Phase II Study of the Pan-Deacetylase Inhibitor Panobinostat in Combination With Bortezomib and Dexamethasone in Relapsed and Bortezomib-Refractory Multiple Myeloma (PANORAMA 2)

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Multiple Myeloma

Disease status

• Multiple myeloma (MM) remains an incurable disease with a high unmet need for pts in the relapsed and refractory treatment setting.

• Novel agents, including the first in class proteasome inhibitor bortezomib (BTZ) and immunomodulatory drugs (IMiDs) lenalidomide and thalidomide, are commonly used for MM treatment.

• Pts with MM refractory to both BTZ and IMiDs have very poor prognosis.
  
  — Median overall survival and event-free survival of 9 and 5 mos, respectively.
  
  — Response rate for subsequent BTZ-containing regimen is 20%.

Panobinostat

*Potent, oral pan-deacetylase inhibitor (pan-DACi)*

- Panobinostat has low nanomolar activity against all class I, II, and IV histone deacetylase (HDAC) enzymes\(^1\)
- Panobinostat increases acetylation of proteins involved in multiple oncogenic pathways\(^1\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class I</th>
<th>IC(_{50}) of Enzyme Inhibition [nM]</th>
<th>Class II</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDAC1</td>
<td>HDAC2</td>
<td>HDAC3</td>
<td>HDAC8</td>
</tr>
<tr>
<td>Panobinostat(^1)</td>
<td>2.5</td>
<td>13.2</td>
<td>2.1</td>
<td>277</td>
</tr>
<tr>
<td>Vorinostat(^1)</td>
<td>75.5</td>
<td>362</td>
<td>57.4</td>
<td>1069</td>
</tr>
<tr>
<td>Romidepsin(^2)</td>
<td>7</td>
<td>28</td>
<td>103</td>
<td>34</td>
</tr>
</tbody>
</table>

Implicated as potential tumor targets in MM

Panobinostat + Bortezomib
Synergistic anti-myeloma activity

- Inhibition of the aggresome and proteasome pathways causes a buildup of intracellular misfolded cytotoxic proteins, leading to MM cell apoptosis\textsuperscript{1-4}

\begin{itemize}
\item Unfolded/misfolded proteins
\item Ubiquitinated protein aggregates
\item Bortezomib
\item Aggresome formation
\item Dynein
\item HDAC6
\item Microtubule
\item Lysosomal degradation
\end{itemize}

Panobinostat + Bortezomib
Activity in BTZ-refractory myeloma patients

In a phase Ib trial, the combination of panobinostat and BTZ demonstrated efficacy in MM pts, including a subset of pts refractory to BTZ therapy.\(^1\)

CR (-IF), immunofixation-negative complete response; MR, minimal response; PR, partial response; sCR, stringent CR; VGPR, very good PR.

PANORAMA 2 Study Design

Phase II, Simon 2-stage study in BTZ-refractory MM

BTZ-refractory disease defined as relapse on or within 60 days of last BTZ-containing line of therapy

- Adult pts
- Relapsed and BTZ-refractory MM
- ≥ 2 prior lines of therapy
- Exposed to IMiDs

Screening

Treatment Phase 1
Eight 3-wk cycles

- Panobinostat
- BTZ
- Dexamethasone

After 8 cycles, continuation into Treatment Phase 2 in pts with clinical benefit

Treatment Phase 2
6-wk cycles until PD

- Panobinostat
- BTZ
- Dexamethasone

Primary endpoint: overall response rate (CR + nCR + PR)°

° Response measured according to modified European Group for Blood and Marrow Transplantation 1998 criteria. CR, complete response; nCR, near CR; PD, disease progression; PR, partial response.
PANORAMA 2

Dosing schedule

Treatment Phase 1 (Cycles 1-8)

- PAN
- BTZ
- Dex

**Week 1**
- PAN: Panobinostat 20 mg oral
- BTZ: Bortezomib 1.3 mg/m² IV
- Dex: Dexamethasone 20 mg oral

**Week 2**

**Week 3**

Treatment Phase 2 (Cycle 9+)

**Week 1**
- PAN: Panobinostat 20 mg oral
- BTZ: Bortezomib 1.3 mg/m² IV
- Dex: Dexamethasone 20 mg oral

**Week 2**

**Week 3**

**Week 4**

**Week 5**

**Week 6**
Study Design

Objectives and assessments

- **Primary efficacy endpoint**
  - Overall response rate (CR + nCR + PR)

- **Secondary endpoints include:**
  - MR, TTR, DOR (from first PR or better)
  - PFS, TTP, OS
  - AEs by CTCAE v4.0, and SAE, ECG, and peripheral neuropathy assessments (FACT/GOG-NTX v4.0)

- **Efficacy assessment by modified EBMT and Uniform Criteria**
  - Disease assessments performed every 3 wks
  - Response confirmed after 6 wks
  - Pts who discontinue treatment for reasons other than PD will have assessments every 6 wks until PD or death

- **ECG monitoring performed throughout the first 8 cycles**

CTCAE, Common Terminology Criteria for Adverse Events; EBMT, European Bone Marrow Transplant organization.

Patient Characteristics
A heavily pretreated, BTZ-refractory patient population

N = 55

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male, %</td>
<td>53/47</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>61 (41-88)</td>
</tr>
<tr>
<td>ECOG performance status 0-1 / 2 / missing, %</td>
<td>93 / 5 / 2</td>
</tr>
<tr>
<td>Prior regimens, median (range)</td>
<td>4 (2-14)</td>
</tr>
<tr>
<td>Prior autologous stem cell transplant, n (%)</td>
<td>35 (64)</td>
</tr>
<tr>
<td>Prior BTZ regimens, median (range)</td>
<td>2 (1-6)</td>
</tr>
</tbody>
</table>

- Pts received multiple prior regimens, including multiple prior BTZ combinations
## Preliminary Response Data

### Activity in BTZ-refractory MM patients

<table>
<thead>
<tr>
<th>Best confirmed response (confirmed at 6 wks)</th>
<th>N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (CR + nCR + PR)</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>–</td>
</tr>
<tr>
<td>Near complete response</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (25%)</td>
</tr>
<tr>
<td><strong>Clinical benefit (CR + nCR + PR + MR)(^1-^3)</strong></td>
<td><strong>27 (49%)</strong></td>
</tr>
<tr>
<td>Minimal response</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

- Responses were typically observed after 1 to 2 cycles
- Stable disease observed in 2 pts; progressive disease in 10 pts

Patient Disposition  

*Prolonged study participation*

- Pts have been on study an average of 4.7 mos (range, < 1-12.5)
- 16 pts completed the first 8 cycles and entered treatment phase 2
  - 10 pts still on study in treatment phase 2
  - 2 pts completed ≥ 12 cycles (48 wks)

<table>
<thead>
<tr>
<th>Patients ongoing</th>
<th>N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Off treatment</strong></td>
<td></td>
</tr>
<tr>
<td>In follow-up</td>
<td>24 (44%)</td>
</tr>
<tr>
<td>Off study</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Death</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Lost due to follow-up</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

N = 55

Patients ongoing 17 (31%)

Off treatment 38 (69%)

In follow-up 24 (44%)

Off study 14 (25%)

Death 11 (20%)

Withdraw consent 2 (4%)

Lost due to follow-up 1 (2%)
### Adverse Events

*Occurring in ≥ 5% (grade 3/4) of patients (n = 51)*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>32 (63%)</td>
<td>27 (53%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (63%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29 (57%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (37%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (59%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (20%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9 (18%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 (16%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>8 (16%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>8 (16%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (14%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (12%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>
Safety

Generally well tolerated with manageable AEs

- Thrombocytopenia, the most common grade 3/4 AE (53%), managed with dose reduction/interruption
  - Less thrombocytopenia observed in the 2 wks on/1 wk off schedule compared with the weekly schedule¹
  - No bleeding AEs in pts with thrombocytopenia

- Treatment-emergent peripheral neuropathy (24% overall), generally mild, with only one grade 3/4 event (2%)

- Fatigue and asthenia (63% and 14% overall), predominantly mild and managed with hydration, dose reduction, and supportive care

- No reports of QTc prolongation

Case Study

58-year-old man with Durie-Salmon stage IIIa λ chain MM

- **History**
  - Right sternal plasmacytoma with multiple lytic bone lesions
  - 30% plasma cells in marrow; normal cytogenetics, counts, kidney function

- **Treatment**

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>Best Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2005</td>
<td>Radiation to sternum; Thal/Dex</td>
<td>PR</td>
</tr>
<tr>
<td>March 2006</td>
<td>Consolidation (high-dose melphalan + ASCT)</td>
<td>VGPR</td>
</tr>
<tr>
<td>January 2009</td>
<td>Len/Dex started after progression</td>
<td>PD</td>
</tr>
<tr>
<td>May 2009</td>
<td>RVD (6 cycles)</td>
<td>SD (→PD)</td>
</tr>
<tr>
<td>November 2009</td>
<td>CyBorD (8 cycles)</td>
<td>SD (→PD)</td>
</tr>
<tr>
<td>March 2010</td>
<td>Thal/Dex (4 cycles)</td>
<td>PD</td>
</tr>
<tr>
<td>October 2010</td>
<td>Enrolled in PANORAMA 2</td>
<td>nCR in November 2010</td>
</tr>
<tr>
<td>December 2011</td>
<td>Ongoing on PANORAMA 2 (cycle 14)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions & Future Directions

• Panobinostat synergizes with BTZ in recapturing responses in heavily pretreated, BTZ-refractory MM pts
  – All pts BTZ refractory: median of 4 prior regimens
  – Clinical benefit rate: 49% (2 nCR, 14 PR, 11 MR)
  – 16 pts completed 8 cycles, 2 pts completed ≥ 12 cycles
  – Treatment ongoing in 17 pts

• Combination generally well tolerated
  – Most common hematologic grade 3/4 AEs proved manageable with dose interruption/reduction
  – Intermittent panobinostat dosing reduced thrombocytopenia

• This study and the phase III PANORAMA 1 trial will further define the role of panobinostat combined with BTZ + Dex in the care of MM pts

• Panobinostat is also being explored in combinations with other agents for MM treatment, including RVD, pomalidomide, carfilzomib, and thalidomide
Acknowledgments

• Patients and their Families
• Investigators and their Clinical Teams
• Preclinical Teams including Teru Hideshima, James Bradner, Enrique Ocio, Laurence Catley, Jesus San Miguel, and Kenneth Anderson
• Study Sites and their Staff

Duke University Medical Center
Cristina Gasparetto
Juliana Weaver Gardner

Georgia Health Sciences University
Jillella Anand
Jo Williams
Robin Dobbins
Rosemary Chandler

Dana Farber Cancer Institute
Paul Richardson
Robert Schlossman
Heather Goddard
Kathy Colson

MD Anderson Cancer Center
Donna Weber
Ana Georgina Melendez
Christine Samuel

Moffitt Cancer Center
Melissa Alsina
Jennifer Paleveda-Pena

Stanford University
Steven Coutre
Nini Estevez

Emory University
Sagar Lonial
Renee Smith

Montefiore Medical Center
Olga Derman
Joe Zaino

Barbara Ann Karmanos Cancer Institute
Jeffrey Zonder
Zhiwe Sun
Carmen Hughes

Somerset Hematology Oncology Associates
Steven Young
Demmie Aguilar

Froedtert & The Medical College of Wisconsin
Hari Parameswaran
Paulette Jacobs
Jordan Anderson

Vanderbilt University Medical Center
Kassim Adetola
Violeta Vartic
Micci Simmons