INTERVIEW

Gareth John Morgan, PhD, FRCPath

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Tracks 1-14

Select Excerpts from the Interview

Tracks 3, 5, 13

DR LOVE: What is your approach to up-front therapy for younger transplant-eligible patients with multiple myeloma?

DR MORGAN: Triplet combinations with an alkylating agent, steroids and an IMiD or a proteasome inhibitor are the current standard. One can choose a combination that will work best for a particular patient. I am in favor of administering triplet rather than doublet therapy to maximize the response. I believe that as more tolerable proteasome inhibitors are developed, the next generation of studies will evaluate quadruplet therapies with an IMiD, a proteasome inhibitor, an alkylating agent and a steroid for these patients.

DR LOVE: How do you care for older patients who are not candidates for a transplant?

DR MORGAN: In older patients, high-dose combination chemotherapy can be toxic. So we must be careful with this population and consider treatment options depending on whether they are frail or more robust.

We administer the cyclophosphamide, lenalidomide and dexamethasone regimen we've developed. I believe that this treatment will be widely adopted because it's well tolerated and elicits good responses. For the frail patient, I believe lenalidomide with low-dose dexamethasone is a good approach.

Track 4

DR LOVE: What is your approach to post-transplant maintenance?

DR MORGAN: I am impressed by post-transplant maintenance data with IMiDs and proteasome inhibitors. Three studies with lenalidomide maintenance have shown impressive results (Attal 2012; McCarthy 2012; Palumbo 2012) with a 1.5- to 2-year improvement in progression-free survival and an overall survival benefit in the CALGB-100104 study. I believe that lenalidomide maintenance is becoming the standard therapy for the future.

The HOVON-65 study compared a thalidomide-based approach to a bortezomib-based approach as maintenance for patients with newly diagnosed multiple myeloma. The bortezomib-based regimen was superior to the thalidomide approach (Sonneveld 2012; [2.1]). This suggests a signal for ongoing bortezomib therapy long term.

2.1

Results of the HOVON-65/GMMG-HD4 Trial: Bortezomib Induction and Maintenance Therapy for Patients with Newly Diagnosed Multiple Myeloma

Progression-free survival (PFS)	PAD → bortezomib	VAD → thalidomide	Hazard ratio	*p*-value
Median PFS (ITT population)	35 mo	28 mo	0.75	0.002
Patients with increased creatinine (>2 mg/dL)	30 mo	13 mo	0.45	0.004
Patients with del(17p13)	22 mo	12 mo	0.47	0.01

PAD = bortezomib/doxorubicin/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; ITT = intention to treat

Sonneveld P et al. *J Clin Oncol* 2012;30(24):2946-55.

Tracks 6-10

DR LOVE: Any comments on carfilzomib? How do you use it currently in your practice?

DR MORGAN: Carfilzomib is an epoxyketone-based proteasome inhibitor, whereas bortezomib is a boronic acid-based inhibitor. Carfilzomib irreversibly inhibits the proteasome, resulting in sustained activity, whereas bortezomib is a reversible inhibitor.

Phase I studies reported that carfilzomib elicited good response rates, was well tolerated and lacked neurotoxicity. The Phase II trial that led to the approval of this agent for patients with relapsed/refractory multiple myeloma demonstrated good responses

2.2

PX-171-003-A1: Results of a Phase II Study of Single-Agent Carfilzomib for Patients with Relapsed/Refractory Multiple Myeloma

Responses	All patients (n = 257)	Patients with unfavorable cytogenetics (n = 71)
Overall response rate	23.7%	29.6%
Complete response	0.4%	0%
Very good partial response	5.1%	4.2%
Partial response	18.3%	25.4%
Clinical benefit rate	37.0%	33.8%
Median progression-free survival	3.7 months	3.6 months
Median duration of response	7.8 months	6.9 months
Select adverse events (n = 266)	**All grades**	**Grade 3 or 4**
Anemia	46%	24%
Thrombocytopenia	39%	29%
Lymphopenia	23%	20%
Fatigue	49%	7.5%
Dyspnea	34%	3.4%
Peripheral neuropathy	12.4%	1.1%

Siegel DS et al. *Blood* 2012;120(14):2817-25.

(Siegel 2012; [2.2]) with carfilzomib, and currently it is being used for that subset of patients. I believe, however, that the triplet of carfilzomib, dexamethasone and lenalidomide or cyclophosphamide would be more effective. Hence, that is what I administer for patients with relapsed/refractory disease.

I have only used carfilzomib up front in clinical trials. The combination of carfilzomib, lenalidomide and dexamethasone could be effective, but we're awaiting the results of the randomized clinical trials. Currently, I believe it would be premature to use carfilzomib in the up-front setting.

DR LOVE: What has been reported in terms of tolerability of carfilzomib?

DR MORGAN: Although carfilzomib is a more potent proteasome inhibitor, it doesn't cause significant neuropathy (2.2). A cardiac signal has been reported and, though we should watch for that, it is not significant enough to restrict the use of the drug in the up-front or relapsed setting. Overall I believe carfilzomib is safer and has better activity than bortezomib.

I have not observed dyspnea in patients to whom I've administered carfilzomib. We should watch for dyspnea and be careful to not overhydrate patients. If a patient develops dyspnea, one must consider the possibility of fluid overload.

DR LOVE: Would you discuss what is known about the recently approved agent pomalidomide in multiple myeloma?

DR MORGAN: When lenalidomide and pomalidomide were first being developed, pomalidomide was the more active compound in vivo but lenalidomide was taken forward first. But now we have this more active agent that is effective when lenalido-

mide fails. Good data exist with pomalidomide in the relapsed/refractory setting, and its use carries a progression-free and overall survival benefit.

The entry criteria for that study were tight, and I believe in the real world they will be relaxed a little. But pomalidomide is still to be used for patients for whom a proteasome inhibitor has failed, lenalidomide has failed and no other obvious choice is available. And I believe it will find a good home there and it will be active (San Miguel 2013; [2.3]).

DR LOVE: Would you discuss the sequencing of carfilzomib and pomalidomide and which one you prefer to use to start therapy?

DR MORGAN: We do not yet have data from clinical trials to address this question. For a patient whose disease relapses quickly after an IMiD-containing regimen, I would suggest switching to an agent with a different mode of action and vice versa.

With carfilzomib, the number and timing of infusions make it difficult for older people or those who travel. So for patients who live far away from the hospital or are frail, I would opt for pomalidomide first. ■

2.3

MM-003: Final Efficacy Analysis of a Phase III Trial of Pomalidomide (Pom) in Combination with Low-Dose Dexamethasone (d) versus High-Dose Dexamethasone (D) for Relapsed/Refractory Multiple Myeloma

Efficacy	Pom + d (n = 302)	D (n = 153)	Hazard ratio	*p*-value
Median PFS	4.0 mo	1.9 mo	0.48	<0.0001
Median OS	12.7 mo	8.1 mo	0.74	0.0285
Overall response rate	31%	10%	—	<0.0001
Select adverse events (Grade 3 or 4)	**Pom + d** (n = 300)		**D** (n = 150)	
Neutropenia	48%		16%	
Anemia	33%		37%	
Thrombocytopenia	22%		26%	
Pneumonia	13%		8%	
Bone pain	7%		5%	
Fatigue	5%		6%	

PFS = progression-free survival; OS = overall survival

San Miguel J et al. *Lancet Oncol* 2013;14(11):1055-66.

SELECT PUBLICATIONS

Attal M et al. **Lenalidomide maintenance after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366(19):1782-91.

McCarthy PL et al. **Lenalidomide after stem-cell transplantation for multiple myeloma.** *N Engl J Med* 2012;366(19):1770-81.

Palumbo A et al. **Continuous lenalidomide treatment for newly diagnosed multiple myeloma.** *N Engl J Med* 2012;366(19):1759-69.

San Miguel J et al. **Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial.** *Lancet Oncol* 2013;14(11):1055-66.