Bortezomib: a new paradigm for treatment of multiple myeloma

Michael W. Schuster, M.D.
The first well-known case of multiple myeloma was that of Mr. McBean described in 1846, 1847, and 1850 by John Darlympe, Henry Bence Jones, and William MacIntyre.

Mr. McBean, a highly respectable tradesman from London.

The term multiple myeloma dates from 1873 and was introduced by von Rusitzky.
Multiple Myeloma: Disease Description

**Epidemiology:**
- U.S. Incidence: 14,600 new cases/yr
- Prevalence: 52,000
- Deaths: 10,800/yr

**Etiology:**
- Multiple myeloma is a malignant proliferation of the plasma cells.
- These cancerous cells destroy normal bone tissue causing pain and crowding normal blood production

**Clinical Features:**
- Osteolytic lesions, bone pain, fractures, anemia, renal insufficiency, hypercalcaemia, and recurrent bacterial infections are most common

**Outcome:**
- Multiple myeloma is the 2nd most common hematological malignancy (after NHL) and is invariably fatal
- 29% 5-year survival rate
History of Myeloma Therapy

- **1950-60s**
  - D- and L-phenylalanine mustards
    - L-isomer = melphalan
  - Melphalan (+ prednisone)
  - High-dose glucocorticoids

- **1970s-80s**
  - Combination chemotherapy
    - VAD
  - High-dose therapy
  - Bone marrow transplantation

- **1990s-2003**
  - Thalidomide
  - Bisphosphonates

*deVita, Cancer Principles and Practice of Oncology*
Multiple Myeloma: Current Treatment

**Diagnosis**
- ~15,000 new cases/yr
- Survival 3-5 yrs

**Relapsed Disease**
- Transient Response
- Survival 1-3 years

**Refractory**
- Survival 6-9 mo
- Deaths 11,000/yr

**First-Line:**
- VAD or CVAD
- MP
- Transplant

**Relapsed:**
- Bortezomib
- VAD or CVAD
- Thalidomide/dex
- Transplant

**Refractory:**
- Bortezomib
- Investigational therapy

*deVita, Cancer Principles and Practice of Oncology*
The proteasome and Its Function

- The proteasome, present and abundant in all cells, degrades ubiquitinated proteins.
- The ubiquitin-proteasome pathway controls protein homeostasis in the cell.
- Ubiquitin “tags” proteins for degradation by the proteasome.
- The ubiquitination process is specific and regulated.
Ubiquitin-Proteasome Pathway

Protein Substrate → Ubiquitinated Protein → 26S Proteasome Complex → Degraded proteins
Bortezomib and Proteasome Inhibition

- Degrades ubiquitinated proteins
- Proteolysis is ATP-dependent
Bortezomib

- Potency, $Ki = 0.6\ \text{nM}$
- Reversible inhibition of the proteasome
- Highly selective
Cellular Impact Proteasome Inhibition

Proteasome inhibitors block the proteasome, producing conflicting regulatory signals and interfering with critical cellular functions.

Normal Cells: less sensitive than cancer cells to proapoptotic effects
Normal Cells: can recover

Cancer Cells: have difficulty processing overload
Cancer Cells: can lead to apoptosis

= proteasome inhibitor
Proteasome inhibition mediated cytotoxicity involves multiple downstream mechanisms.

In non-clinical studies bortezomib:

- Stabilized cell-cycle regulatory proteins
- Inhibited NF-κB activation
- Inhibited Anti-angiogenic
- Induced apoptosis
- Was not susceptible to multiple resistance mechanisms tested
BORTEZOMIB MOA: Proteasome Inhibition, NF-κB, and Multiple Myeloma

Cytokines activate cell-surface receptors → Signaling pathways → NF-κB inhibited by IκB

IκB targeted for degradation → Proteasome

NF-κB activated transcription → Anti-apoptotic factors

Activated NF-κB translocates to the nucleus

Degraded IκB

Enzymes and cell cycle regulators

(Cytokines → Cell adhesion molecules (Microenvironment))

(Microenvironment)
VELCADE™ (bortezomib) for Injection
SUMMIT (025):
A Phase II Study of
VELCADE™
(bortezomib) for Injection

Paul G. Richardson,1 Bart Barlogie,2 James Berenson,3 Seema Singhal,4 Ann Traynor,4 Sundar Jagannath,5 David Irwin,6 Vincent Rajkumar,7 Gordan Srkalovic,8 Melissa Alsina,9 Raymond Alexanian,10 David Siegel,11 Robert Orlowski,12 David Kuter,13 Steven Limentani,14 Dixie Esseltine,15 Gretchen Richards,15 Michael Kauffman,15 Julian Adams,15 David P. Schenkel,15 and Kenneth C. Anderson1

1Dana-Farber Cancer Institute, 2University of Arkansas, 3Cedars-Sinai Medical Center, 4Northwestern University Medical Center, 5St Vincent’s Comprehensive Cancer Center, 6Alta Bates Cancer Center, 7Mayo Clinic, 8Cleveland Clinic Foundation, 9H. Lee Moffitt Cancer Center, 10M.D. Anderson Cancer Center, 11Carol G. Simon Cancer Center, 12University of North Carolina at Chapel Hill, 3Massachusetts General Hospital, 14Charlotte Medical Clinic, 15Millennium Pharmaceuticals, Inc
SUMMIT: Study Design

- Open-label, single-arm, multi-center phase II study in 202 patients
- Overall response rate determined by an Independent Review Committee using criteria by Bladé et al
- Response rate also evaluated using SWOG criteria
SUMMIT: Entry Criteria

- Relapsed following at least 2 prior therapies for multiple myeloma and refractory to most recent therapy (N=202)
- Measurable disease
  - Or non-measurable disease (nonsecretory or oligosecretory)
- Karnofsky Performance Status score ≥60
- Hematologic status:
  - Platelets ≥30 x 10^9/L
  - Hemoglobin ≥8 g/dL
  - ANC ≥1.0 x 10^9/L
- Creatinine clearance ≥30 ml/minute
- Liver enzymes ≤3 x ULN
SUMMIT: Treatment Plan

- Bortezomib 1.3 mg/m² IV push over 3-5 seconds

- 21-day cycle
  - Administered on days 1, 4, 8, and 11 with a 10-day rest period (days 12-21)
  - 72 hours between doses

- 8-cycle study period
  - For CR patients, 2 cycles beyond confirmed CR
  - Extension protocol available for patients experiencing benefit
### SUMMIT: Patient/Disease Characteristics

<table>
<thead>
<tr>
<th>Total Enrolled</th>
<th>N=202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of multiple myeloma since diagnosis (years)</td>
<td>4.0</td>
</tr>
<tr>
<td>Median age, years</td>
<td>59 (34-84)</td>
</tr>
<tr>
<td>M protein: IgG / IgA / Light Chain</td>
<td>60% / 24% / 14%</td>
</tr>
<tr>
<td>Median creatinine clearance (mL/min)</td>
<td>73.9 (13.8-220)</td>
</tr>
<tr>
<td>Karnofsky Performance Status score ≤70</td>
<td>20%</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL</td>
<td>44%</td>
</tr>
<tr>
<td>Platelet count &lt;75 x 10⁹/L</td>
<td>21%</td>
</tr>
<tr>
<td>Median β2 microglobulin (mg/L)</td>
<td>3.5</td>
</tr>
<tr>
<td>Abnormal cytogenetics</td>
<td>35% (60/172)</td>
</tr>
<tr>
<td>Chromosome 13 deletion</td>
<td>15% (26/172)</td>
</tr>
</tbody>
</table>
### SUMMIT: Prior Therapies Received

<table>
<thead>
<tr>
<th>Prior Therapies</th>
<th>(N=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior steroids, e.g., dexamethasone, VAD</td>
<td>99%</td>
</tr>
<tr>
<td>Any prior alkylating agents, e.g., MP, VBMCP</td>
<td>92%</td>
</tr>
<tr>
<td>Any prior thalidomide therapy</td>
<td>83%</td>
</tr>
<tr>
<td>Any prior anthracyclines, e.g., VAD, mitoxantrone</td>
<td>81%</td>
</tr>
<tr>
<td>Received at least 2 of the above</td>
<td>98%</td>
</tr>
<tr>
<td>Received at least 3 of the above</td>
<td>92%</td>
</tr>
<tr>
<td>Received all 4 of the above</td>
<td>66%</td>
</tr>
<tr>
<td>High-dose therapy, including stem cell transplant</td>
<td>64%</td>
</tr>
<tr>
<td>Prior experimental or other types of therapy</td>
<td>44%</td>
</tr>
</tbody>
</table>
# Response Rates

## Bortezomib Alone (n=188)*

<table>
<thead>
<tr>
<th>Category</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response + Partial Response</td>
<td>27.7%</td>
</tr>
<tr>
<td>( \geq 50% ) Reduction in M protein (Bladé et al)</td>
<td>(95% CI=21, 35)</td>
</tr>
<tr>
<td>Clinical remission (SWOG)</td>
<td>17.6%</td>
</tr>
<tr>
<td>( \geq 75% ) Reduction in M protein</td>
<td>(95% CI=12, 24)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>2.7%</td>
</tr>
<tr>
<td>( 100% ) Reduction in M protein by immunofixation (Bladé et al)</td>
<td>(95% CI=1, 6)</td>
</tr>
<tr>
<td>Kaplan-Meier Estimated Median Duration of Response</td>
<td>365 days</td>
</tr>
<tr>
<td></td>
<td>(95% CI= 224, NE†)</td>
</tr>
</tbody>
</table>

*N 188/202 patients were evaluable for response.
† NE= Not Estimable
Response Rates

Bortezomib Alone (n=188)*1

- 2.7% CR (95% CI = 1, 6) in heavily pre-treated patient population

- 27.7% CR (95% CI = 21, 35)

- 17.6% SWOG Clinical Remission (95% CI = 12, 24)

- ≥50% ≥75% Reduction in M protein

*188/202 patients were evaluable for response

SUMMIT: Duration of Response with Bortezomib (CR+PR)*1

Percent patients maintaining response over time (n=52)

Median duration of response = 12 months (365 days; 95% CI = 224, NE)

Median time to response was 38 days (range 30-127 days)

*188/202 patients were evaluable for response. NE = not estimable.

SUMMIT: Overall Survival Curves with Bortezomib*1

Percent overall survival over time (N=202)

Median overall survival = 16 months* (range <1 to 18+ months)

*As of October 2002.

Duration of Response and Survival

- Response independent of number and types of prior therapies
- Median time to response
  - 38 days (range 30 to 127 days)
- Median duration of response
  - 365 days (95% CI 224, NE)
- Median survival
  - 16 months (range <1 to 18+ months)
A Phase II Multicenter Randomized Study of the Proteasome Inhibitor Bortezomib (VELCADE™, formerly PS-341) in Multiple Myeloma (MM) Patients (Pts) Relapsed After Front-line Therapy

Sundar Jagannath 1, Bart Barlogie 2, James Berenson 3, David Siegel 4, David Irwin 5*, Paul G. Richardson 6, Michael Schuster, 7 Raymond Alexanian 8, Steven A. Limentani 9, Melissa Alsina 10, Dixie-Lee Esseltine 11, Michael Kauffman 11, Julian Adams 11, David P. Schenkein 11 and Kenneth C. Anderson 6. 1St. Vincent's Catholic Medical Center, New York, NY; 2University of Arkansas, Little Rock, AR; 3Cedars-Sinai Medical Center, Los Angeles, CA; 4Carol G. Simon Cancer Center, Morristown, NJ; 5Alta Bates Comprehensive Cancer Center, Berkeley, CA; 6Dana-Farber Cancer Institute, Boston, MA; 7 New York Presbyterian Hospital, New York, NY; 8M.D. Anderson Cancer Center, Houston, TX; 9Charlotte Medical Clinic, Charlotte, NC; 10H. Lee Moffitt Cancer Center, Tampa, FL and 11Millennium Pharmaceuticals, Inc., Cambridge, MA.
Clinical Rationale

- Demonstrated activity seen in advanced relapsed and refractory myeloma
- Several doses and schedules tested in Phase I/II trials
- Current trial designed as a pilot study to explore the activity of two dose levels in an earlier patient population (relapsed myeloma)
Study Design

- Open-label, multicenter, randomized phase II trial (10 sites in USA)
  - Bortezomib 1.0 and 1.3 mg/m²/dose

- Primary endpoint: overall response rate (CR, PR, MR)
  - Independent review committee (IRC) using Bladé criteria

- Secondary endpoints:
  - Response rate with dexamethasone, safety/tolerability, pharmacodynamics, QOL, pharmacogenomics
Entry Criteria

▶ Inclusion
- History of relapse or failure to respond to front-line therapy for myeloma
- Measurable disease
- KPS ≥ 60
- Platelets ≥ 30 x 10⁹/L, Hgb ≥ 8 g/dL, ANC ≥ 1.0 x 10⁹/L
- Creatinine clearance ≥ 30 mL/min
- Liver enzyme: ≤3 x ULN

▶ Exclusion
- No POEMS or plasma cell leukemia
- Impaired kidney function requiring dialysis
Treatment Plan

- Bortezomib 1.0 or 1.3 mg/m² IV push, no premedication
- Twice weekly x2 weeks followed by 1-week rest
  - Administered on days 1, 4, 8, and 11
- Dexamethasone permitted if suboptimal response after 2 cycles (PD patients) or 4 cycles (SD patients)
  - 20 mg PO on days 1-2, 4-5, 8-9, 11-12
- Maximum of 8 cycles
  - For CR patients, 2 cycles beyond confirmed CR
  - Extension protocol for responding patients
IRC Assessments

- Objective cycle-by-cycle assessments
- Confirmed response
  - 6 weeks following initial assessment
- Prevention of potential bias
  - IRC members unaware whether dexamethasone added to treatment
- Response data following administration of dexamethasone not included in bortezomib alone analysis
  - Analysis for response to bortezomib alone and all treatment
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>1.0 mg/m²</th>
<th>1.3 mg/m²</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=28</td>
<td>N=26</td>
<td>N=54</td>
</tr>
<tr>
<td>Age in Years (median)</td>
<td>65</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Range (39-82)</td>
<td>(39-82)</td>
<td>(30-84)</td>
<td>(30-84)</td>
</tr>
<tr>
<td>KPS ≤ 70</td>
<td>11%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Hemoglobin &lt;10.0 g/dL</td>
<td>21%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>Platelet count &lt;75 x 10⁹/L</td>
<td>19%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>BM plasma cells biopsy</td>
<td>46%</td>
<td>38%</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>1.0 mg/m²</td>
<td>1.3 mg/m²</td>
<td>Total</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>N=28</td>
<td>N=26</td>
<td>N=54</td>
</tr>
<tr>
<td>Myeloma: IgG, IgA, Other (%)</td>
<td>54/29/17</td>
<td>65/23/12</td>
<td>59/26/15</td>
</tr>
<tr>
<td>Yrs from initial Dx (median)</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Creatinine clearance (median)</td>
<td>71</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td>β2-microglobulin (mg/L) (median)</td>
<td>8.4</td>
<td>3.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Abnormal cytogenetics</td>
<td>29%</td>
<td>48%</td>
<td>38%</td>
</tr>
</tbody>
</table>
Previous Therapies

- Prior SCT: 48%
- Thalidomide: 30%
- Anthracyclines: 54%
- Alkylators: 72%
- Steroids: 98%

Median number of prior therapies, 3 (range 1-7)
Response (%) to Bortezomib Alone

<table>
<thead>
<tr>
<th></th>
<th>1.0 mg/m² (N=27)</th>
<th>1.3 mg/m² (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall&lt;sup&gt;a&lt;/sup&gt; (CR+PR+MR)</td>
<td>33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50</td>
</tr>
<tr>
<td>CR&lt;sup&gt;IF-&lt;/sup&gt;</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>CR&lt;sup&gt;IF+&lt;/sup&gt;</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>MR</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>SD</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>PD</td>
<td>30</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 pt with nonsecretory myeloma inevaluable for response

<sup>b</sup> 11% and 12% were not IRC evaluable in 1.0 and 1.3 dose groups, respectively; numbers rounded to the nearest integer
### Response (%) to Bortezomib Alone or with Dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>1.0 mg/m² (N=27: 16 combination)</th>
<th>1.3 mg/m² (N=26: 12 combination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall&lt;sup&gt;a&lt;/sup&gt; (CR+PR+MR)</td>
<td>44</td>
<td>62</td>
</tr>
<tr>
<td>CR&lt;sup&gt;IF-&lt;/sup&gt;</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>CR&lt;sup&gt;IF+&lt;/sup&gt;</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td>MR</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>SD</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>PD</td>
<td>30</td>
<td>19</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1 pt with nonsecretory myeloma inevaluable for response;
<sup>b</sup> 7% and 8% were not IRC evaluable in 1.0 and 1.3 dose groups, respectively; numbers rounded to the nearest integer.
Time to Progression on Bortezomib Alone (n=54)

Median follow-up: 8.8 months
Median TTP 321 days (11 months)
Overall Survival (n=54)

Median survival, not reached at 8.8 months follow-up
### Most Common Adverse Events (1.0 mg/m²)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>G1-2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per. Neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No deaths within 20 days of last dose
Most Common Adverse Events
(1.3 mg/m²)

- Nausea
- Diarrhea
- Constipation
- Thrombocytopenia
- Neutropenia
- Anemia
- Fatigue
- Arthralgia
- Insomnia
- Headache
- Per. Neuropathy

- 1 death within 20 days of last dose (pneumonia with sepsis); unlikely related to study drug
CREST Study

- A small, dose-response study in 54 patients
- Responses observed with 1.0 mg/m² and 1.3 mg/m² doses
  - 1 CR observed at both 1.3 and 1.0 mg/m²
  - Overall response (CR + PR):
    - 38% at 1.3 mg/m²
    - 30% at 1.0 mg/m²
Bortezomib Versus Dexamethasone in Relapsed Multiple Myeloma: A Phase 3 Randomized Study (APEX)

A Report of the Interim Analysis

Paul G. Richardson,1 Pieter Sonneveld,2 Michael W. Schuster,3 David Irwin,4 Edward A. Stadtmauer,5 Thierry Facon,6 Jean-Luc Harousseau,7 Dina Ben-Yehuda,8 Sagar Lonial,9 Hartmut Goldschmidt,10 Donna Reece,11 Jesus F. San Miguel,12 Joan Bladé,13 Mario Boccadoro,14 Jamie Cavenagh,15 William S. Dalton,16 Anthony L. Boral,17 David Schenkein,17 Kenneth C. Anderson1

1Dana-Farber Cancer Institute, 2University Hospital Rotterdam, 3New York-Presbyterian Hospital, 4Alta Bates Cancer Center, 5University of Pennsylvania Cancer Center, 6Hospital Claude Huriez, 7Hotel Dieu Hospital, 8Hadassah University Hospital, 9Emory University, 10Universitaetsklinikum Heidelberg, 11Princess Margaret Hospital, 12Hospital Universitario de Salamanca, 13Universitario de Barcelona 14Università di Torino, 15St. Bartholomew’s Hospital, 16H. Lee Moffitt Cancer Center, 17Millennium Pharmaceuticals, Inc.
Treatment Plan

Randomization

Bortezomib

8 cycles

1.3 mg/m² IV push
D 1, 4, 8, 11 q 3-wk cycle

Induction

4 cycles

40 mg PO
D 1–4, 9–12, 17–20 q 5-wk cycle

3 cycles

1.3 mg/m² IV push
D 1, 8, 15, 22 q 5-wk cycle

Maintenance

5 cycles

40 mg PO
D 1–4 q 4-wk cycle

273 treatment days

280 treatment days

Richardson et al. ASCO 2004; Abstract 6511
Time to Progression (Interim Analysis)

58% improvement in median TTP

Median TTP: Bortezomib 5.7 mos  
Dexamethasone 3.6 mos

Richardson et al.  ASCO 2004; Abstract 6511
Results of Interim Analysis (APEX)

- Significant TTP benefit ($P < 0.0001$) with bortezomib vs dexamethasone
  – 58% increase in median TTP

- Early survival advantage prior to crossover

- Trend toward lower incidence of severe and life-threatening infections

- No difference in TSE (small number of

Richardson et al. ASCO 2004; Abstract 6511
<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Bortezomib %</th>
<th>Dexamethasone %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events ≥ G3*</td>
<td>66</td>
<td>56</td>
</tr>
<tr>
<td>Adverse events G4*</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Treatment-related mortality†</td>
<td>&lt; 1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Safety population.
†ITT population.

Richardson et al. ASCO 2004; Abstract 6511
Mean Platelet Count During Treatment

- Bortezomib arm: platelet counts measured on days 1, 4, 8, 11 of each 21-day cycle
- Dexamethasone arm: platelet counts measured every 3 weeks

Richardson et al. ASCO 2004; Abstract 6511
APEX Survival at Final Analysis*
(Includes Crossover)

Overall survival, $P < 0.01$
1-year survival, $P < 0.01$
Median follow-up in survivors approx 8 mo

*January 13, 2004

Richardson et al. ASCO 2004; Abstract 6511
First-line Therapy With Bortezomib (VELCADE®, Formerly PS-341) in Patients With Multiple Myeloma (MM)

Sundar Jagannath,1 Brian G.M. Durie,1 Jeffrey Wolf,1 Elber Camacho,1 David Irwin,1 Jose Lutzky,1 Marti McKinley,1 Eli Gabayan,1 Amitabha Mazumder,1 John Crowley,2 David Schenkein3

1Salick Health Care Research Network, Los Angeles, CA; 2Center for Research & Biostatistics, Seattle, WA; 3Millennium Pharmaceuticals, Inc., Cambridge, MA
Treatment Plan

- Bortezomib 1.3 mg/m² 2x/week x2 q 3 weeks for a maximum of 6 cycles
- Patients received bortezomib alone for the first 2 cycles
- Dex 40 mg on day of and after each bortezomib dose was added if
  - After 2 cycles for patients who achieve less than a PR
  - After 4 cycles for patients who achieve less than a CR (immunofixation negative)
  - Dex dose was twice the dose used in the phase 2 bortezomib trials (SUMMIT/CREST)\textsuperscript{5,6}

Jagannath et al. ASCO 2004; Abstract 6551
## Current Best Overall Responses (n = 24)

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (8)</td>
</tr>
<tr>
<td>NCR</td>
<td>4 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (54)</td>
</tr>
<tr>
<td>MR</td>
<td>4 (17)</td>
</tr>
<tr>
<td>SD</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*Responses based on paraprotein.

- Overall CR/NCR/PR 79%  
  - Overall > SD 96%

- Bortezomib alone induced CR/NCR in 6 patients; 2 of these NCR patients received dexamethasone and response status remained unchanged.

Jagannath et al. ASCO 2004; Abstract 6551
## Cycle 2 Response and Best Overall Response (n = 24)

<table>
<thead>
<tr>
<th></th>
<th>Cycle 2 Response* (n = 24, n %)</th>
<th>Best Overall Response* (n = 10, n %)</th>
<th>Bortezomib + Dexamethasone (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bortezomib</td>
<td>Bortezomib</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NCR</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>PR</td>
<td>8 (33)</td>
<td>4 (17)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>MR</td>
<td>8 (33)</td>
<td>1 (4)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (21)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Responses based on paraprotein.

Overall CR/NCR/PR 79%

Jagannath et al. ASCO 200; Abstract 6551
Confirmation of Remission: PET Scan

Pretreatment After 4 Cycles

Plasmacytomas

Jagannath et al. ASCO 2004; Abstract 6551
Peripheral Neuropathy (N=24)

- Painful neuropathy per NCI CTC v2
  - Grade 2: 3 patients
  - Grade 3: 2 patients, both off study

- Grade 3 neuropathy resolved completely 4 months post-treatment

Jagannath et al. ASCO 2004; Abstract 6551
A Randomized phase III trial of thalidomide plus dexamethasone versus dexamethasone in newly diagnosed multiple myeloma (E1A00): A trial coordinated by the Eastern Cooperative Oncology Group

S.V. Rajkumar, E,¹ E. Blood,² D.H. Vesole,³ R. Shepard,⁴ P.R. Greip,¹

¹Mayo Clinic, ²Dana Farber Cancer Institute, ³Medical College of Wisconsin, ⁴University of Virginia
Treatment Plan

Randomization

Thalidomide + Dexamethasone

4 cycles

Thal 200 mg PO QD
Dex D1-4, 9-12, 17-20

RR 80%

Dexamethasone

40 mg PO
D 1–4, 9–12, 17–20

RR 53%

RR = ≥ 50% decrease M-protein

Rajkumar et al. ASCO 2004; Abstract 6508
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Thal/De</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>DVT</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Sinus Bradycardia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Death</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Toxicity ≥ G4</td>
<td>31%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Rajkumar et al. ASCO 2004; Abstract 6508
Oral melphalan, prednisone and thalidomide for newly diagnosed myeloma patients

A. Palumbo, A. Bertoli, P. Musto, M. Nunzi, V. De Stefano, L. Catalano, T. Caravita, C. Cangialosi, S. Bringen, M. Boccadoro

Italian Multiple Myeloma Study Group
Treatment Plan

- Thalidomide 100mg PO QD
- Melphalan 4mg/m² PO D1-7, Qmo
- Prednisone 40mg/m² PO D1-7, Qmo

Palumbo et al. ASCO 2004; Abstract 6549
## Best Overall Responses

<table>
<thead>
<tr>
<th>Response*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>26</td>
</tr>
<tr>
<td>NCR</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td>93</td>
</tr>
<tr>
<td>NR</td>
<td>7</td>
</tr>
</tbody>
</table>

*Responses based on paraprotein.

Palumbo et al. ASCO 2004; Abstract 6549
### Toxicity/Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>38%</td>
</tr>
<tr>
<td>Neutropenia ≥G3</td>
<td>14%</td>
</tr>
<tr>
<td>Constipation</td>
<td>28%</td>
</tr>
<tr>
<td>Infection</td>
<td>26%</td>
</tr>
<tr>
<td>DVT</td>
<td>19%</td>
</tr>
<tr>
<td>Death</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

N=42

Palumbo et al. ASCO 2004; Abstract 6549
PAD Combination Therapy
(Bortezomib/Adriamycin and Dexamethasone) for Untreated Multiple Myeloma

J. D. Cavenagh,1 N. Curry,1 J. Stec,2 C. Morris,3 M. Drake,3 S. Agrawal,1 D. Schenkein,2 D. Esseltine,2 H. Oakervee1

1St Bartholomew’s Hospital, London, UK
2Millennium Pharmaceuticals, Inc., Cambridge, MA, USA;
3Belfast City Hospital, Belfast, UK
Objectives

► Primary objectives
  – Evaluate feasibility of collecting peripheral blood stem cells (PBSCs) after PAD
  – Assess engraftment after high-dose therapy (HDT)

► Secondary objectives
  – Assess safety and toxicity
  – Determine response rates, progression-free survival, and overall survival
  – Perform pharmacodynamic assessments

Cavenagh et al. ASCO 2004; Abstract 6550
## Treatment

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib 1.3 mg/m²</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Dexamethasone 40 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycles 2–4</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib 1.3 mg/m²</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Dexamethasone 40 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Induction (4 cycles prior to transplantation)
- Bortezomib 1.3 mg/m² by IV bolus on days 1, 4, 8, and 11
- Doxorubicin administered by continuous infusion or IV push to cohorts at escalating dose levels (0, 4.5, 9.0 mg/m²/day) on days 1–4
- Dexamethasone 40 mg p.o
  - Cycle 1: days 1–4, 8–11, and 15–18
  - All subsequent cycles: days 1–4

Cavenagh et al. ASCO 2004; Abstract 6550
Responses

- 95% CR/PR after $\geq 1$ cycle of treatment (n = 21)
  - 1 CR after bortezomib + dexamethasone alone
  - 2 CRs after PAD

- 94% CR/PR rate after 4 cycles (n = 18)

Cavenagh et al. ASCO 2004; Abstract 6550
Serum/Urinary Myeloma Protein Response by PAD Cycle

- Mean M-protein levels decreased significantly following cycle 1 of treatment and continued to decrease after subsequent cycles.

Cavenagh et al. ASCO 2004; Abstract 6550
Outcome after PBSCT

- 11 of 15 mobilized patients have received MEL200/PBSCT
- 8 of 11 assessed 3 months post MEL200
  - 5 improved response
  - 2 PR unchanged
  - 1 VGPR unchanged
- Hematopoietic recovery (n = 11)
  - Median days until neutrophil count > 0.5 x 10^6/L = 17
    (range, 1–24)
  - Median days until platelet count > 20 x 10^9/L = 13
    (range, 10–33)

Cavenagh et al. ASCO 2004; Abstract 6550
Conclusions

- PAD combination therapy demonstrated encouraging activity in previously untreated patients with multiple myeloma
  - 94% CR/PR rate after 4 cycles
  - 15 of 16 patients successfully mobilized
  - 11 of 15 successfully transplanted thus far
  - All 8 evaluable patients achieved PR or better following PBSCT (2 CR, 4 VGPR, 2 PR), some had improved response

- Major toxicity is painful neuropathy
  - Primarily grade 1
  - Generally appeared in cycle 3 or 4
  - Neuropathic symptoms are improving in all patients after completion of therapy
Chemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) improves complete response (CR), remission duration and survival as initial therapy of chronic lymphocytic leukemia (CLL)


MD Anderson Cancer Center
Fludarabine, Cyclophosphamide, and Rituximab (FCR) in Untreated CLL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Course 1</th>
<th>Courses 2-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² day 1*</td>
<td>500 mg/m² day 1*</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>25 mg/m² days 2-4†</td>
<td>25 mg/m² days 1-3†</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>250 mg/m² days 2-4†</td>
<td>250 mg/m² days 1-3†</td>
</tr>
<tr>
<td></td>
<td>†Allopurinol/tumor lysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>precautions required.</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment repeated q 28 days for 6 cycles of therapy.

*Prophylaxis with TMP/SMX + valacyclovir optional.
†Allopurinol/tumor lysis precautions required.

Keating et al. ASCO 2004; Abstract 6565
### Response, Response Duration, Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th># Pts</th>
<th>%CR</th>
<th>%PR</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F+P</td>
<td>137</td>
<td>31</td>
<td>54</td>
<td>30mo</td>
</tr>
<tr>
<td>74mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F+C/M</td>
<td>135</td>
<td>32</td>
<td>55</td>
<td>43mo</td>
</tr>
<tr>
<td>92mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCR</td>
<td>224</td>
<td>71</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

Keating et al. ASCO 2004; Abstract 2565
Conclusions: Study 024

- Bortezomib was active in relapsed MM pts
  - Overall response 33% and 50% at 1.0 and 1.3 mg/m²
- Additional responses seen with addition of Dex
  - Overall response 44% and 62% respectively
- CRs observed at both 1.0 and 1.3 mg/m²
Conclusions: Study 024

- Possible dose response observed for both clinical benefit and toxicity
- Clinically significant toxicity included diarrhea, fatigue and peripheral neuropathy
  - 15% of pts discontinued due to a treatment-related adverse event
- Definitive Phase III trial (APEX) is actively recruiting pts
Combined Velcade & Chemotherapy

- Pre-clinical experiments show that Bortezomib can kill myeloma cell lines at lower doses when combined with chemotherapy.
- Phase I/II study presented at ASH from Cedars-Sinai group, combining Bortezomib with Melphalan.
- Bortezomib given days 1, 4, 8, & 11 @ 0.7 mg/M2.
- Melphalan given po d1-4 q 28 days @0.025-0.25 mg/kg.

Combined Velcade & Chemotherapy

- 15 pre-treated pts. ages 33-70
- 2-7 prior therapies
- Grade III myelosuppression
- 67% PR
- 13% MR
- 20% SD
Combined Velcade and Thalidomide

- Little Rock group presented Phase I/II trial at ASH
- Velcade given days 1,4,8,11 q 21 days @ 1 mg/M2 + Thalidomide 50-100 mg
- Dex could be added if no PR after 2 cycles
- 78% resistant to Thalidomide
- 72% had prior tandem transplant
- 22% CR rate after 8 cycles
- 53% MPR > 50%

*Zangari et al*, Abstract #830 appears in Blood, Volume 102, issue 11, November 16, 2003
Combine Velcade/Thalidomide
Reduction in Myeloma Protein by Cycle
Trial of Velcade/Doxil

- Chapel Hill group presented Phase I/II data at ASH
- Velcade given d1,4,8,& 11 q 21 days @ 0.9-1.5 mg/M2
- Doxil given day 4 @ 30 mg/M2
- Grade ¾ toxicities included fatigue, cytopenias, neuropathy, Gi problems, palmer erythrodysesthesia
- MTD 1.5 mg/M2 of Velcade

Orlowski et al, Abstract #1639 appears in Blood, Volume 102, issue 11, November 16, 2003
Trial of Velcade/Doxil

- 5/22 myeloma pts. With CR, 2 pts with near-CR, and 8 pts with PR
- No cardiac toxicities
- Dose reductions occurred frequently at 1.4 and 1.5 mg/M2 of Velcade
Safety and Tolerability of VELCADE™ (bortezomib) for Injection
Pooled Safety Results in Phase II Multiple Myeloma Studies with Bortezomib

- N=228
  - Includes patients receiving 1.3 mg/m² starting dose in SUMMIT and CREST Phase II trials

- Median number of prior therapies
  - SUMMIT was 6 (n=202)
  - CREST was 3 (n=26)
Combined Safety Data from SUMMIT and CREST Trials*1

On-Study adverse events (≥30% overall) in Phase II clinical trials at 1.3 mg/m² dose (N=228)

- Nausea: 64%
- Diarrhea: 51%
- Decreased appetite & anorexia: 43%
- Constipation: 43%
- Vomiting: 36%
- Thrombocytopenia: 43%
- Anemia: 32%
- Asthenia (fatigue, malaise, weakness): 65%
- Peripheral Neuropathy: 37%
- Pyrexia: 36%

**Legend:**
- Blue: Grades 1-2†
- Light blue: Grade 3†
- Yellow: Grade 4†
Combined Safety Data from SUMMIT and CREST Trials*

- At baseline, more than 80% of patients had signs of peripheral neuropathy
- Incidence of febrile neutropenia was <1%
- The most common adverse events leading to discontinuation were peripheral neuropathy (6%), gastrointestinal events (5%), thrombocytopenia (4%), and fatigue (2%)
- A total of 113 (50%) of the 228 patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%)

*AEs reported for all events, drug related or not.
Bortezomib: Indication and Usage

- Bortezomib is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The effectiveness of bortezomib is based on response rates. There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.
Bortezomib: Contraindications and Warnings

Contraindication

- Bortezomib is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

Warnings

- Bortezomib should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

- **Pregnancy Category D:** Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib.
Bortezomib: Precautions

- **Peripheral Neuropathy**: Treatment with bortezomib may be associated with a peripheral neuropathy that is predominately sensory, although rare cases of mixed sensorimotor neuropathy have been reported. Patients with pre-existing symptoms and/or signs of peripheral neuropathy may experience worsening during treatment with bortezomib. Patients should be monitored for symptoms of neuropathy, such as numbness, a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain.

- **Hypotension**: Treatment with bortezomib may be associated with orthostatic/postural hypotension throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated.

- **Gastrointestinal Adverse Events**: Nausea, diarrhea, constipation, and vomiting may occur during treatment with bortezomib.
Thrombocytopenia: Complete blood counts including platelet counts should be frequently monitored throughout treatment with bortezomib. Thrombocytopenia was maximal at Day 11 and usually recovered by the next cycle. Onset is most common in Cycles 1 and 2 but can continue throughout therapy. There have been reports of gastrointestinal and intracerebral hemorrhage in association with thrombocytopenia induced by bortezomib.

Patients with Hepatic or Renal Impairment: Patients with renal and hepatic impairment should be closely monitored for toxicities.

Animal Toxicity Findings: Toxicities observed with chronic administration in animals included severe anemia and thrombocytopenia; gastrointestinal, neurological and lymphoid system toxicities; and multifocal hemorrhage in the brain, eye and heart. At doses twice the recommended clinical dose, animals experienced profound hypotension and bradycardia resulting in myocardial damage and death.