

Panobinostat for the Treatment of Multiple Myeloma

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Abstract

Panobinostat is a potent oral deacetylase inhibitor that alters gene expression through epigenetic mechanisms and inhibits protein degradation. It was recently approved by the FDA and EMA for use in combination with bortezomib and dexamethasone in patients with multiple myeloma who have received ≥ 2 prior regimens, including bortezomib and an immunomodulatory drug. Panobinostat was approved based on results from the phase III PANORAMA 1 trial in patients with relapsed or relapsed and refractory multiple myeloma, which showed that panobinostat

plus bortezomib and dexamethasone significantly extended progression-free survival (median, 12.0 months) compared with placebo plus bortezomib and dexamethasone (median, 8.1 months; $P < 0.0001$). Additional ongoing trials are evaluating panobinostat in combination with other partners in the relapsed/refractory and newly diagnosed treatment settings. This review focuses on panobinostat and its mechanism of action, pharmacokinetics, and clinical data in the treatment of relapsed or relapsed and refractory multiple myeloma. *Clin Cancer Res*; 21(21); 4767–73. ©2015 AACR.

Introduction

Multiple myeloma is a hematologic malignancy that accounts for approximately 1% of all neoplasms and 13% of hematologic malignancies (1). It is characterized by proliferation of clonal plasma cells within the bone marrow and extramedullary sites that in most instances secrete a monoclonal protein. Typical clinical characteristics include hypercalcemia, renal insufficiency, anemia, and bone disease ("CRAB" features). Other manifestations of the disease include increased risk of infection and peripheral neuropathy (2). It has been estimated there were 24,050 new cases of multiple myeloma and 11,090 deaths due to multiple myeloma in the United States in 2014 (1).

Survival of patients with multiple myeloma has significantly improved over the past decade with the introduction of the proteasome inhibitors (PI) bortezomib and carfilzomib and immunomodulatory drugs (IMiD) thalidomide, lenalidomide, and pomalidomide (3, 4). However, these therapies are not curative, and nearly all patients with multiple myeloma eventually relapse and require further therapy. The prognosis among patients with disease refractory to IMiDs and PIs is poor; among this group, only approximately 22% respond to subsequent therapy, and among those who do respond, the median event-free survival is < 5 months and median overall survival (OS) is 9 months (3). Thus, there is a need for new treatments, particularly those with mechanisms of action that are distinct from those of IMiDs and PIs (4).

Panobinostat belongs to a novel class of compounds called deacetylase (DAC) inhibitors and was recently approved by the

FDA and EMA for use in combination with bortezomib and dexamethasone to treat patients with multiple myeloma who have received ≥ 2 prior regimens, including bortezomib and an IMiD. This review focuses on important clinical aspects of panobinostat, including its mechanism of action, pharmacokinetic profile, and clinical data derived from studies of the agent in relapsed or relapsed and refractory multiple myeloma.

Mechanism of Action

Panobinostat inhibits a broad range of DACs (Fig. 1), which are also known as histone DACs (HDAC) because histones were the first known targets of DACs. It is now known that DACs regulate the acetylation of approximately 1,750 proteins involved in diverse biologic processes, including DNA replication and repair, chromatin remodeling, gene transcription, cell-cycle progression, protein degradation, and cytoskeletal reorganization (5). Overexpression of DACs has been observed in multiple myeloma and is associated with poor outcomes (6).

Panobinostat is an inhibitor of all class I (HDACs 1, 2, 3, and 8), class II (HDACs 4, 5, 6, 7, 9, and 10), and class IV (HDAC 11) HDACs, with half maximal inhibitory concentrations in the nanomolar range for all class I, II, and IV HDACs. The potency of panobinostat was 10-fold greater for all HDACs compared with vorinostat, another pan-DAC inhibitor that was investigated for the treatment of multiple myeloma, and panobinostat is among the most potent pan-DAC inhibitors in clinical development (7, 8).

Panobinostat is thought to elicit antitumor activity primarily through epigenetic modulation of gene expression and inhibition of protein metabolism. Inhibition of class I HDACs, which target histones and transcription factors such as p53, may help reactivate epigenetically silenced tumor suppressor genes (e.g., *p21*; refs. 9, 10) and modify gene expression via inhibition of signal transducer and activator of transcription 3, Akt, and hypoxia-inducible factor 1 α (8).

Panobinostat has also been shown to act synergistically with the PI bortezomib. This synergy can be explained in part via the

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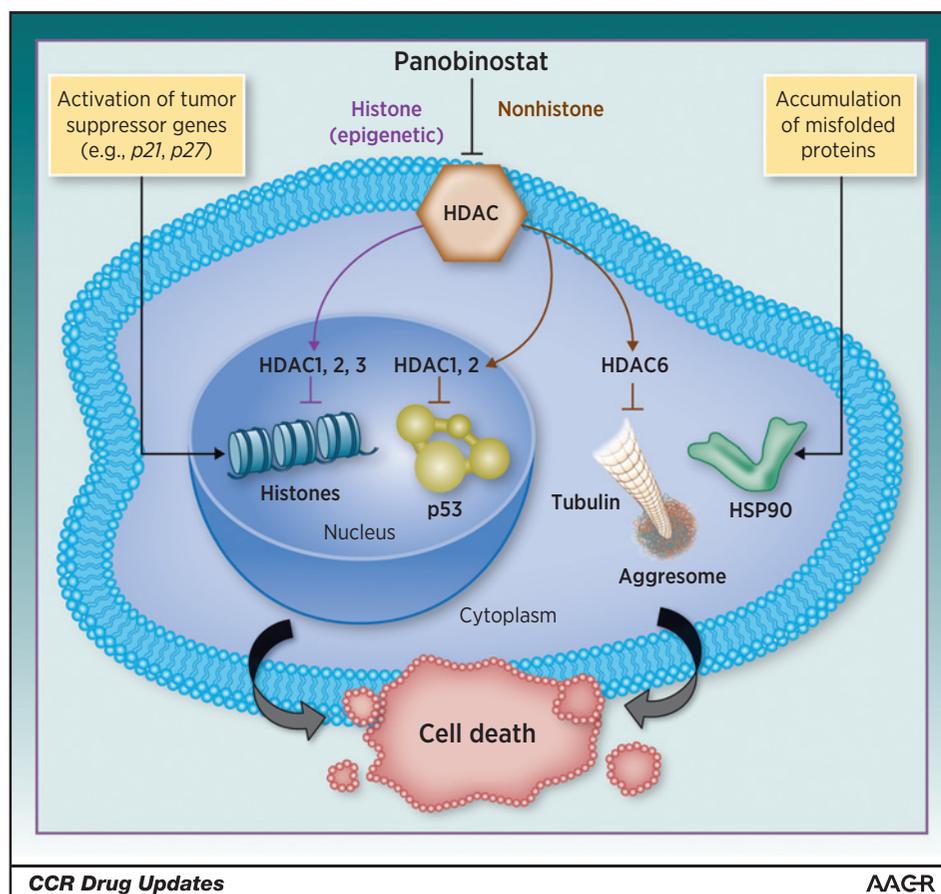


Figure 1. Panobinostat inhibits a broad range of DACs that target histone and nonhistone proteins implicated in epigenetic dysregulation and protein degradation. Adapted with permission from Novartis Pharmaceuticals Corporation (ref. 39).

effects of panobinostat on protein degradation. Multiple myeloma cells have high levels of protein turnover and hence a susceptibility to PIs which inhibit metabolism and elimination of proteins generated within the cell and through this mechanism produce a proapoptotic signal. However, there is an alternative pathway of protein metabolism wherein if the proteasome cannot eliminate these proteins quickly enough, the proteins form aggregates known as aggresomes that are transported by microtubules to an autophagosome, where they are degraded by lysosomes. HDAC6 interaction with tubulin and the motor protein, dynein, is critical to the transport of these protein aggregates for degradation. Inhibition of HDAC6 leads to hyperacetylated microtubules and inefficient aggresome-mediated degradation. Bortezomib inhibits proteasome degradation of protein and induces aggresome formation; coadministration of bortezomib and panobinostat, and simultaneous inhibition of the proteasome and aggresome pathways, results in synergistic cytotoxicity (11). In addition, *in vitro* and *in vivo* models of multiple myeloma have demonstrated that panobinostat in combination with bortezomib plus dexamethasone or the IMiD lenalidomide plus dexamethasone enabled dysregulation of additional genes that were not altered by doublet therapy alone (12).

Pharmacokinetics

Panobinostat was rapidly absorbed following a single 20-mg oral dose, with a time to maximum absorption of 2 hours. The

median maximum concentration was 21.2 ng/mL, and the median area under the curve was 96 ng·h/mL (13).

Panobinostat was extensively metabolized into at least 77 metabolites. Contributions of the liver and kidney to the elimination of panobinostat were comparable, with mean percentages of unchanged panobinostat recovered in urine and feces of only approximately 2% and 3%, respectively. Both cytochrome P450 (CYP) and non-CYP enzymes may play a significant role in panobinostat metabolism, with minor contributions from CYP2D6 and CYP2C19. The primary metabolic pathways of panobinostat are reduction, hydrolysis, oxidation, and glucuronidation processes. The terminal elimination half-life of panobinostat is approximately 30 hours (13).

Coadministration of bortezomib (1.3 mg/m²) and panobinostat (20 mg) did not significantly affect the mean exposure of either agent. Dexamethasone (20 mg) reduced panobinostat exposure by approximately 20% (14).

Clinical Development

The development of panobinostat for the treatment of multiple myeloma was primarily based on five clinical trials from phase I to phase III that included 1,099 patients in total. One study included patients with advanced hematologic malignancies, while the others included only patients with multiple myeloma.

A single-arm, open-label, multicenter phase Ia/II study was conducted to determine the maximum tolerated dose (MTD) of

panobinostat administered via two dosing schedules: three times per week every week or every other week. The study included 176 adult patients with hematologic malignancies that had progressed on or after available standard treatments or for whom no standard therapy existed. In patients with multiple myeloma or lymphoma, 40 mg of panobinostat three times weekly and 60 mg three times every other week were the recommended phase II doses for the two dosing schedules. Among the patients with multiple myeloma ($n = 12$), 1 achieved a partial response. Overall, common panobinostat-related grade 3/4 adverse events (AE) included thrombocytopenia (42%), fatigue (21%), and neutropenia (21%). The most common dose-limiting toxicities included thrombocytopenia, fatigue, and cardiac-related events (15).

The safety and efficacy of panobinostat monotherapy were further investigated in a single-arm, open-label, multicenter phase II study in 38 adult patients with symptomatic multiple myeloma who had received ≥ 2 prior lines of therapy (median, 5) and who had disease refractory to their most recent line of therapy. Panobinostat was administered at a dose of 20 mg three times weekly until disease progression, intolerance, or withdrawal of consent. The activity of panobinostat monotherapy was modest, with 1 patient achieving partial response, 1 achieving minimal response, and 9 achieving stable disease. Common grade 3/4 AEs included neutropenia (32%), thrombocytopenia (26%), and anemia (18%). One patient had a single episode of Fridericia corrected QT (QTcF) interval prolongation of >480 ms, and 2 patients experienced a single >60 -ms increase in QTcF from baseline (16).

Because panobinostat monotherapy had only modest activity in multiple myeloma but showed synergy when administered in combination with bortezomib in a preclinical study, a phase Ib dose-escalation and dose-expansion study assessing this combination was conducted in 63 adult patients with relapsed or relapsed and refractory multiple myeloma. In the dose-escalation phase ($n = 47$), panobinostat was administered three times per week at a starting dose of 10 mg and bortezomib was administered intravenously two times per week for 2 weeks at a starting dose of 1.0 mg/m^2 during each 3-week cycle. At the investigator's discretion, patients could also receive 20 mg of dexamethasone on the day of and day after bortezomib administration. The MTD was established at 20 mg of panobinostat plus 1.3 mg/m^2 of bortezomib. The overall response rate (ORR) was 45% among all patients and 53% among those who received the MTD. Responses in the MTD cohort were durable, with a median duration of response of 509 days. Common grade 3/4 AEs included thrombocytopenia (85%), neutropenia (64%), and asthenia (30%). Only 1 patient experienced a prolonged QT interval; 2 patients each had a myocardial infarction (14).

For the dose-expansion phase ($n = 15$), a noncontinuous dosing schedule (2 weeks on, 1 week off) was chosen to reduce the risk of thrombocytopenia and the need for dose interruptions. In addition, dexamethasone was given to all patients based on preclinical (12) and emerging clinical efficacy data. The ORR in the dose-expansion phase was 73%, including 20% who achieved at least a very good partial response. Of note, responses were observed in some patients with bortezomib-refractory and bortezomib and IMiD-refractory disease. Common grade 3/4 AEs in the dose-expansion phase were thrombocytopenia (67%), neutropenia (47%), diarrhea (20%), and fatigue (20%; ref. 14). These results warranted further development of the panobinostat-bortezomib-dexamethasone combination in the PANobinostat ORAL in Multiple Myeloma (PANORAMA) program.

PANORAMA 2 was a single-arm, open-label, multicenter, phase II study of panobinostat in combination with bortezomib and dexamethasone in 55 adult patients with bortezomib-refractory multiple myeloma. Patients had received ≥ 2 prior regimens (median, 4; range, 2–11); 98.2% had received prior lenalidomide in addition to having disease refractory to bortezomib. The study consisted of two treatment phases (TP); TP1 consisted of eight 3-week cycles and TP2 consisted of 6-week cycles until disease progression, death, toxicity, or withdrawal of consent. During both phases, patients received 20 mg of panobinostat three times per week using a 2-weeks-on, 1-week-off schedule. Patients also received 1.3 mg/m^2 of intravenous bortezomib two times per week during the first 2 weeks of each cycle in TP1 and once weekly during weeks 1, 2, 4, and 5 of each cycle during TP2. During both phases, patients received dexamethasone the day of and after bortezomib administration (17).

Responses included near complete (2%), partial (33%), and minimal (18%) responses for an ORR of 35% and a clinical benefit rate (CBR) of 53% (17). Among the 14 patients with high-risk cytogenetics—defined as $\text{del}(17p)$, $t(4;14)$, or $t(14;16)$ —the ORR was 43% and the CBR was 71%; among the 8 patients who had $\text{del}(17p)$, the ORR was 38% and the CBR was 88% (18). The median progression-free survival (PFS) was 5.4 months (17), and the median OS was 17.5 months (18). These results provide proof of concept that panobinostat is able to revert bortezomib resistance in some myeloma patients. Common grade 3/4 AEs were thrombocytopenia (64%), diarrhea (20%), fatigue (20%), anemia (15%), neutropenia (15%), and pneumonia (15%). No significant cardiac abnormalities were observed. Four on-treatment deaths occurred, but none were assessed as treatment related (17).

PANORAMA 1 was a randomized, multicenter, placebo-controlled, double-blind phase III trial conducted in 768 adult patients with relapsed or relapsed and refractory multiple myeloma, excluding patients with primary- or bortezomib-refractory multiple myeloma, who had received one to three prior treatments (48% received ≥ 2 prior therapies). Patients were randomized to receive panobinostat ($n = 381$) or placebo ($n = 387$) in combination with bortezomib and dexamethasone. The treatment doses and schedule were identical to those used in PANORAMA 2 (17), except that TP2 was limited to four cycles (19).

Median PFS was significantly longer in the panobinostat arm (12.0 months) than in the placebo arm (8.1 months; $P < 0.0001$), and a subgroup analysis revealed a PFS benefit in all subgroups, including patients with prior bortezomib and/or IMiD treatment. A recent subanalysis has confirmed the clinical benefit in patients with prior exposure to bortezomib and IMiDs or bortezomib and IMiDs with ≥ 2 prior therapeutic regimens (20). These data supported the approval of the combination of panobinostat with bortezomib and dexamethasone by the FDA and the EMA. There was also a trend toward increased OS in the panobinostat arm versus the placebo arm (33.6 months vs. 30.4 months; $P = 0.26$) at an interim analysis. The ORRs for the two study arms were similar (61% vs. 55%; $P = 0.09$), but the rate of high-quality responses (complete and near-complete responses) was nearly twice as high in the panobinostat arm (28% vs. 16%; $P = 0.00006$). The median duration of response was 13.1 months versus 10.9 months in the panobinostat and placebo arms, respectively (19).

Grade 3/4 laboratory abnormalities and AEs were more common in the panobinostat arm and included thrombocytopenia

Table 1. Trials of FDA-approved novel agents for the treatment of relapsed or refractory multiple myeloma

Study name	Phase	N	Median age, y	Number of prior regimens	Treatment	Response rates	Survival	Reference
Bortezomib (BTZ)								
APEX	III	333	62 (10th, 90th percentiles, 48, 74)	Median, 2 (range, 1-4+)	BTZ	ORR: 38%; CR: 6%; PR: 32%	1-y OS: 80%	(30)
MMY-3021	III	74	64.5 (range, 38-86)	1 prior: 65%; >1 prior: 35%	i.v. BTZ	ORR: 42%; CR: 8%; PR: 34%	PFS: 8.0 mo 1-y OS: 76.7%	(25)
MMY-3021	III	148	64.5 (range, 42-88)	1 prior: 62%; >1 prior: 38%	s.c. BTZ	ORR: 42%; CR: 6%; PR: 36%	PFS: 10.2 mo 1-y OS: 72.6%	(25)
Lenalidomide (Len)								
MM-009	III	177	64 (range, 36-86)	1 prior: 38.4%; >1 prior: 61.6%	Len-Dex	ORR: 61.0%; CR: 14.1%; nCR: 10.2%; PR: 36.7%	OS: 29.6 mo	(31)
MM-010	III	176	63 (range, 33-84)	1 prior: 31.8%; >1 prior: 68.2%	Len-Dex	ORR: 60.2%; CR: 15.9%; nCR: 8.5%; PR: 35.8%	OS: 36+ mo	(32)
NCT00378209	II	64	65 (range, 32-83)	Median, 2 (range, 1-3)	Len-BTZ-Dex	ORR: 64%; CR: 11%; nCR: 14%; VGPR: 3%; PR: 36%	PFS: 9.5 mo OS: 30 mo	(33)
Carfilzomib (CFZ)								
PX-171-003-A1	II	266	63 (range, 37-87)	Median, 5 (range, 1-20)	CFZ, 20 mg/m ² then 27 mg/m ²	ORR: 23.7%; CR: 0.4%; VGPR: 5.1%; PR: 18.3%	PFS: 3.7 mo OS: 15.6 mo	(34, 35)
NCT01351623	II	44	63 (range, 45-86)	Median, 5 (range, 1-11)	CFZ, 20 mg/m ² then 56 mg/m ² with slower (30-min) infusion	ORR: 55%; CR: 2%; VGPR: 21%; PR: 31%	PFS: 4.1 mo OS: 20.3 mo	(35)
ASPIRE	III	396	64 (range, 38-87)	Median, 2 (range, 1-3)	CFZ-Len-Dex	ORR: 87.1%; sCR: 14.1%; CR: 17.7%; VGPR: 38.1%; PR: 17.2%	PFS: 26.3 mo 2-y OS: 73.3%	(36)
Pomalidomide (Pom)								
MM-002	II	108	61 (range, 37-88)	>2 prior: 95%	Pom	ORR: 18%; CR: 2%; PR: 16%	PFS: 2.7 mo OS: 13.6 mo	(37)
MM-002	II	113	64 (range, 34-88)	>2 prior: 95%	Pom-Dex	ORR: 33%; CR: 3%; PR: 30%	PFS: 4.2 mo OS: 16.5 mo	(37)
MM-003	III	302	64 (range, 35-84)	Median, 5 (range, 2-14)	Pom-Dex	ORR: 31%; sCR or CR: 1%; VGPR: 5%; PR: 26%	PFS: 4.0 mo OS: 12.7 mo	(38)
Panobinostat (PAN)								
PANORAMA 2	II	55	61 (range, 41-88)	Median, 4 (range, 2-11)	PAN-BTZ-Dex	ORR: 34.5%; nCR: 1.8%; PR: 32.7%	PFS: 5.4 mo	(17)
PANORAMA 1	III	387	63 (range, 56-69)	1 prior: 51%; 2-3 prior: 49%	PAN-BTZ-Dex	ORR: 60.7%; CR: 11%; nCR: 17%; PR: 33%	PFS: 11.99 mo OS: 33.64 mo	(19)

Abbreviations: APEX, Assessment of Proteasome Inhibition for Extending Remissions; CR, complete response; Dex, dexamethasone; i.v., intravenous; nCR, near complete response; NR, not reported; PR, partial response; s.c., subcutaneous; sCR, stringent complete response; VGPR, very good partial response.

(67% vs. 31%), lymphopenia (53% vs. 40%), diarrhea (26% vs. 8%), asthenia or fatigue (24% vs. 12%), and peripheral neuropathy (18% vs. 15%). There were a few instances of QTcF prolongation in both arms: 5 patients in the panobinostat arm and 2 in the placebo arm had a maximum QTcF value >480 ms, and 3 patients in the panobinostat arm and 4 in the placebo arm had a QTcF increase >60 ms from baseline. The rate of discontinuation due to AEs was higher in the PAN arm (36%) than in the placebo arm (20%). On-treatment deaths occurred in 8% of patients in the panobinostat arm and 5% of patients in the placebo arm (19).

Safety

The safety profile of panobinostat was consistent across the clinical trials. AEs were primarily gastrointestinal and hematologic. The gastrointestinal events (diarrhea, nausea, and vomiting)

were generally grade 1/2 events that could be managed through the use of antidiarrheal medication, proper hydration, and antiemetics. The frequency of diarrhea may also be improved through appropriate dose modifications of panobinostat and/or bortezomib (14).

The most common hematologic laboratory abnormality was thrombocytopenia, which was significantly reduced via non-continuous dosing of panobinostat, considering platelet counts tended to recover during the off-treatment week. Although trials in the PANORAMA program administered panobinostat in a 2-weeks-on,1-week-off schedule, ongoing trials of panobinostat in novel combinations are currently evaluating every-other-week and 3-weeks-on,1-week-off treatment schedules (21-23). Despite a relatively high incidence of grade 3/4 thrombocytopenia, platelet transfusions (33%), severe hemorrhages (4%), and discontinuations due to thrombocytopenia (2%) were infrequent (19).

Table 2. Current clinical trials of panobinostat in multiple myeloma

Phase	N	Patient population	Treatment	Primary endpoints	Institution	ClinicalTrials.gov ID
I	28	Rel or R/R	PAN + Len + BTZ + Dex	MTD, RP2D	Dana-Farber Cancer Institute	NCT01965353
I/II	38	Newly diagnosed	PAN + Len + BTZ + Dex	MTD	MD Anderson Cancer Center	NCT01440582
II	27	Rel or R/R	PAN + Len + Dex	ORR	Mount Sinai School of Medicine	NCT01651039
I/II	54	Rel or R/R	PAN + Thal + BTZ + Dex + PAN maintenance	DLT, ORR	University of Leeds	NCT02145715
I	48	Rel and/or ref	PAN + CFZ	MTD	Emory University	NCT01549431
I	66	R/R	PAN + CFZ	MTD	MD Anderson Cancer Center	NCT01301807
I/II	80	R/R	PAN + CFZ	MTD, ORR	Sarah Cannon Research Institute Developmental Innovations	NCT01496118
I	6	Rel or ref	PAN + ixazomib + Dex	DLT	Case Comprehensive Cancer Center	NCT02057640
I/II	148	Recurrent multiple myeloma, non-Hodgkin lymphoma, or Hodgkin lymphoma	PAN + everolimus	MTD, ORR	Mayo Clinic	NCT00918333

Abbreviations: BTZ, bortezomib; CFZ, carfilzomib; Dex, dexamethasone; DLT, dose-limiting toxicity; ID, identification; Len, lenalidomide; PAN, panobinostat; Ref, refractory; Rel, relapsed; RP2D, recommended phase II dose; R/R, relapsed and refractory; Thal, thalidomide.

Electrocardiogram analyses showed a low frequency of QTcF prolongation (1% and 0.5% QTcF > 480 ms in the panobinostat and placebo arms, respectively, and 0.8% and 1.1% QTcF > 60-ms increase from baseline, respectively). In addition, T-wave and ST-segment changes were generally asymptomatic. The risk of cardiac toxicity can be reduced by monitoring electrocardiogram scans and electrolyte levels and interrupting treatment in the event of QT prolongation. Deaths due to cardiac toxicity were rare: Myocardial infarction was the principal cause of death in <1% in the panobinostat arm and 0% in the placebo arm; cardiac arrest was the principal cause of death in <1% in each arm (19). The rate of cardiac-related deaths for the panobinostat-bortezomib-dexamethasone combination was similar to that for single-agent carfilzomib (1.5%; ref. 24). The addition of panobinostat to bortezomib plus dexamethasone did not increase the risk or severity of peripheral neuropathy, which is a common bortezomib-related AE. In the PANORAMA 1 trial, peripheral neuropathy (all grades) occurred in 61% of patients in the panobinostat group and 67% of patients in the placebo group, and grade 3/4 peripheral neuropathy occurred in 18% and 15% of patients in the panobinostat and placebo groups, respectively (19).

In all studies of the panobinostat-bortezomib-dexamethasone combination summarized here, bortezomib was administered intravenously, and patients received twice-weekly dosing during TP1 of both PANORAMA 1 and PANORAMA 2. Recent data have demonstrated that subcutaneous administration as well as once-weekly dosing of bortezomib improve tolerability (25, 26). Thus, the safety profile of the triple combination may be improved with subcutaneous, once-weekly administration of bortezomib.

Panobinostat in the Treatment of Multiple Myeloma

Significant advances in the treatment of multiple myeloma have been made over the past decade; however, approvals have primarily been limited to agents in two classes (PIs and IMiDs; Table 1), with the notable exception of liposomal doxorubicin given in combination with bortezomib. An unmet need remains for patients with relapsed or refractory disease (3, 4). It is

therefore critical to develop agents with novel mechanisms of action.

Results from the phase III PANORAMA 1 trial of panobinostat in combination with bortezomib and dexamethasone demonstrated that panobinostat is the first DAC inhibitor with clear clinical benefit, as evidenced by a statistically significant and clinically meaningful improvement in median PFS in patients with relapsed or relapsed and refractory multiple myeloma (19). On the basis of results of the PANORAMA 1 trial, the FDA, on February 23, 2015, approved panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who received ≥ 2 prior regimens, including bortezomib and IMiDs (27). The FDA concluded that the benefit:risk ratio appeared to be greater in this more heavily pretreated population. Panobinostat therefore addresses an unmet need for patients whose disease progresses following PI and IMiD therapy.

Several ongoing trials are evaluating panobinostat with other combination partners (Table 2), including next-generation PIs (carfilzomib or ixazomib), an IMiD (lenalidomide) plus dexamethasone, and bortezomib plus an IMiD (thalidomide or lenalidomide) and dexamethasone in the relapsed/refractory setting. Panobinostat as maintenance therapy will be evaluated following combination therapy with bortezomib, thalidomide, and dexamethasone. Two trials are investigating the combination of panobinostat-lenalidomide-bortezomib-dexamethasone, one in the up-front setting and the other in the relapsed setting. These and other trials will provide insights on optimal dosing and administration, optimal combination partners, and therapeutic settings.

Conclusions and Future Directions

Panobinostat is the first DAC inhibitor approved by the FDA for the treatment of relapsed multiple myeloma and has been submitted for approval to regulatory agencies globally. In combination with bortezomib and dexamethasone, panobinostat increases PFS and the rate of high-quality responses. Although this combination led to a higher rate of AEs and AE-related discontinuations than those that occurred with placebo, bortezomib and dexamethasone, proactive management of common AEs, including panobinostat and/or bortezomib dose

interruptions or reductions, should help mitigate AEs in the clinic. Also, anti-diarrheal therapy at the first signs of symptoms and thorough platelet monitoring with transfusion when clinically necessary should be considered during treatment. In addition, recent data suggest that subcutaneous and once-weekly bortezomib dosing can improve tolerability. Current trials investigating combinations of panobinostat and bortezomib are evaluating these alternative bortezomib administration schedules and dosing strategies. Panobinostat is therefore a valuable addition to the current treatment options for relapsed multiple myeloma, and it opens the door for further development of agents in this class with similar mechanisms of action (28). Moreover, clinical trials are ongoing to evaluate additional rationally designed combinations incorporating panobinostat in the upfront, relapsed/refractory, and maintenance multiple myeloma settings (29, 40).

Disclosure of Potential Conflicts of Interest

J.P. Laubach reports receiving commercial research grants from Celgene, Millennium Pharmaceuticals, Novartis Pharmaceuticals Corporation, and Onyx. P. Moreau is a consultant/advisory board member for Amgen, Bristol-

Myers Squibb, Celgene, Janssen, Novartis Pharmaceuticals Corporation, and Takeda. J.F. San-Miguel is a consultant/advisory board member for Bristol-Myers Squibb, Celgene, Janssen, Merck, Millennium Pharmaceuticals, Novartis Pharmaceuticals Corporation, and Onyx. P.G. Richardson is a consultant/advisory board member for Johnson & Johnson, Novartis Pharmaceuticals Corporation, and Takeda. No other potential conflicts of interest were disclosed.

Authors' Contributions

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References

- Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
- Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15:e538–48.
- Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia* 2012;26:149–57.
- Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014;28:1122–8.
- Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science* 2009;325:834–40.
- Mithraprabhu S, Kalf A, Chow A, Khong T, Spencer A. Dysregulated class I histone deacetylases are indicators of poor prognosis in multiple myeloma. *Epigenetics* 2014;9:1511–20.
- Richardson PG, Laubach JP, Lonial S, Moreau P, Yoon SS, Hungria VT, et al. Panobinostat: a novel pan-deacetylase inhibitor for the treatment of relapsed or refractory multiple myeloma. *Expert Rev Anticancer Ther* 2015;15:737–48.
- Atadja P. Development of the pan-DAC inhibitor panobinostat (LBH589): successes and challenges. *Cancer Lett* 2009;280:233–41.
- Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. *Mol Oncol* 2007;1:19–25.
- Kalushkova A, Fryknas M, Lemaire M, Fristedt C, Agarwal P, Eriksson M, et al. Polycomb target genes are silenced in multiple myeloma. *PLoS One* 2010;5:e11483.
- Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Neri P, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood* 2006;108:3441–9.
- Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernandez-Lazaro D, et al. *In vitro* and *in vivo* rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. *Haematologica* 2010;95:794–803.
- Clive S, Woo MM, Nydam T, Kelly L, Squier M, Kagan M. Characterizing the disposition, metabolism, and excretion of an orally active pan-deacetylase inhibitor, panobinostat, via trace radiolabeled 14C material in advanced cancer patients. *Cancer Chemother Pharmacol* 2012;70:513–22.
- San-Miguel JF, Richardson PG, Gunther A, Sezer O, Siegel D, Blade J, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. *J Clin Oncol* 2013;31:3696–703.
- DeAngelo DJ, Spencer A, Bhalla KN, Prince HM, Fischer T, Kindler T, et al. Phase Ia/II, two-arm, open-label, dose-escalation study of oral panobinostat administered via two dosing schedules in patients with advanced hematologic malignancies. *Leukemia* 2013;27:1628–36.
- Wolf JL, Siegel D, Goldschmidt H, Hazell K, Bourquelot PM, Bengoudifa BR, et al. A phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. *Leuk Lymphoma* 2012;53:1820–3.
- Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparotto C, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. *Blood* 2013;122:2331–7.
- Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparotto C, et al. Time to event analyses in PANORAMA 2: a phase 2 study of panobinostat, bortezomib, and dexamethasone in patients with relapsed and bortezomib-refractory multiple myeloma [abstract]. In: Proceedings of the 55th ASH Annual Meeting and Exposition; 2013 Dec 7–10; New Orleans, LA. Washington (DC): American Society of Hematology; 2013. Abstract nr 1970.
- San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol* 2014;15:1195–1206.
- San Miguel JF, Hungria VTM, Yoon S, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma who received prior bortezomib and IMiDs: a predefined subgroup analysis of PANORAMA 1. *J Clin Oncol* 33, 2015 (suppl; abstr 8526).
- Kaufman JL, Zimmerman T, Rosenbaum CA, Nooka AK, Heffner LT Jr, Harvey RD, et al. Phase I study of the combination of carfilzomib and panobinostat for patients with relapsed and refractory myeloma: a multiple myeloma research consortium (MMRC) clinical trial [abstract]. In: Proceedings of the 56th ASH Annual Meeting and Exposition; 2014 Dec 6–9; San Francisco, CA. Washington (DC): American Society of Hematology; 2014. Abstract nr 32.

22. Berdeja JG, Gregory TK, Matous J, Hart LL, Owera R, Mace JR, et al. A phase I/II study of the combination of panobinostat (PAN) and carfilzomib (CFZ) in patients (pts) with relapsed or relapsed/refractory multiple myeloma (MM). *J Clin Oncol* 33, 2015 (suppl; abstr 8513).
23. Chari A, Cho HJ, Parekh SS, Dhadwal A, Garcia K, Morgan G, et al. A phase II study of panobinostat with lenalidomide and weekly dexamethasone in myeloma. *J Clin Oncol* 33, 2015 (suppl; abstr 8528).
24. Wang M, Cheng J. Overview and management of cardiac and pulmonary adverse events in patients with relapsed and/or refractory multiple myeloma treated with single-agent carfilzomib. *Oncology (Williston Park)* 2013;27 Suppl 3:24–30.
25. Moreau P, Pylypenko H, Grosicki S, Karamanesh I, Leleu X, Grishunina M, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011;12:431–40.
26. Bringhen S, Larocca A, Rossi D, Cavalli M, Genuardi M, Ria R, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood* 2010;116:4745–53.
27. FARYDAK (panobinostat) capsules, for oral use, prescribing information [PDF on the Internet]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2015 [cited 2015 Jun 1]. Available from: <http://www.pharma.us.novartis.com/product/pi/pdf/farydak.pdf>.
28. Laubach JP, Voorhees PM, Hassoun H, Jakubowiak A, Lonial S, Richardson PG. Current strategies for treatment of relapsed/refractory multiple myeloma. *Expert Rev Hematol* 2014;7:97–111.
29. Lonial S, Mitsiades CS, Richardson PG. Treatment options for relapsed and refractory multiple myeloma. *Clin Cancer Res* 2011;17:1264–77.
30. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487–98.
31. Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357:2133–42.
32. Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357:2123–32.
33. Richardson PG, Xie W, Jagannath S, Jakubowiak A, Lonial S, Raje NS, et al. A phase II trial of lenalidomide, bortezomib and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood* 2014;123:1461–9.
34. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 2012;120:2817–25.
35. Lendvai N, Hilden P, Devlin S, Landau H, Hassoun H, Lesokhin AM, et al. A phase 2 single-center study of carfilzomib 56 mg/m² with or without low-dose dexamethasone in relapsed multiple myeloma. *Blood* 2014;124:899–906.
36. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015;372:142–52.
37. Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood* 2014;123:1826–32.
38. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:1055–66.
39. Richardson PG, Hungria VM, Yoon S-S, Beksac M, Dimopoulos MA, Elghandour A, et al. Characterization of the incidence and management of gastrointestinal toxicity in the phase 3 Panorama 1 study of panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma [abstract]. In: Proceedings of the 56th ASH Annual Meeting and Exposition; 2014 Dec 6–9; San Francisco, CA. Washington (DC): American Society of Hematology; 2014. Abstract nr 2120.
40. Mitsiades CS, Davies FE, Laubach JP, Joshua D, San Miguel J, Anderson KC, et al. Future directions of next-generation novel therapies, combination approaches, and the development of personalized medicine in myeloma. *J Clin Oncol* 2011;29:1916–23.