. *Lancet* 2016;387(10027):1551-60; [3] Usmani SZ et al. *Blood* 2016;[Epub ahead of print].

SELECT PUBLICATIONS

Berdeja JG et al. **Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma.** *Haematologica* 2015;100(5):670-6.

Lonial S et al. **Elotuzumab therapy for relapsed or refractory multiple myeloma.** *N Engl J Med* 2015;373(7):621-31.