

A Phase II Study of Bortezomib (Velcade®), Cyclophosphamide (Cytoxan®), Thalidomide (Thalomid®) and Dexamethasone as First-Line Therapy for Multiple Myeloma

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Disclosures

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Research Support/P.I.	Millennium Pharmaceuticals, Inc.,
Employee	N/A
Consultant	Millennium Pharmaceuticals, Inc., Celgene, Inc.
Major Stockholder	N/A
Speakers' Bureau	Millennium Pharmaceuticals, Inc., Celgene, Inc.
Scientific Advisory Board	N/A

Presentation includes discussion of the following off-label use of a drug or medical device: frontline use of bortezomib in MM

Introduction

- ▶ **The aim of frontline therapy is to reduce tumor burden and achieve prolonged remission**
- ▶ **Better response to frontline therapy**
 - improves survival
 - Obviates need for second transplant

Phase II Trials:

- ▶ **Bortezomib and dexamethasone is effective induction therapy**
 - CR/nCR 18% and CR + PR 88% - Jagannath Br J Haematol 2005
 - CR/nCR 21% and CR + PR 66% - Harousseau Haematologica 2006

Phase III Trials:

- ▶ **BD is superior to VAD as induction therapy**
 - CR/nCR 20% and CR + PR 82% - Harousseau ASH 2006

Background

- ▶ **Goal: Double the CR/nCR rate from 20% to 40%**
- ▶ **Achieve by combining all four classes of active agents**
 - **Dexamethasone – most potent glucocorticoid**
 - **Cyclophosphamide – alkylating agent with less stem cell toxicity**
 - **Bortezomib - a first-in-class proteasome inhibitor**
 - **Thalidomide – an IMiD approved for frontline use**

A Phase II Multicenter Trial in Newly Diagnosed MM BCD x 3 Followed by BTD x 3

Objectives

▶ Primary Objectives

- To assess the response rate to BCD x 3 / BTD x 3 in newly diagnosed myeloma patients**
- Primary target to achieve \geq CR/nCR of \geq 40%**

▶ Secondary Objective

- To determine the safety and tolerability of BCD/BTD**
- To assess VGPR rate versus Bortezomib/dexamethasone**

Patient Eligibility

- ▶ Patients with newly diagnosed MM requiring treatment
- ▶ Inclusion criteria
 - No previous chemotherapy; KPS \geq 50%
 - Measurable disease
 - Age \geq 18 years
- ▶ Exclusion criteria
 - HIV
 - Hemodialysis
 - Plasma cell leukemia

Protocol Flow Diagram

Newly Diagnosed Symptomatic Myeloma

Bortezomib / Cyclophosphamide / Dexamethasone

(1.3 mg/m²)*

(300mg/m²)**

(40mg)***

Three 21 day courses

*Bortezomib days 1, 4, 8, 11

** Cyclophosphamide iv 300mg/m² days 1 and 8

*** Dexamethasone 40mg days 1, 2, 4, 5, 8, 9, 11, 12

Bortezomib / Thalidomide / Dexamethasone

(1.0 mg/m²)

(100mg daily)

(40mg)

Three 21 day courses

*Bortezomib days 1, 4, 8, 11

** Thalidomide 100 mg daily

*** Dexamethasone 40mg days 1, 4, 8, 11

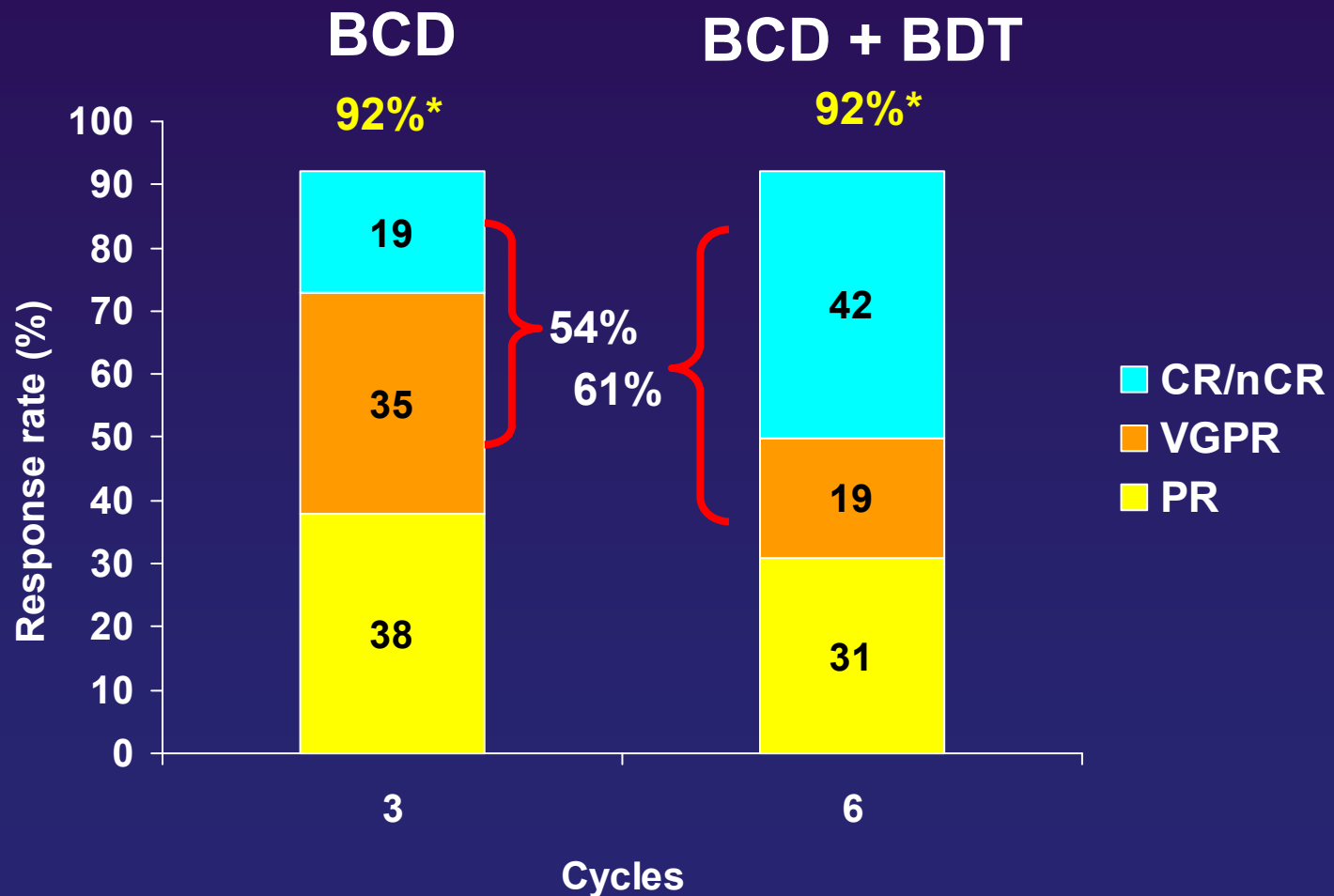
Baseline Patient Characteristics (N = 30)

Characteristic

Mean age, years (range)	58 years (38-78)
Male, %	67 %
Median KPS, % (range)	90 (60–100) %
β_2 -microglobulin ≥ 4 mg/L, %	38 %
Serum creatinine, ≥ 2 mg/dl (“B”)	13 %
Durie–Salmon stage III, %	73 %
Type of myeloma (%)	
IgG	71 %
IgA	11 %
Light-chain disease	18 %

Cumulative Best Response (N = 26)**

** 4 patients too early for full response assessment



*2 patients "stable" throughout 6 cycles

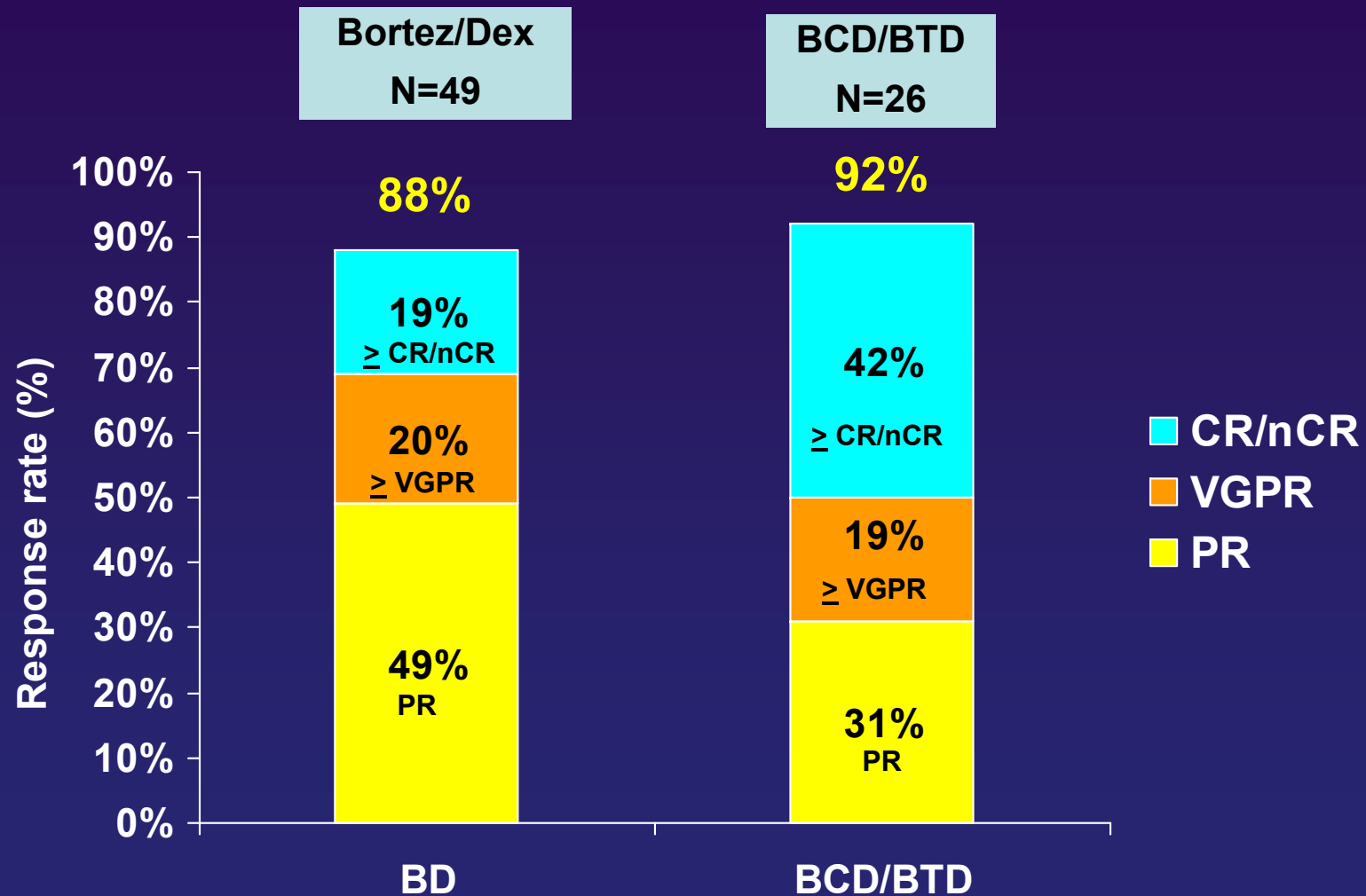
Current Follow-Up

- ▶ All evaluable patients completed ≥ 4 cycles; 85% completed 6 cycles.
- ▶ 7 patients have undergone transplantation
- ▶ Harvest/transplant has proceeded smoothly, without any harvesting or other issues.

Safety: First 26 Patients

- ▶ Bortezomib related neuropathy Gd ≥ 2 : 20% (5 pts)
- ▶ Neuropathy after starting Thalidomide (Gd ≥ 2): : 15% (4 pts)
 - 15% patients discontinued Bortezomib or Thalidomide
- ▶ Dexamethasone toxicities (Gd ≥ 2)(Insomnia/Hyperglycemia): 15%
- ▶ Cytoxan[®] toxicities (Neutropenia/Pneumonia) (Gd ≥ 2): : 12%
 - Cytoxan[®] held in 1 patient
- ▶ There were no DVT/PE (aspirin prophylaxis after thalidomide)
- ▶ There were no treatment-related mortality
 - However, 1 patient died while on no therapy 2 months after achieving nCR and completing all therapy. Died suddenly (unknown cause) post-op elective hernia repair

Comparison With Prior Study



Conclusion

- ▶ **Bortezomib, cyclophosphamide, dexamethasone followed by bortezomib, thalidomide and dexamethasone was effective**
 - Response rate was >90%, with VGPR >60%
 - CR/nCR = 42% (exceeds goal of \geq 40%)
 - Improved over Btz-Dex alone
- ▶ **The combination was well tolerated with 85% completing all 6 cycles**
- ▶ **Adverse events were predictable and manageable**
 - CTC gr \geq II Neurotoxicity encountered in 35%
 - Discontinued therapy from toxicity 15%
 - Painful neuropathy completely resolved
- ▶ **Stem cell harvest was successful and engraftment was prompt**

Collaborators

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