5 Minute JournalClub

Key ASH Presentations
Issue 3, 2012

Deacetylase Inhibitors Vorinostat or Panobinostat for Relapsed/ Refractory Multiple Myeloma

For more visit ResearchToPractice.com/5MJCASH2012

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Develop an understanding of the emerging efficacy and toxicity data with novel agents in order to inform future patients with newly diagnosed and relapsed or refractory multiple myeloma about protocol and nonprotocol options.
- Assess the clinical benefits and risks of deacetylase inhibitors in combination with proteasome inhibitors for relapsed and refractory multiple myeloma.
- Evaluate the preliminary safety profiles and response outcomes observed in studies of next-generation proteasome inhibitors for patients with relapsed or refractory and previously untreated multiple myeloma.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2012/3/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Sagar Lonial, MD
Professor
Vice Chair of Clinical Affairs
Director of Translational Research, B-Cell Malignancy Program
Department of Hematology and Medical Oncology
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Merck and Company Inc, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc.

Paul G Richardson, MD
Associate Professor of Medicine
Harvard Medical School
Clinical Director of the Jerome Lipper Center for Multiple Myeloma
Dana-Farber Cancer Institute
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company, Celgene Corporation, Keryx Biopharmaceuticals Inc, Millennium: The Takeda Oncology Company, Nereus Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abbott Laboratories, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics and Teva Pharmaceuticals.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/ Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Last review date: January 2012
Expiration date: January 2013

5 MinuteJournalClub

Key ASH Presentations
Issue 3, 2012

To go directly to slides and commentary for this issue, **click here**.


Paul G Richardson, MD

When the New England Patriots' Rob Gronkowski dived futilely for Tom Brady's final "Hail Mary" pass in Sunday night's Super Bowl, I flipped off the TV and sat down with my notes from a recent conversation with Gronk's Boston neighbor Dr Paul Richardson, a dynamic Englishman from Surrey and a profoundly knowledgeable member of Dana-Farber's powerhouse myeloma team. Dr Richardson can always be counted on to contribute a plethora of ASH papers and presentations (he had 6 orals in December), and this was part of the reason I wanted his take on the hottest new myeloma data emerging at the conference. Our recent 90-minute breathless run through the happenings was mainly focused on emerging and currently unapproved agents, and as is always the case with myeloma nowadays, there was a lot to talk about.

1. Carfilzomib

As Dr Richardson was the lead investigator on the landmark front-line Phase II trial of RVD (lenalidomide, bortezomib, dex), I was particularly interested in his perspective on Dr Andrzej Jakubowiak's second presentation of data on the so-called CRd regimen (lenalidomide, carfilzomib, low-dose dex) also in this setting. Like RVD, CRd was shown to have response rates approaching 100%, so perhaps it was to be expected that our conversation quickly led to a review of the toxicity profile of this irreversible proteasome inhibitor. While Dr Richardson noted the impressive reduced risk of peripheral neuropathy (PN), he also commented on 2 other somewhat unexpected side effects of CRd, specifically dyspnea (12% of patients) that may be cardiac related due to fluid challenge and renal impairment and hyperglycemia (76%) that may be greater than would be expected from corticosteroids alone. Regardless, Dr Richardson thinks CRd may become a critical alternative for many patients up front, but right now he, like most investigators, believes carfilzomib clearly offers an important alternative in later-line disease.

2. MLN9708

Dr R called this oral boronic acid peptide proteasome inhibitor similar to bortezomib "the myeloma news of the meeting" and labeled the related ASH data set evaluating the agent up front combined with len/dex as "a knockout...huge." This once- or twice-weekly pill causes some skin toxicity but no PN, and when combined with len/dex as an all-oral up-front regimen, responses were observed in all 15 patients. Similarly, Dr Richardson presented data in the relapsed setting where useful activity was seen "even in the ninth inning," and it seems likely that MLN9708 will soon get a catchier moniker and quickly move forward in development.

3. Pomalidomide

This third-generation IMiD already has an impressive safety and efficacy track record, and significant responses have been observed in patients with disease progressing on lenalidomide and/or thalidomide. At ASH, more encouraging data were reported that further illustrate the striking activity of this agent alone or with dex and shed light on potential dosing strategies that might be appropriate for younger patients (continuous) and older, more frail individuals (3 weeks on, 1 week off). Either way it's a therapy most investigators — including Dr R — are ready to use if approved.

4. Elotuzumab

At ASH, Dr Sagar Lonial presented an intriguing data set on this humanized monoclonal antibody targeting human CS1, a cell surface glycoprotein that is highly expressed in more than 95% of patients with myeloma. Elotuzumab acts primarily through NK cell-mediated ADCC that may be compromised because of underlying immune dysfunction in myeloma, but in vitro work suggests synergistic activity when combined with the immune modulator lenalidomide. In this Phase II study in relapsed/refractory disease the elotuzumab/lenalidomide/low-dose dex combination was well tolerated and highly active (82% response rate) and as such has now moved into Phase III testing.

5. HDAC inhibitors

Data sets with vorinostat and panobinostat (both in combination with bortezomib) were reported at ASH, and although Dr Richardson and others believe there is a future role for this approach, the optimal doses, schedules and partner agents have yet to be defined.

Next we journey back to the solid tumor world and investigator perspectives on daily management of a common tumor that could dearly benefit from some myeloma-like progress...cancer of the pancreas.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Deacetylase Inhibitors Vorinostat or Panobinostat for Relapsed/Refractory Multiple Myeloma

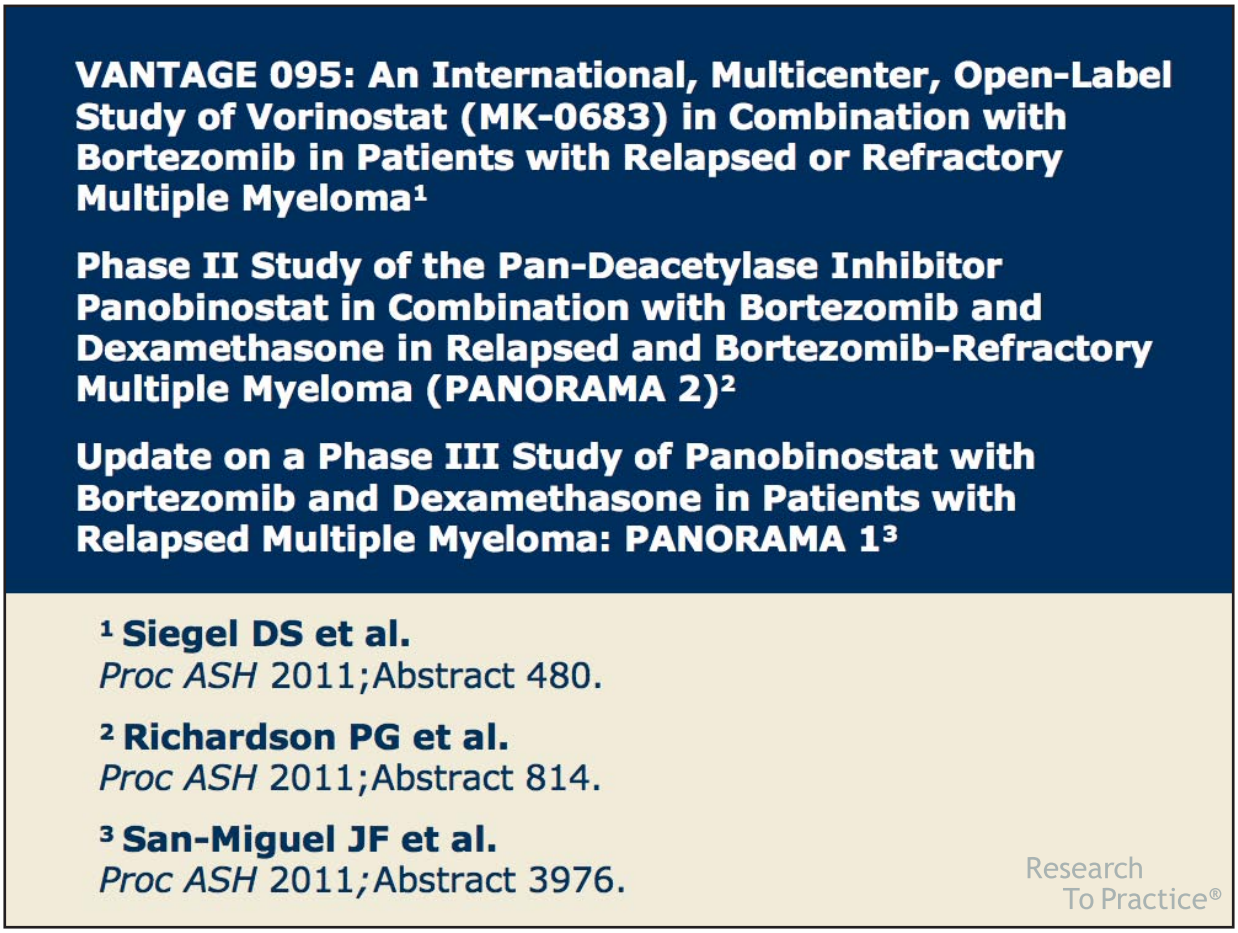
Presentations discussed in this issue

Siegel DS et al. **Vantage 095: Vorinostat in combination with bortezomib in salvage multiple myeloma patients: Final study results of a global Phase 2b trial.** *Proc ASH* 2011;**Abstract 480**.

Richardson PG et al. **Phase II study of the pan-deacetylase inhibitor panobinostat in combination with bortezomib and dexamethasone in relapsed and bortezomib-refractory multiple myeloma (PANORAMA 2).** *Proc ASH* 2011;**Abstract 814**.

San-Miguel JF et al. **Update on a Phase III study of panobinostat with bortezomib and dexamethasone in patients with relapsed multiple myeloma: PANORAMA 1.** *Proc ASH* 2011;**Abstract 3976**.

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Paul G Richardson, MD (1/24/12)



VANTAGE 095: An International, Multicenter, Open-Label Study of Vorinostat (MK-0683) in Combination with Bortezomib in Patients with Relapsed or Refractory Multiple Myeloma

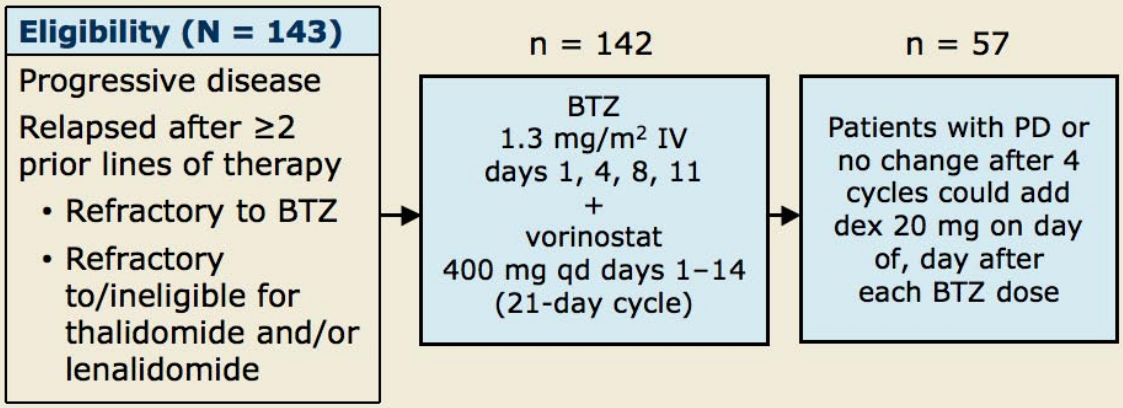
Siegel DS et al.
Proc ASH 2011;Abstract 480.

Background

- Despite the significant advances in multiple myeloma (MM) treatment in the past decade, all patients eventually experience relapse from successive treatment regimens with progressively shorter response durations (*Blood* 2007;110:3557).
- Outcomes are poor for patients who received multiple therapies and whose disease is relapsed and refractory following bortezomib and lenalidomide, with the estimated median survival being approximately 9 months (*Haematologica* 2010;Abstract 0376).
- Epigenetic changes, such as acetylation of histone or nonhistone proteins, are recognized as important factors in cancer development.
- Vorinostat is a histone deacetylase (HDAC) inhibitor that blocks the enzymatic activity of HDAC1, HDAC2, HDAC3, and HDAC6.

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

VANTAGE 095: Study Design



Primary Endpoint: Overall response rate (ORR)

Secondary endpoints: Overall survival (OS), progression-free survival, time to progression, duration of response (DOR), safety

BTZ = bortezomib; PD = progressive disease; Dex = dexamethasone

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Research To Practice®

Efficacy (IMWG criteria)

Baseline factor (N = 136)*	ORR	CBR	OS
Prior lines of therapy			
<5 (n = 72)	18%	35%	10.9 mo
≥5 (n = 64)	17%	30%	11.4 mo
Previous BTZ regimens			
1 (n = 65)	18%	37%	11.7 mo
>1 (n = 71)	17%	28%	10.8 mo
Previous IMiD regimens			
≤2 (n = 85)	22%	38%	11.2 mo
>2 (n = 50)	10%	24%	10.9 mo

Median overall survival = 11.2 mo
Median progression-free survival = 3.13 mo

* Six patients missing post-baseline assessment
CBR = clinical benefit rate

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Research To Practice®

Select Adverse Events (AEs)

Adverse event (N = 142)	Any grade	Grade 1/2	Grade 3/4
Hematologic (≥20%)			
Anemia	52%	14%	38%
Thrombocytopenia	70%	2%	68%
Neutropenia	37%	5%	32%
Nonhematologic (≥25%)			
Nausea	57%	50%	7%
Diarrhea	54%	37%	17%
Fatigue	49%	36%	13%
Vomiting	37%	33%	4%
Pyrexia	27%	23%	4%

- Other AEs of interest: Neuropathy, Grade 1/2 = 20%, Grade 3/4 = 2%; febrile neutropenia, Grade 3/4 = 4%
- Deaths due to AE = 4%, deaths due to drug-related AE < 1%

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Research To Practice®

Author Conclusions

- The combination of vorinostat and bortezomib is active in patients whose disease is considered refractory to prior bortezomib and IMiDs:
  - ORR = 17%; CBR by IMWG criteria = 31%
  - Median DOR of 6.3 months (CBR)
- The median OS was 11.2 months with a 2-year OS rate of 32%.
- The combination is generally well tolerated in patients with heavily pretreated disease, with 27% of patients completing ≥8 cycles.
- The combination of vorinostat and bortezomib may offer a new treatment option for patients with heavily pretreated, double-refractory myeloma.

Siegel DS et al. *Proc ASH* 2011;Abstract 480.

Research To Practice®

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

Richardson PG et al.

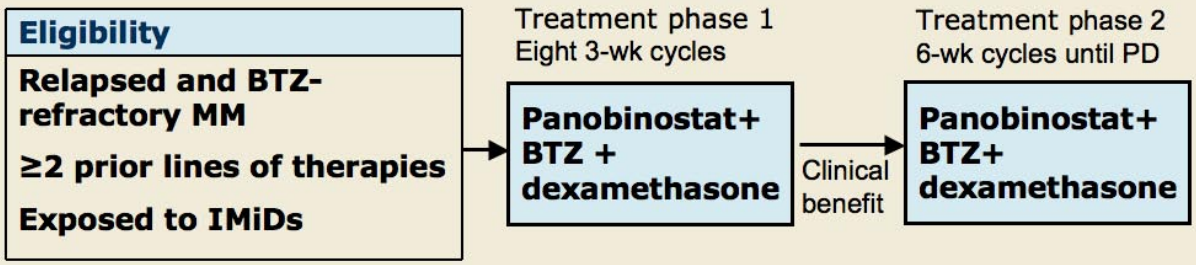
Proc ASH 2011;Abstract 814.

Background

- The proteasome inhibitor bortezomib (BTZ) and the immunomodulatory drug (IMiD) lenalidomide are commonly used for multiple myeloma (MM) treatment (*N Engl J Med* 2003;348:2609; *N Engl J Med* 2007;357:2123)
- Patients with MM refractory to both BTZ and IMiDs have a very poor prognosis (*Leukemia* 2012;26:149)
- Panobinostat is a potent pan-deacetylase inhibitor that increases acetylation of proteins involved in multiple oncogenic pathways (*Cancer Lett* 2009;280:233).
- Panobinostat and BTZ have synergistic antimyeloma activity via targeting of the aggresome and proteasome pathways (*Blood* 2006;108:3441).
- In a Phase Ib trial, the combination of panobinostat and BTZ demonstrated efficacy in patients with MM, including in a subset of patients with disease refractory to BTZ therapy (European Hematology Association 2011;Abstract 0314).
- **Current study objective**: Conduct a single-arm, open-label, Phase II study evaluating the efficacy and safety of panobinostat, BTZ and dexamethasone in patients with BTZ-refractory MM.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

PANORAMA 2 Study Design and Baseline Characteristics



Baseline characteristics	N = 55
Median age (years)	61
ECOG performance status 0-1/2/missing (%)	93/5/2
Median prior regimens	4
Median prior BTZ regimens	2
Prior autologous stem cell transplant (%)	35

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Research To Practice®

Preliminary Response Data

Best confirmed response*	N = 55
Overall response	29%
Complete response (CR)	—
Near complete response (nCR)	4%
Partial response (PR)	25%
Minimal response (MR)	20%
Clinical benefit (CR + nCR + PR + MR)	49%
Very good partial response	6%

* Confirmed at 6 wk
- Responses typically observed after 1-2 cycles
- Stable disease: 2 patients; progressive disease: 10 patients

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Research To Practice®

Select Adverse Events

Adverse events (n = 51)	All	Grade 3/4
Thrombocytopenia*	63%	53%
Fatigue	63%	16%
Diarrhea	57%	14%
Anemia	37%	16%
Nausea	59%	6%
Neutropenia	20%	12%
Hypotension	18%	6%
Pneumonia	16%	14%

* Thrombocytopenia managed with dose reduction/interruption.
- Treatment-emergent peripheral neuropathy (24% overall) was generally mild, only 2% Grade 3/4.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Research To Practice®

Author Conclusions

- Panobinostat synergizes with BTZ in recapturing responses in patients with heavily pretreated, BTZ-refractory MM.
  - Clinical benefit rate = 49%
  - Treatment ongoing in 17 patients
- The combination of panobinostat and BTZ is generally well tolerated.
  - Most common hematologic Grade 3/4 AEs proved manageable with dose interruption/reduction.
- This study and the Phase III PANORAMA 1 trial will further define the role of panobinostat combined with BTZ and dexamethasone in the care of patients with MM.

Richardson PG et al. *Proc ASH* 2011;Abstract 814.

Research To Practice®

Update on a Phase III Study of Panobinostat with Bortezomib and Dexamethasone in Patients with Relapsed Multiple Myeloma: PANORAMA 1

San-Miguel JF et al.
Proc ASH 2011;Abstract 3976.

Research To Practice®

PANORAMA 1 Study Design

Target Accrual: 672 (Closed)

Eligibility

- Relapsed/refractory MM
- 1-3 prior lines of therapy
- Prior BTZ therapy allowed
- BTZ-refractory MM (failure to achieve minimal response or disease progression within 60 days of last BTZ-containing regimen) not permitted

R

Treatment phase 1
BTZ twice wkly

Panobinostat + BTZ + DEX
3-wk cycles x 8

Clinical benefit

Treatment phase 2
BTZ once wkly

Panobinostat + BTZ + DEX
6-wk cycles x 4

Placebo+ BTZ + DEX

Primary endpoint: Progression-free survival
Secondary endpoint: Overall survival

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Research To Practice®

Adverse Events (Abstract Only)

Adverse events*	All grades	Grade 3/4
Diarrhea	36%	10%
Thrombocytopenia	41%	29%
Anemia	24%	10%
Fatigue	24%	9%
Neutropenia	12%	8%
Peripheral neuropathy	19%	3%

* n = 267 patients who received 1 dose of treatment

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Author Conclusions

- Preliminary analysis of pooled safety data (blinded) from the first 267 patients treated in PANORAMA 1 demonstrated no new or unexpected AEs.
- The results of PANORAMA 1 along with PANORAMA 2 will help determine the potential role of panobinostat in the treatment of patients with relapsed and refractory MM.

San-Miguel JF et al. *Proc ASH* 2011;Abstract 3976.

Research To Practice®

Investigator Commentary: Future Role of Deacetylase Inhibitors — Vorinostat and Panobinostat — in MM

Deacetylase inhibitors definitely have a role in MM treatment in my view, especially in combination, but we need to study all the agents and know where to administer them, at what dose and schedule and with what partner. Agents like vorinostat and panobinostat are in the same class, and GI side effects, fatigue and thrombocytopenia are a potential challenge with this group. Panobinostat partners very well with bortezomib in combination with dexamethasone, and efficacy has been seen even in patients with bortezomib-refractory disease, with a Phase III comparative trial approaching completion. Conversely, vorinostat is promising in combination with lenalidomide, as well as with bortezomib, although results from the Phase III VANTAGE trial were somewhat disappointing, perhaps due to difficulties with the optimal dose and schedule used for these 2 drugs in that particular study. Romidepsin is very active in combination with bortezomib, with fatigue and thrombocytopenia but not GI toxicity as dose-limiting side effects. Studies combining it with lenalidomide are now underway. Finally, an HDAC6-specific inhibitor (ACY-1215) has just entered clinical trial as a single agent and shows early promise, especially in terms of tolerability.

Interview with Paul G Richardson, MD, January 24, 2012

Research
To Practice®