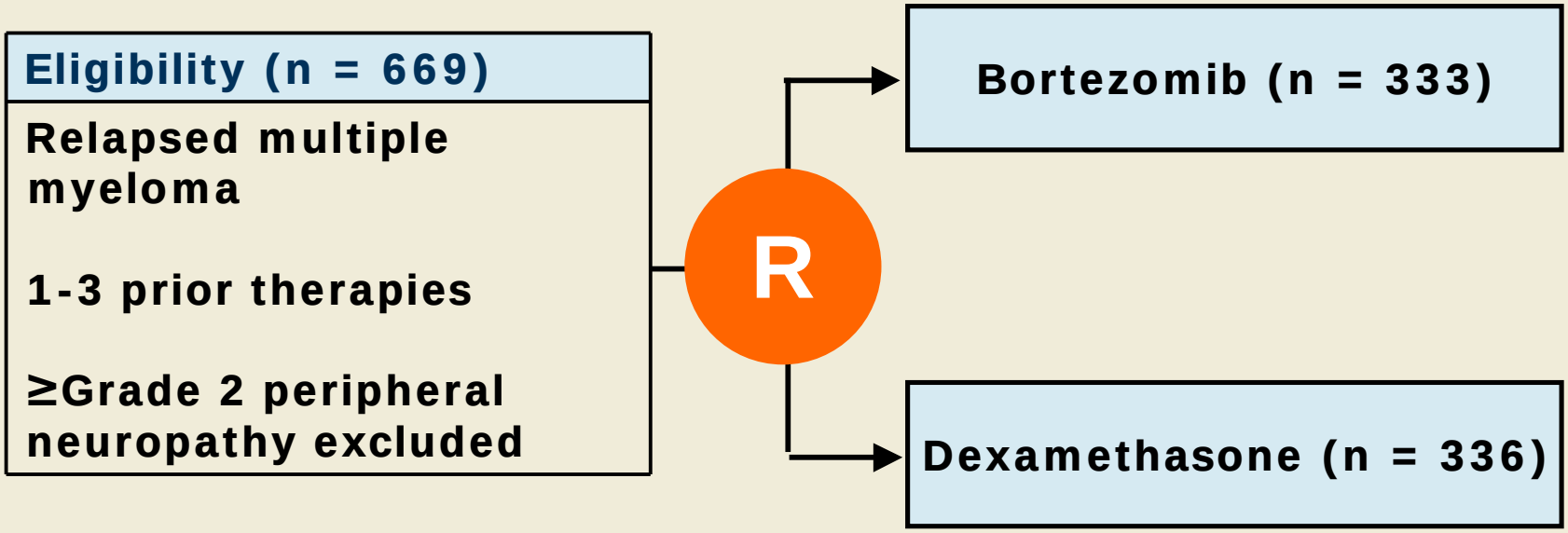
Reversibility of Symptomatic Peripheral Neuropathy with Bortezomib in the Phase III APEX Trial in Relapsed Multiple Myeloma: Impact of a Dose-Modification Guideline

Richardson PG et al.

BR J Haematol 2009;144(6):895-903.

APEX Trial Comparing Bortezomib with Dexamethasone



Bortezomib 1.3 mg/m^2 on d1, 4, 8 and 11 for eight 21-d cycles, and then on d1, 8, 15 and 22 for three 35-d maintenance cycles

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903;
Richardson PG et al. *N Engl J Med* 2005;353(24):2487-98.

Dose-Modification Guideline in APEX Trial for Bortezomib-Associated Neuropathy

- Grade 1 without pain
  - No action
- Grade 1 with pain or Grade 2
  - Reduce bortezomib dosage to 1.0 mg/m^2
- Grade 2 with pain or Grade 3
  - Withhold bortezomib until toxicity resolves, then reinitiate at a dose of 0.7 mg/m^2 once weekly
- Grade 4
  - Discontinue bortezomib

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Neuropathy in APEX Trial

	All patients with ≥G 2 neuropathy (n = 91)	≥G 2 neuropathy; dose modification (n = 72)	≥G 2 neuropathy; no dose modification (n = 19)
Improvement/resolution of neuropathy	58 (64%)	49 (68%)	9 (47%)
No improvement/resolution of neuropathy	33 (36%)	23 (32%)	10 (53%)

Mostly sensory neuropathy (98%) observed; incidence and severity was independent of age, prior thalidomide or vincristine therapy, and diabetes history.

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Dose-Modification Guidelines and Reversibility of Neuropathy

- 91/331 (27%) patients developed ≥G2 neuropathy.
  - 72/91 had dose modifications per guidelines.
  - 19/91 had no dose modifications (protocol violations).
- 49/72 (68%) patients who had dose modifications experienced improvement or resolution of their neuropathy.
- 9/19 (47%) patients who did not have dose modifications experienced resolution of their neuropathy.

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Effect of Dose Modification for Neuropathy on Outcome

Evaluable patients	RR (CR + PR)	CR	Median TTP (mo)	Median OS (mo)
All (N = 315)	43%	9%	6.2	29.7
No neuropathy (n = 196)	38%	6%	5.6	23.2
G ≥ 2 neuropathy (n = 86)	50%	14%	6.3	Not estimable
Dose modified (n = 68)	59%	16%	6.9	Not estimable
No dose modification (n = 18)	17%	6%	2.9	14.9

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Summary and Conclusions

- Bortezomib-associated neuropathy is predominantly sensory and is reversible in the majority of patients.
- Bortezomib-associated neuropathy is unaffected by age, prior therapies with neurotoxic agents or history of diabetes and thus may be mechanistically distinct.
- Bortezomib dose modification may ameliorate bortezomib-associated neuropathy.
- Bortezomib dose modification for peripheral neuropathy does not appear to adversely affect efficacy or outcome.

Richardson PG et al. *Br J Haematol* 2009;144(6):895-903.

Faculty Comments

DR RICHARDSON: We showed that bortezomib-associated neuropathy is largely reversible with the use of a dose-modification guideline.

Another important part of the analysis is that dose modification did not adversely affect outcome. In addition, the neuropathy was unaffected by age, prior therapies with neurotoxic agents or history of diabetes, so bortezomib-associated neuropathy could be mechanistically distinct from other etiologies.

DR JAGANNATH: It is important to note the bortezomib is reasonably well tolerated. While 27 percent of patients may develop ≥ Grade II neuropathy, only 9 percent had Grade III events.

In addition, compliance with dose-modification guidelines leads to a greater reversibility of neuropathy without adversely affecting the outcome.

Influence of Cytogenetics in Patients with Relapsed or Refractory Multiple Myeloma Treated with Lenalidomide Plus Dexamethasone: Adverse Effect of Deletion 17p13

Reece D et al.
Blood 2009;114(3):522-5.

Introduction

- Poor prognosis exists for patients with multiple myeloma (MM) carrying t(4;14) or del(17p13) (*Blood* 2007;109:3489).
- Negative prognostic impact of t(4;14) is overcome with bortezomib (*N Engl J Med* 2008;359:906).
- Limited data exist on the role of lenalidomide in patients with “high-risk” cytogenetic abnormalities.
- **Current study objective**:
  - Determine effects of del(13q), t(4;14) and del(17p13) in patients treated with lenalidomide (R) and dexamethasone (D) for relapsed or refractory MM.

Reece D et al. *Blood* 2009;114(3):522-5.

Methods

- Post hoc subanalysis was performed on 130 patients from three Canadian centers in the Expanded Access Program database (MM-016 study), with available FISH studies for del(13q), t(4;14) and del(17p13).
  - Median follow-up at 19.7 months
  - Primary outcome: Time to progression (TTP)
  - Secondary outcome: Overall survival (OS)
- Matched pair analysis was performed for the subgroup of patients with t(4;14) to address the inherent imbalance in clinical characteristics and short period of follow-up.

Reece D et al. *Blood* 2009;114(3):522-5.

Effect of Cytogenetics on Treatment Efficacy

	All patients (n = 130)	del(13q) (n = 54)	del(17p13) (n = 12)	t(4;14) (n = 28)
Response (>minimal)	83.1%	77.8% (p = 0.007)	58.3% (p < 0.001)	78.5% (p = 0.06)
Median TTP (mo)	7.1	5.9 (HR = 1.42; p = 0.09)	2.22 (HR = 2.82; p < 0.001)	8.0 (HR = 1.44; p = 0.137)
Median OS (mo)	22.7	14.7 (HR = 1.43; p = 0.152)	4.67 (HR = 3.23; p < 0.001)	23.7 (HR = 1.04; p = 0.910)

Hazard ratio (HR) and p*-values for abnormality versus none (matched)*

Reece D et al. *Blood* 2009;114(3):522-5.

Discussion

- The combination of lenalidomide and dexamethasone is an effective therapy for relapsed/refractory MM.
  - Patients with either del(13q) or t(4;14) experienced median TTP and OS comparable to those without the corresponding cytogenetic abnormality.
- Patients with del(17p13), however, had significantly worse outcomes (TTP = 2.2 mo; OS = 4.67 mo).
- Lenalidomide appears to be ineffective in patients with del(17p13), and novel therapeutic approaches are needed for this subgroup.

Reece D et al. *Blood* 2009;114(3):522-5.

Faculty Comments

DR GIRALT: This subanalysis of patients participating in the lenalidomide expanded access program shows the influence of cytogenetics on outcome. TTP was 7.1 months for the whole group, but patients with the 17p deletion had a poor prognosis with a TTP of only two months and a median survival of 4.6 months.

Although patients with del(17p) may respond to lenalidomide induction, their overall outcome remains extremely poor, and further investigational strategies are needed for these patients.

Faculty Comments (Continued)

Younger patients with these cytogenetic abnormalities could be considered for more aggressive therapies, such as allogeneic transplant.

Another important result of the study is that patients who had the 4;14 translocation had relatively good outcomes with lenalidomide-based therapy, with a median TTP of approximately eight months.

Safety and Efficacy of Single-Agent Lenalidomide in Patients with Relapsed and Refractory Multiple Myeloma

Richardson P et al.
Blood 2009;114(4):772-8.

Introduction

- Lenalidomide has demonstrated clinical benefit in the treatment of relapsed or refractory multiple myeloma (MM) as monotherapy and in combination with dexamethasone (*Blood* 2002;100:3063; *Blood* 2006;108:3458).
- Significant adverse events resulted from the addition of dexamethasone to lenalidomide, including:
  - Deep vein thrombosis, infections and hyperglycemia
- **Current study objective**:
  - Efficacy and safety of single-agent lenalidomide, 30 mg once daily, as therapy for relapsed and refractory MM
  - Primary endpoint: At least partial response

Richardson P et al. *Blood* 2009;114(4):772-8.

Phase II Study of Lenalidomide as Treatment for Relapsed and Refractory MM

Protocol ID: NCT00065351

Eligibility (n = 222)
Relapsed or refractory MM
Disease progression during or within 60 days of salvage regimen
≥2 prior treatment regimens, not including SCT

→ **Lenalidomide, 30 mg once daily, d1-21 q 28 days until progression or unacceptable toxicity**

Richardson P et al. *Blood* 2009;114(4):772-8.

Clinical Response (Intent to Treat)

	≤2 Prior Treatment Regimens (n = 73)	≥3 Prior Treatment Regimens (n = 149)
CR + PR	26%	26%
Complete response (CR)	1%	3%
Partial response (PR)	25%	23%
Minimal response (MR)	19%	17%
Stable disease	48%	48%
Progressive disease	1%	5%

Richardson P et al. *Blood* 2009;114(4):772-8.

Efficacy (Intent to Treat)

	Overall (n = 222)	CR + PR (n = 58)	CR + PR + MR (n = 98)
Median PFS (mo)	4.9*	14.5	10.4
Median TTP (mo)	5.2†	14.5	10.4
Median OS (mo)	23.2‡	33.9	28.0
1-year survival rate	67%	73%	79%

** 73% of patients had disease progression or died.*
† 69% of patients had disease progression.
‡ 60% of patients died.

Richardson P et al. *Blood* 2009;114(4):772-8.

Discussion

- Lenalidomide monotherapy at 30 mg/day is an active therapy with long-term benefit in patients with relapsed and refractory MM.
- Similar response was obtained in patients who received prior thalidomide, bortezomib or after prior stem cell transplant, respectively.
  - ORR = 41%, 46% and 39%, respectively (data not shown)
- Toxicity was acceptable. Common Grade 3/4 adverse events were neutropenia (60%), febrile neutropenia (4%), thrombocytopenia (39%) and anemia (20%).
- These data support the treatment option of single-agent lenalidomide.

Richardson P et al. *Blood* 2009;114(4):772-8.

Faculty Comments

DR RICHARDSON: Single-agent lenalidomide at the dose and schedule in this Phase II study showed a robust response rate and impressive PFS and time to disease progression. The median overall survival in this relapsed and refractory population is almost two years, that's quite remarkable, and unprecedented.

Among patients who achieved at least a PR, the survival is approaching three years. The results suggest that if patients respond to this regimen, they can enjoy particularly long disease control.

Faculty Comments (Continued)

DR JAGANNATH: The study showed that lenalidomide monotherapy at 30 mg/day is an active therapy and that the toxicity is favorable. The drug is effective irrespective of the number of prior therapies.

The PFS is approximately five months, but in those patients who achieved responses, the responses were quite durable in this heavily pretreated group.

The results show that for patients having achieved a response, especially CR or PR, outcomes were improved.