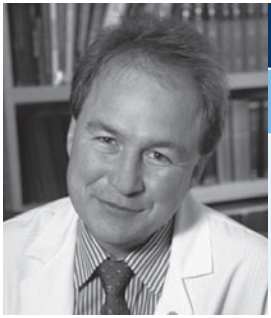

INTERVIEW

Paul G Richardson, MD

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Tracks 1-22

Track 1 Updated survival analysis from the VISTA trial of VMP versus MP for patients with untreated multiple myeloma (MM) — Further evidence for use of triplet therapy as initial systemic therapy

Track 2 Immediate versus delayed autologous transplantation after immunomodulatory agent-based induction therapy in patients with newly diagnosed MM

Track 3 Improved survival and response with bortezomib-containing induction regimens versus nonbortezomib-containing induction regimens in transplant-eligible patients with MM

Track 4 A Phase III trial evaluating conventional-dose therapy with lenalidomide, bortezomib and dexamethasone (RVD) versus high-dose treatment with stem cell transplant in MM

Track 5 Duration of lenalidomide maintenance therapy in MM

Track 6 Use of lenalidomide maintenance and potential incorporation of subcutaneous bortezomib into this approach for patients with MM and abnormal cytogenetics

Track 7 Perspective on the risk of second primary cancers with post-transplant maintenance lenalidomide in MM

Track 8 Subcutaneous versus weekly intravenous administration of bortezomib in MM

Track 9 Use of an attenuated RVD regimen in older patients with MM

Track 10 Management of myeloma-associated renal dysfunction in the era of novel therapies

Track 11 Attenuated neurotoxicity with the second-generation proteasome inhibitors carfilzomib and marizomib

Track 12 Care of patients with newly diagnosed MM and acute renal failure

Track 13 Final results from a Phase I/II study of carfilzomib, lenalidomide and low-dose dexamethasone (CRd) as first-line therapy in MM

Track 14 Carfilzomib-associated toxicities

Track 15 Development of carfilzomib as an orally administered agent

Track 16 Toward incorporating carfilzomib into the treatment algorithm for MM

Track 17 Initial Phase I/II study results with the novel proteasome inhibitor MLN9708 as a single agent in relapsed/refractory MM and in combination with lenalidomide and dexamethasone in previously untreated MM

Track 18 Mechanism of action and activity of elotuzumab, a humanized monoclonal immunoglobulin G1 antibody targeting CS1

Track 19 MRC Myeloma IX study: Zoledronic acid in patients with MM with or without bone disease

Track 20 **Case discussion:** An 88-year-old woman has IgA lambda monoclonal gammopathy and ISS Stage III MM with 80% involvement of plasma cells in the bone marrow and widespread diffuse bony lesions

Track 21 Clinical use of bortezomib/dexamethasone in elderly patients with high-risk MM and bone disease

Track 22 Salvage therapy with an attenuated RVD regimen after disease progression in elderly patients with MM

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: What are your thoughts on using a 3-drug combination as initial systemic therapy for multiple myeloma (MM) rather than opting for a 2-drug regimen and keeping the third agent in reserve?

DR RICHARDSON: That may be one of the most fundamentally important questions in MM treatment today. The VISTA trial demonstrates that holding additional agents in reserve may be the wrong approach in symptomatic MM. In the 5-year follow-up presented at ASH 2011, the authors reported a highly significant 13.3-month increase in median overall survival with the 3-drug regimen of bortezomib/melphalan/prednisone (VMP) compared to MP even though the trial allowed for substantial crossover with salvage treatments such as bortezomib and IMiDs for patients receiving MP (San

1.1

Phase III VISTA Trial: 5-Year Overall Survival Analyses of Patients with Previously Untreated Multiple Myeloma

Patient population	VMP	MP	Hazard ratio	*p*-value
Intent to treat (n = 344, 338)	56.4 mo	43.1 mo	0.69	0.0004
Patients (pts) receiving subsequent therapy (n = 215, 246)	55.7 mo	46.4 mo	0.75	0.016
Pts receiving VMP vs pts receiving first-line MP + pts receiving MP and salvage bortezomib (n = 344, 237)	56.4 mo	45.4 mo	0.71	0.0029

V = bortezomib; M = melphalan; P = prednisone

San Miguel JF et al. *Proc ASH* 2011;**Abstract 476**.

1.2

Meta-Analysis of Phase III Trials of Bortezomib-Containing Induction Regimens (BCIR) versus Nonbortezomib-Containing Induction Regimens (NBCIR) for Transplant-Eligible Patients with Multiple Myeloma

	BCIR versus NBCIR	
Response rate (n = 4)*	Pooled odds ratio	*p*-value
Postinduction Overall response rate	2.619	<0.000
Post-ASCT Overall response rate	1.907	<0.000
Response rate (n = 4)*	Pooled hazard ratio	*p*-value
Three-year progression-free survival	0.723	0.000
Three-year overall survival	0.789	0.016

ASCT = autologous stem cell transplant
* Number of Phase III randomized, controlled trials analyzed
$p \leq 0.000$ or $p = 0.016$ indicates that bortezomib-based induction regimens result in improved efficacy and demonstrates the superiority of BCIR over NBCIR.

Nooka AK et al. *Proc ASH* 2011;**Abstract 3994**.

Miguel 2011; [1.1]). The response rates were robust and the clinical benefit derived from the salvage strategies appeared to be durable, which is unprecedented. These data inform community clinicians that administering the best drug combinations up front carries "no penalty" to clinical benefit later. The best combinations can be used up front to generate optimal response by intensifying consolidation and maintenance treatments and then salvage therapies later.

Another interesting data set at ASH 2011 from a meta-analysis of randomized trials reported that bortezomib-based therapy in transplant-eligible patients is associated with a response rate advantage. In addition, bortezomib as a part of pretransplant therapy was associated with improved overall survival (Nooka 2011; [1.2]).

Tracks 13-15

DR LOVE: Would you discuss results recently reported with carfilzomib, lenalidomide and low-dose dexamethasone (CRd) as first-line therapy in MM?

DR RICHARDSON: This study provides validation of the concept that combining a proteasome inhibitor and an immunomodulator provides synergy. The authors reported an overall response rate of 94% and a dramatic reduction in neurotoxicity with an emergent rate of peripheral neuropathy of 24% (Jakubowiak 2011; [1.3]). A higher signal for neuropathy was previously reported with RVD. That's why I believe these results are such an important step forward, because the rate of neurotoxicity reported with CRd is dramatically reduced but at the same time the regimen has similar response outcomes compared to RVD.

Significant rates of hyperglycemia and shortness of breath associated with infusions, which were ascribed to fluid hydration required for the CRd combination, were reported. Even though carfilzomib treatment has the potential for renal impact, this can be managed by hydration together with the use of dexamethasone. Essentially, the CRd regimen was well tolerated, but we have to be aware of the potential side effects.

I am excited about the evolution of the CRd regimen, particularly if and when oral carfilzomib becomes available. This will circumvent the inconvenience associated with

1.3

Responses in a Front-Line Phase I/II Study of Carfilzomib, Lenalidomide and Low-Dose Dexamethasone for Patients with Multiple Myeloma

Parameter	ORR	CR/nCR	≥VGPR
No. of treatment cycles			
1+ (n = 49)	94%	53%	65%
4+ (n = 35)	100%	71%	89%
8+ (n = 28)	100%	75%	89%
12+ (n = 19)	100%	79%	100%
CFZ dose (mg/m^2)			
20 (n = 4)	100%	75%	100%
27 (n = 13)	100%	85%	100%
36 (n = 32)	91%	38%	47%

ORR = overall response rate; CR = complete response; nCR = near CR; VGPR = very good partial response; CFZ = carfilzomib

Jakubowiak AJ et al. *Proc ASH* 2011;**Abstract 631**.

intravenous administration. Although oral carfilzomib is not quite ready for prime time, it is under evaluation in clinical trials (NCT01129349).

Track 17

DR LOVE: Would you discuss what is currently known about the oral proteasome inhibitor MLN9708?

DR RICHARDSON: Oral MLN9708 is a boronate peptide that has undergone Phase I/II testing as a single agent (NCT00963820) and in combination with lenalidomide/dexamethasone. In the up-front setting, the lenalidomide/dexamethasone/MLN9708 combination produced a response rate of 100% in evaluable patients with MM (Berdeja 2011; [1.4]). Except for the occurrence of manageable Grade 2 or lower skin rashes, it was well tolerated. As a single agent in the relapsed setting, we have observed clear responses even after bortezomib failure.

MLN9708 has qualitative differences from bortezomib, making it attractive. Unlike bortezomib, it does not appear to induce neurotoxic effects. Presently, 4 proteasome inhibitors have the potential to be therapeutic choices in the future: bortezomib, carfilzomib, MLN9708 and marizomib. ■

1.4

Efficacy and Safety of Oral MLN9708 in Combination with Lenalidomide and Dexamethasone for Patients with Previously Untreated Multiple Myeloma

Preliminary response*	Patients (n = 15)
≥Partial response through 4 cycles	100%
Complete response	27%
Very good partial response	33%
Partial response	40%
Select adverse events (AEs)	
Any AE/drug-related AEs	15/13
Grade ≥3 AEs/drug-related Grade ≥3 AEs	11/9
Peripheral neuropathy (PN)	
Grade 1 drug-related PN	3
Grade >1 PN	0

* IMWG uniform criteria and minimal response and near-complete response
AEs were transient and manageable with standard supportive care or dose reduction/discontinuation.

Berdeja JG et al. *Proc ASH* 2011;**Abstract 479**.

SELECT PUBLICATIONS

Jakubowiak AJ et al. **Final results of a frontline phase 1/2 study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in multiple myeloma (MM).** *Proc ASH* 2011;**Abstract 631**.

Nooka AJ et al. **The improved efficacy of bortezomib containing induction regimens (BCIR) versus non-bortezomib containing induction regimens (NBCIR) in transplant-eligible patients with multiple myeloma (MM): Meta-analysis of phase III randomized controlled trials (RCTs).** *Proc ASH* 2011;**Abstract 3994**.

San Miguel JF et al. **Continued overall survival benefit after 5 years' follow-up with bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in patients with previously untreated multiple myeloma, and no increased risk of second primary malignancies: Final results of the phase 3 VISTA trial.** *Proc ASH* 2011;**Abstract 476**.