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Role of Histone Deacetylase Inhibitors in Relapsed Refractory Multiple Myeloma: A Focus on Vorinostat and Panobinostat

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Abstract

Multiple myeloma is a neoplastic plasma cell disorder that is characterized by clonal proliferation of plasma cells in the bone marrow, monoclonal protein in the blood and/or urine, and associated organ dysfunction and biomarkers. There have been multiple recent advances in the relapsed and refractory setting. Major steps forward include the introduction of proteasome inhibitors (bortezomib and carfilzomib) and immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) in various combinations. These drugs have changed the management of multiple myeloma and have extended overall survival in the past decade. Established curative therapy is not yet available for patients diagnosed with multiple myeloma, supporting the development of new treatment targets. Histone deacetylase inhibitors have multiple proposed mechanisms of action in the treatment of multiple myeloma. Both vorinostat and panobinostat have demonstrated some activity against multiple myeloma, and due to the benefits reported with panobinostat, the U.S. Food and Drug Administration has recently approved the drug for the treatment of relapsed and refractory multiple myeloma. In this article, we describe the pharmacology, efficacy, and toxicity profile of vorinostat and panobinostat and their possible place in therapy.

Keywords

histone deacetylase inhibitors; HDAC; multiple myeloma; panobinostat; vorinostat; treatment; refractory; relapsed

Multiple myeloma (MM) is a malignant disorder of plasma cells characterized by hypercalcemia, anemia, renal insufficiency, lytic bone disease, and/or myeloma-related events (elevated serum free chains, focal lesions by magnetic resonance imaging, or high levels of plasma cells in the bone marrow).¹ According to data from the Surveillance, Epidemiology, and End Results program, an estimated 26,850 new cases of MM will be diagnosed in 2015, contributing to 11,240 deaths.² Historical treatment strategies have focused on the utilization of chemotherapy resulted in poor long-term outcomes. Immunomodulatory drugs (IMiDs), such as thalidomide, lenalidomide and pomalidomide,

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and proteasome inhibitors, such as bortezomib and carfilzomib, have revolutionized the management of MM. These drugs, especially in combination, have impressive outcomes in front-line, relapsed, and refractory settings and have become the cornerstones of therapy. Despite these advances, there is no established curative therapy available for patients diagnosed with multiple myeloma. Indeed, most patients eventually relapse and, unfortunately, will subsequently die from their disease. Relapsed MM meets the criteria for progression of disease and requires new therapy after an initial response. In contrast, relapsed and refractory MM (RRMM) is defined as disease that is unresponsive to salvage therapy and progresses on treatment or within 60 days of the last therapy in patients who achieved a minimal response (MR) before progression of disease.³ A median overall survival of 9 months and event-free survival of 5 months is observed in patients who are relapsed and refractory following IMiD and bortezomib therapy.⁴ Clearly, novel strategies to treat RRMM are warranted.

HDAC Inhibitors

Epigenetics is defined as the alteration in gene expression without direct impact on genetic sequence. There are two primary epigenetic modifications that drive oncologic processes: DNA methylation and histone modification.^{5, 6} Histones are the major protein component of chromatin that, when complexed with DNA, form nucleosomes. Amino acid terminal ends of histones are subject to modification via a variety of epigenetic changes, including acetylation, phosphorylation, ubiquitylation, and sumoylation. Gene expression via histones is regulated by the opposing functionality of histone acetyl transferases and histone deacetylases (HDACs). This occurs by the addition or elimination of acetyl groups at the lysine terminal residue of the histone. Acetylation of the terminus results in neutralization of electrostatic charge, creating an open, relaxed state of chromatin. In contrast, deacetylation yields a condensed form of chromatin, which limits transcription factor binding, thus silencing important facets of cancer cell development and survival.⁵⁻⁷

There are 18 individually identified HDAC enzymes, divided into four classes based on the structural similarity to yeast proteins and location within the cell (Table 1). Inhibitors of HDAC are broken down into several individual classes based on chemical structure that include short-chain fatty acids, hydroxamic acids, benzamides, cyclic peptides, and electrophilic peptides, which inhibit HDACs at various concentrations (Table 2).⁸ Despite the primary proposed activity on histone proteins, it has since been discovered that deacetylation occurs on a large variety of enzymes and cellular proteins. Several critical enzymes to cancer growth and survival are targeted by deacetylases, including α -tubulin, p53, steroid receptors, Bcl-6, Hsp90, and HIF-1.^{6, 8-12} As an example, preclinical data showed that exposure to panobinostat resulted in transcriptional changes in 1120 total genes, highlighting the vast impact of these agents on cell development, proliferation, and survival.¹³

Role of HDAC Inhibition in Myeloma

Although the exact mechanism of activity has not been fully elucidated, there are several proposed mechanisms of action for HDAC inhibitors in myeloma cell lines.

Upregulation of Factors that Block Cell Cycle Promotion (p21)

The cell cycle in malignant cells is mediated via cyclins and cyclin-dependent kinases (CDKs), as well as their inhibitors, including p16, p21, and p27.¹⁴ Phosphorylation of the retinoblastoma protein (pRB), mediated by interleukin-6 and CDKs appears to be fundamental to MM cell growth.¹⁵ All HDAC inhibitors produce cell cycle arrest in the G1/S phase secondary to impact on cell cycle-dependent cyclins and CDK, and subsequent accumulation of cells in the G0/G1 phase. Early preclinical data with vorinostat revealed growth arrest as a result of increased levels of p21 and p53, phosphorylation of pRB and cell cycle arrest, in addition to decreased levels of cyclin D1 and CDK4.

Regulation of Proapoptotic and Antiapoptotic Proteins and Caspase-Mediated Direct Toxicity

Apoptosis of cancer cells can be driven by a family of death-inducing proteases, termed caspases, which are activated and then execute cell death via a proteolytic cascade.¹⁶ HDAC inhibitors have been shown to impact both the intrinsic and extrinsic pathways of caspase-mediated apoptosis, by affecting translocation of mitochondrial proteins, cytochrome-c and APAF-1, upregulation of APAF-1, and cleaving of caspases 3 and 9.¹² Down-regulation of intrinsic caspase activity and antiapoptotic survival mechanisms are mediated via the BCL-2 family of proteins. Members of this family regulate permeability transition pore (PTP) to block mitochondrial exit of cytochrome-c and activation of procaspases via complex formation with APAF-1. Proapoptotic factors allow for PTP opening, cytochrome-c release, and complex formation with antiapoptotic proteins, thus inhibiting their activity. MM cells exhibit high expression of BCL-2 and BCL-xL, which results in chemotherapy resistance. Upregulation of proapoptotic proteins has been demonstrated with panobinostat, romidepsin, and entinostat.⁸ Unfortunately, vorinostat preclinical data suggest that inherent elevated levels of BCL-2 within myeloma cell lines may overcome the proapoptotic effects and lead to continued cell proliferation.¹⁵

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in combination with HDAC inhibitors was able to induce apoptosis in myeloma cell lines via extrinsic caspase activity.¹⁷ TRAIL induces apoptosis via crosslinking to death receptors DR4 and DR5, yielding recruitment of adapter proteins and activation of extrinsic caspase via a death-inducing signal complex. HDAC inhibitors significantly augmented the TRAIL response via upregulation of DR4/5.

Aggresome Pathway and Synergy with Proteasome Inhibitors

HDAC and proteasome inhibitors have demonstrated greater efficacy when used in combination in clinical trials. The mechanisms of action of both drug classes in MM are associated with alterations in protein degradation pathways, which are vital for MM cell survival. Studies have identified multiple mechanisms for synergy including enhanced cytochrome-c release, caspase and PARP cleavage, and inactivation of nuclear factor- κ B.¹⁸ However, the most understood model for the synergy between proteasome inhibitors and HDAC inhibitors is the dual inhibition of the proteasome and aggresome pathways (Figure 1).¹⁹

Proteasome inhibition causes accumulation of intracellular misfolded and/or unfolded proteins, which triggers the unfolded protein response signaling pathway to protect cells against cellular stress. A functional unfolded protein response is critical for the survival of MM cells due to the overproduction of immunoglobulins.^{20, 21}

Recent studies have demonstrated that the aggresomes provide an alternative pathway for metabolism of misfolded proteins and develop when production of misfolded ubiquitinated proteins exceeds the capacity of proteasome to degrade them. Therefore, targeting both the proteasome with bortezomib and the aggresome with HDAC inhibitors, such as panobinostat, in the tumor cells will induce greater accumulation of polyubiquitinated proteins, resulting in increased cellular stress and apoptosis.²²

Vorinostat

Pharmacology and Pharmacokinetics

Vorinostat, otherwise known as suberoylanilide hydroxamic acid, is an oral nonselective class I and class II HDAC inhibitor that is US Food and Drug Administration (FDA) approved for the treatment of relapsed or refractory cutaneous T-cell lymphoma at a dosage of 400 mg once/day.^{8, 23} In recent years, vorinostat has shown promise in the treatment of MM in combination therapy and has been studied at dosages up to 800 mg once/day.

Initial studies showed that sex, race, and age did not significantly affect the pharmacokinetics of vorinostat. Because renal clearance of vorinostat does not play a major role in its elimination (< 1% is excreted unchanged in the urine), there are no dose adjustments necessary in patients with renal insufficiency.⁸ Vorinostat is hepatically metabolized via glucuronidation and hydrolysis followed by β -oxidation. The impact of hepatic insufficiency was evaluated and pharmacokinetic data demonstrated that the mean area under the curve (AUC) increases by 50% compared with the mean AUC in those with normal hepatic function.⁸ Recommended dose adjustments for mild-moderate impairment (bilirubin 1–3 times the upper limits of normal [ULN] or AST >ULN) and for severe impairment (bilirubin >3 times the ULN) are 300 mg/day and 100–200 mg/day, respectively.²³ Although in vitro analysis of UGT enzyme activity has suggested a 45% decrease in glucuronidation activity in patients homozygous for UGT2B17*2, other studies were able to conclude that this difference was acceptable and no dose adjustments are necessary for those patients.²⁵ The absolute oral bioavailability of vorinostat is approximately 43% when fasting. When taken with a high-fat meal, there was a 38% increase in AUC with a decrease in the rate of absorption causing a nearly 2.5-hour delay in the T_{max} .^{24, 26} For this reason, it is recommended that vorinostat be taken with food.

Unlike other HDAC inhibitors, vorinostat has limited drug interactions. In vitro studies assessing drug interaction potential have shown that at clinically relevant doses, vorinostat does not act as an inhibitor or inducer on any cytochrome P450 (CYP) enzymes; simultaneously its metabolism is not mediated via the CYP enzymes or P-glycoprotein.^{24, 26} Inducers and inhibitors of glucuronidation and hydrolysis may potentially affect vorinostat pharmacokinetics; however, due to the number of UGTs involved in its metabolism, a strong inhibitor on any one pathway is unlikely to result in a clinically meaningful effect.²⁴

Clinical Trials

Based on promising preclinical observations, vorinostat has been combined with proteasome inhibitors and IMiDs as well as conventional chemotherapy in RRMM.^{9, 27} The ability of vorinostat to act as a chemosensitizer by suppressing DNA synthesis and inducing down-regulation of caspase inhibitors helps explain its role in enhancing the antitumor activity when combined with conventional chemotherapeutic agents or IMiD therapy.^{9, 27}

Table 3 summarizes the vorinostat clinical trials in MM. In a phase I trial, 20 RRMM patients were treated with combination of vorinostat, bortezomib, and pegylated liposomal doxorubicin. Of these patients, 61% achieved a partial response (PR) or greater, and of those that did respond, all had received prior IMiDs, 65% had prior bortezomib therapy, and 50% had prior anthracycline therapy.^{9, 32} Another phase I trial looked at the addition of vorinostat (at a dosage of 300–400 mg/day on a 7-days-on/7-days-off schedule in a 28-day cycle) to lenalidomide and dexamethasone therapy and found that 47% of patients had achieved a PR or greater.²⁹ Of that population, 31% had previously received lenalidomide therapy.²⁹

The combination of vorinostat with bortezomib in patients with RRMM has been extensively studied. A phase I dose escalation trial evaluated vorinostat at doses of 100–500 mg/day for 8 days of each 21-day cycle and bortezomib 1–1.3 mg/m² intravenous (IV) on days 1, 4, 8, and 11 in RRMM patients who had received at least three prior lines of therapy. Of the 21 patients who were evaluated, 2 achieved a very good partial response (VGPR), 7 achieved a PR, and 10 patients showed stable disease (SD). In the nine patients who were considered bortezomib refractory, three patients achieved a PR and four showed signs of SD.³⁰

The VANTAGE 095 was a global phase IIb trial that studied the combination of bortezomib and vorinostat in 143 patients who had received a median of four prior lines of treatment. The overall response rate (ORR) was 17% with a median duration of response (DOR) of 6.3 months. The median progression-free survival (PFS) was 3.13 (95% confidence interval [CI] 2.4–4.3), and the overall survival (OS) was 11.2 months (95% CI 8.5–14.4) with a 2-year OS rate of 32%. A vorinostat dosage of 400 mg/day on days 1–14 of a 21-day cycle was well tolerated, with 27% of patients being able to complete at least eight cycles of therapy.³⁴ These results led to the phase III VANTAGE 088 trial, which randomized 635 bortezomib-naïve patients to receive either bortezomib alone or bortezomib in combination with vorinostat at the previously mentioned dose. The median PFS was 7.63 months (95% CI 6.87–8.4) in the bortezomib-plus-vorinostat group in comparison to 6.83 months (95% CI 5.67–7.73) in the bortezomib-alone arm ($p=0.01$, hazard ratio [HR] 0.77, 95% CI 0.64–0.94).³⁵ Median time to progression (TTP) was longer in the bortezomib-plus-vorinostat group (7.73 months) versus the placebo group (7.03 months) ($p=0.0184$, HR 0.79, 95% CI 0.64–0.94). Median follow-up for OS was 14.2 months for both groups. It is important to note that neither VANTAGE 095 nor VANTAGE 088 included dexamethasone in their regimen, which is a main component to all MM regimens, and this may therefore have affected the results.^{34, 35}

At this time, researchers are continuing to evaluate the efficacy of vorinostat efficacy in combination with other myeloma agents, but its pharmaceutical manufacturer is no longer

pursuing an FDA indication for MM. Despite the small difference in PFS and no difference in OS, vorinostat can be prescribed off-label and is listed in the National Comprehensive Cancer Network guidelines as a treatment option in patients with RRMM.

Safety of Vorinostat

Vorinostat has been shown to cause gastrointestinal, constitutional, and hematologic adverse events that are mainly grade 2 or less.²⁸ The most common gastrointestinal side effects include diarrhea, nausea, dysgeusia, weight loss, and vomiting. Fatigue and anorexia are the most common constitutional adverse events reported in trials.^{28, 34, 35} In terms of hematologic side effects, the phase I trial that combined vorinostat, bortezomib, and pegylated liposomal doxorubicin found the DLT to be grade 4 thrombocytopenia and was seen in two of six patients. This led to an amendment in cohort and dosing schedule modification to give vorinostat 400 mg/day only on days 4–11.^{28, 32} In the phase 2 trial, the hematologic side effects included anemia (30%), neutropenia (17%) and thrombocytopenia (52%), which were reversible with no bleeding or life-threatening infections.³⁵ Vorinostat also increased the risk of grade 3 thrombocytopenia compared with placebo when combined with bortezomib. Most hematologic adverse events rapidly recovered within 2–3 weeks following an intervention ranging from dose modification, dose holiday, or discontinuation.³⁴

Despite a higher frequency of adverse events with vorinostat in the phase 3 trial, the median exposure of the study treatment was longer in the vorinostat group. Patients completed a median of seven cycles in the vorinostat arm in comparison to six cycles in the placebo arm. The authors concluded that the adverse events were manageable and could be tolerated enough to continue receiving therapy.³⁵ There are conflicting reports as to whether QTc prolongation is seen in patients treated with vorinostat.^{30, 36} In one trial, vorinostat appeared to have little effect on the QTc interval.³⁶ However, in one of the phase I trials, prolongation of the QTc was noted in 9 of 23 patients (grade 1 in 7 patients and grade 2 in 2 patients).³⁰ None of the patients had a prior history of arrhythmias or cardiac disease or were taking concomitant medications that would have put them at a higher risk. Currently, vorinostat does not carry any warnings or precautions related to QTc prolongation.

Panobinostat

Pharmacology and Pharmacokinetics

Panobinostat is a potent oral pan-deacetylase inhibitor with activity against all class I, II, and IV histone deacetylase enzymes (including HDAC-6, which is a key component of the aggresome pathway IC₅₀ values of panobinostat were lower than those for vorinostat, belinostat, and mocetinostat, with a 10-fold greater potency compared with vorinostat).³⁷

On February 2015, the FDA granted accelerated approval to panobinostat in patients with MM who have at least received two prior regimens. The approved dosing for patients with MM is 20 mg orally every other day for 3 doses (i.e., Monday–Wednesday–Friday) during weeks 1 and 2 in a 21-day cycle (in combination with bortezomib and dexamethasone).

Treatment can be continued for up to eight cycles at the same dosing if tolerated and if there is clinical benefit.³⁸

Panobinostat pharmacokinetics are linear and time dependent.³⁷ Peak concentrations are seen within 2 hours of administration, with drug clearance consisting of 29–51% excreted in the urine and 44–77% excreted in the feces. Initial pharmacokinetic studies showed that sex, race, age, and body surface area did not affect panobinostat clearance. The metabolism of panobinostat is complex and involves multiple pathways, including reduction, hydrolysis, oxidation, and glucuronidation. The oxidation metabolism of panobinostat is mediated by human CYP via CYP3A4 (70–98%) with minor involvement of CYP2D6 and CYP2C19.³⁹ In a clinical trial evaluating the effect of ketoconazole (a potent CYP3A4 inhibitor) on the pharmacokinetics and safety of panobinostat, it was demonstrated that the C_{max} and AUC of panobinostat increased by 1.6- and 1.8-fold, respectively, without a change in T_{max} and half-life.⁴⁰ Therefore, if the combination with a strong CYP3A4 inhibitor is unavoidable, dose reduction to 10 mg is recommended. Due to their inherent CYP3A inhibitory effects, star fruit, pomegranate, and grapefruit should be avoided in patients on panobinostat therapy. There is limited evidence demonstrating the influence of inhibitors and inducers of glucuronidation on the concentration of panobinostat, but clinicians should take this into consideration while prescribing and monitoring patients.

The absolute oral bioavailability of panobinostat is approximately 21%. Food produced minor changes in drug exposure specifically oral bioavailability and systemic absorption, but C_{max} was reduced and T_{max} was slightly prolonged after food intake. Thus, panobinostat can be given without regard to food intake. However, it was shown that nausea and vomiting appeared less common in patients after a high-fat meal compared with after a low-fat meal or with an empty stomach.⁴¹

Clinical Trials

Table 4 summarizes the major clinical trials evaluating oral panobinostat. The initial phase I trials assessing panobinostat monotherapy were carried out in solid and hematologic malignancies using an IV formulation.^{42, 43} In early studies, grade 3 QTc prolongation and cardiac arrhythmias were reported with IV panobinostat administered once daily on days 1–7 and therefore the IV formulation was discontinued.⁴⁴ However, this type of cardiac toxicity seems to occur more frequently when HDAC inhibitors are delivered IV on consecutive days, which was also seen with belinostat (another HDAC inhibitor). Because of their pharmacokinetic differences (higher C_{max} and AUC with IV formulation), the oral formulation was evaluated.⁴⁴

The safety and efficacy of oral panobinostat were studied in a phase Ia/II study in patients with hematologic malignancies, including MM.⁴⁵ In this trial, panobinostat was given as a single agent on a Monday–Wednesday–Friday schedule every week or every other week. The maximum tolerated dose (MTD) was dependent on the malignancy and treatment schedule. The response rates showed 1 of the 12 MM patients with a PR. After this trial, single agent panobinostat was evaluated at a dosage of 20 mg 3 times/week for 2 weeks for a 21-day cycle in heavily pretreated RRMM patients. However, the results of the single agent

trials were again very modest (one PR and one MR).⁴⁶ Due to limited activity as a single agent, subsequent studies focused on combination therapies.

Combination studies of panobinostat with proteasome inhibitors have been the most promising. One of the earliest trials was a phase Ib trial where panobinostat was given 3 times/week for 3 weeks along with bortezomib in a 21-day cycle. The panobinostat MTD found in the trial was 20 mg. In the expansion phase, panobinostat was given 3 times/week for only 2 weeks to allow for count recovery, and dexamethasone was added starting with cycle 2 at a dose of 20 mg with each bortezomib dose. The ORRs for the dose escalation and dose expansion were 73.3% and 52.9%, respectively. It is important to note that among the bortezomib-refractory patients, the ORR was 26.3% and 42.1% had at least an MR.⁴⁷

PANORAMA 2 was a phase II single-arm trial that evaluated panobinostat, bortezomib, and dexamethasone in heavily pretreated/bortezomib refractory patients with a median of four prior lines of therapy. In this two-stage trial, panobinostat, bortezomib, and dexamethasone were administered in the first stage as a 21-day schedule for a total of eight cycles. Only patients who showed clinical benefit proceeded to the second stage of the trial where the combination was given as a 6-week cycle. The ORR was 34.5%, median PFS was 5.4 months (95% CI 2.6–6.7 mo), and median OS was 17.5 months.⁴⁸ The phase III multicenter randomized placebo-controlled trial, PANORAMA 1, compared bortezomib/dexamethasone to combination panobinostat, bortezomib, and dexamethasone in RRMM patients who had received one to three prior regimens.⁴⁹ The other treatment groups received bortezomib IV biweekly, dexamethasone orally on the day of and day after bortezomib plus placebo, or panobinostat. The ORR was not statistically significant when comparing the 2 groups (60.7% vs 54.6%, $p=0.09$). However, the proportion of patients who achieved a complete remission (CR) or near CR was significantly higher in the patients that received panobinostat (27.6% vs 15.6% $p=0.00006$). Median PFS was significantly longer in the panobinostat group compared with the placebo group (11.99 vs 8.08 mo; $p<0.001$, HR 0.63, 95% CI 0.52–0.76). The median OS was not statistically significant (33.64 vs 30.39 mo; $p=0.26$, HR 0.87, 95% CI 0.69–1.10).⁴⁹

The promising results of these trials led to studies evaluating panobinostat in combination with carfilzomib. In the phase I/II trial that combined panobinostat and carfilzomib in the treatment of RRMM with a median of five lines of prior therapy, a standard 3 + 3 dose escalation design was used to determine dose-limiting toxicities (DLTs). Panobinostat was administered 3 times every other week for 3 weeks and carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 in a 28-day cycle. There were no DLTs identified in this trial. At 24 months, the ORR was 67% (33% PR and 33% VGPR) and median PFS at 7.7 months (95% CI 4.4–16.8) and OS was 67% (95% CI 0.48–0.79).⁵⁰

Panobinostat in combination with lenalidomide and dexamethasone has also been evaluated. A phase Ib study assessed the combination of panobinostat given with lenalidomide and pulse dexamethasone in a 28-day cycle.⁵¹ The MTD for panobinostat was 20 mg in this combination. Of the 30 patients evaluated for response in the trial, 17 showed response (1 sCR (stringent complete remission), 1 CRs, 7 VGPRs, and 8 PRs). In the phase II trial evaluating the combination, modifications in dosages were done where panobinostat was

given at 20 mg 3 times weekly only every other week (instead of weekly) and dexamethasone was given as 40 mg weekly (instead of four-day pulse dexamethasone given as 40 mg on days 1–4, days 9–12 and days 17–20). Of the 13 patients evaluated, there were 3 VGPRs, 2 PRs, 3 MRs, and 4 SDs and 1 progression of disease for an ORR of 38%. In the trial, three patients who were lenalidomide refractory remained on treatment for up to 16 months including two patients with gain 1q21 that have attained VGPRs.⁵²

Finally, panobinostat has been combined with the alkylating agent melphalan and evaluated in the relapsed and refractory setting. In a phase I/II trial, the combination was studied and the dosing and schedule were modified 3 times during the trial due to tolerability issues.⁵⁴ The MTD was found to be 20 mg for panobinostat and 0.05 mg/kg for melphalan (both given on days 1, 3, and 5 in a 28-day cycle). However, efficacy and toxicities seem to be directly correlated; therefore, even though the MTD found was tolerated, no responses were seen at that dose. Soon after, another phase II trial was attempted combining oral melphalan–prednisone–thalidomide and panobinostat for a 28-day cycle.⁵³ The ORR was 38.5%, but there was no panobinostat dose found to be safe with melphalan–prednisone–thalidomide at this dosing schedule due to high rate of DLTs. Therefore, it is important to note that panobinostat in combination with melphalan is both toxic and ineffective.

Safety of Panobinostat

In all panobinostat clinical trials, the most common adverse events were thrombocytopenia, neutropenia, anemia, diarrhea, and fatigue regardless of the disease targeted.

Thrombocytopenia is the most common DLT and hematologic toxicity (with 64–98% of patients experiencing any grade thrombocytopenia).^{48, 49} It usually results in a platelet nadir during the second week of therapy and is self-limited with a rebound to near-baseline platelet levels during the week off treatment. Thrombocytopenia induced by HDAC inhibitors is a class effect seen with vorinostat and results in reversible inhibition of maturation of megakaryocytes and the related release of proplatelets.⁵⁵ In the PANORAMA 1 trial, the median platelet counts recovered to baseline levels at the beginning of each cycle.⁴⁹ Thrombocytopenia was managed with platelet transfusions and dose reductions or interruption of panobinostat.^{47–49} Clinical trials with panobinostat have also reported grade 3–4 hemorrhage at low frequencies (4% in PANORAMA 1, which have resulted in five deaths).⁴⁹

Diarrhea is one of the most common non-hematologic toxicities documented with panobinostat. In the PANORAMA 2 trial, there were 71% of patients who experienced all-grade diarrhea, of which 20% was grade 3/4. In PANORAMA 1, 68% had all-grade diarrhea (those included 25% grade 3/4), which led to 4% of the patients discontinuing the drug.^{48, 49} Therefore, panobinostat has a black box warning for severe diarrhea. The onset of diarrhea can occur at any time, so patients need to be monitored closely for hydration status and electrolyte abnormalities. Antimotility agents need to be implemented at the onset of diarrhea.³⁸

In regard to cardiac toxicities, panobinostat has been reported to cause hypokalemia and hypocalcemia, which can lead to or worsen QTc prolongation.³⁸ In pharmacokinetic studies, it was thought that BJB432—the metabolite of panobinostat—might be a potential cause for

the QT prolongation, although this has not been confirmed.⁴⁶ Despite the lower risk of QT prolongation with the oral formulation, there were T-wave changes and ST-T segment changes with panobinostat in the phase III trial, but all patients seemed to be asymptomatic.⁴⁹ However, the medication has a black box warning for cardiac ischemic events, including arrhythmias and ECG changes.³⁸ Panobinostat should not be initiated in patients who have a baseline QTc of greater than 450 msec or a history of recent myocardial infarction or unstable angina. Concomitant QTc-prolonging agents should also be avoided.³⁸

Other HDAC Inhibitors and Novel Agents

Other HDAC inhibitors have also been evaluated in MM. Romidepsin has been studied in a phase II trial of 12 patients with RRMM. Although no objective response was achieved, 4 of 12 patients with secretory MM showed evidence of M protein stabilization.⁵⁶ When used in combination with bortezomib and dexamethasone, 25 patients with RRMM who had received one prior therapy achieved more promising results. In this cohort, 18 of 25 patients achieved an objective response (2 CRs, 13 PRs, and 7 VGPRs). The MTD of romidepsin was 10 mg/m² on days 1, 8, and 15 every 28 days with a median of five cycles administered.⁵⁷ Belinostat, another novel HDAC inhibitor, has also been investigated in combination therapy with bortezomib or dexamethasone. A phase I dose-escalation study enrolled 16 patients with advanced hematologic malignancies refractory to standard therapy and a median of four prior chemotherapy regimens.⁵⁸ Four of the 16 patients carried an MM diagnosis; escalating cohorts were administered belinostat as a 30-minute infusion on days 1–5, and study doses were 600, 900, and 1000 mg/m²/day. An MTD of 1000 mg/m²/d was demonstrated in solid tumor patients in a parallel study. The most common side effects were nausea (50%), vomiting (31%), fatigue (31%), and flushing (31%). In the MM patients, two grade 4 renal failure events occurred with metabolic abnormalities consistent with tumor lysis syndrome.⁵⁹ Two phase II belinostat combination trials have been conducted to date in patients with RRMM. The first trial, which assessed belinostat in combination with bortezomib, was terminated due to DLTs when two of the first four patients treated developed acute renal insufficiency during the first cycle.⁶⁰ The second study was conducted in patients who had failed two prior therapies. In this study, belinostat 1000 mg/m²/day was tested either as monotherapy on days 1–5 in a 21-day cycle or in combination with dexamethasone.⁶¹ Of the 24 patients enrolled, 12 patients were evaluable. These patients had received a median of four cycles; six of these patients went on to receive belinostat plus dexamethasone. In the monotherapy group, six SDs and six progressions of disease were recorded; in the combination group, one patient had an MR and five had SD. Grade 3/4 events reported included anemia in two patients, infection, respiratory distress, thrombocytopenia, hyperglycemia, and fatigue.

To minimize toxicity seen with the use of pan-deacetylase inhibitors and to maintain efficacy, a more specific histone deacetylase-6 (HDAC-6) inhibitor known as rocilinostat (ACY-1215) is currently under investigation. HDAC-6 is a class IIb cytoplasmic HDAC responsible for shuttling ubiquitinated proteins to the aggresome for degradation.⁶² This oral agent has shown activity in preclinical models as a single agent and in combination with bortezomib. There are three ongoing phase I dose-finding clinical trials evaluating the use of

rocilinoestat in combination with lenalidomide and dexamethasone, pomalidomide and dexamethasone, or bortezomib and dexamethasone, respectively.^{62, 63}

Similarly, AR-42, another orally bioavailable phenylbutyrate-based class I/II HDAC inhibitor, is currently under investigation as a therapeutic agent in several malignancies, including multiple myeloma. In vitro and in vivo studies report significant antitumor activity with higher potency compared with vorinostat. Potential mechanisms of action include suppression of gp-130 and STAT3 activation. Downstream signaling factors Bcl-xL and cyclin D1 were also downregulated, leading to G1/G2 cell cycle arrest and apoptosis.⁶⁴

Histone Deacetylase Inhibitors Role in Therapy

The introduction of novel agents has dramatically improved outcomes for patients with RRMM. However, there is no established curative therapy for patients diagnosed with MM. Consequently, most patients with MM ultimately relapse and have a limited duration of response. The choice of salvage therapy is affected by several considerations such as initial therapy, degree and duration of response to primary therapy, age, performance status, and previous toxicities. New strategies such as next-generation proteasome inhibitors and IMiDs are currently part of the treatment paradigm. Other agents with different mechanisms of action, such as histone deacetylators, monoclonal antibodies, and small molecule inhibitors, are also being considered.⁵⁸

Due to their role in tumorigenesis, HDACs have been considered a therapeutic target that could prove efficacious in numerous hematologic malignancies. Currently, only four HDAC inhibitors have been approved by the FDA—romidepsin, vorinostat, and belinostat for T-cell lymphomas and, most recently, panobinostat for MM.

Both vorinostat and panobinostat have demonstrated minimal single-agent activity in refractory MM. The combination of vorinostat, bortezomib, and dexamethasone in patients with bortezomib-sensitive RRMM showed a minimal increase in PFS compared with placebo. Panobinostat combined with bortezomib and dexamethasone has shown greater activity specifically in patients with heavily pretreated or bortezomib-refractory disease as reported in PANORAMA 2 and PANORAMA 1, respectively. Interestingly, there was a clinically meaningful improvement in median PFS but no difference in ORR when the three-drug combination was compared with bortezomib and dexamethasone. However, in these clinical trials there was a high incidence of toxicities, specifically thrombocytopenia and diarrhea, which prevented some patients from continuing therapy. There was also a high incidence of peripheral neuropathy (15% and 27.3%), which may have been due to the route and schedule of the bortezomib (IV and twice/week dosing). Therefore, although quality-of-life data are not yet available, panobinostat is likely to affect quality of life in a substantial subset of patients (specifically in the 25% of patients that experience grade 3/4 diarrhea). Another barrier to using panobinostat is the possibility of cardiac toxicities associated with this medication, including QTc prolongation, arrhythmias, T-wave changes—all of which may be a concern in a predominantly elderly MM patient population. Therefore, patients' past medical history, comorbidities, home medications, and performance status will play a major role in whether they are candidates for this combination therapy. Nevertheless,

because most MM patients ultimately relapse, the availability of alternative treatment options is an advantage.

Currently, other combination strategies evaluating the use of panobinostat with other proteasome inhibitors (carfilzomib/ixazomib) and IMiDs are being undertaken (Table 5). Further trials are needed to evaluate whether other treatment combinations including ixazomib and monoclonal antibodies such as daratumumab and elotuzumab are better tolerated with improved efficacy. This is important since MM is heterogeneous, associated with complex gene abnormalities, and multiple signaling aberrations. Therefore, combining various medications with different mechanisms of action is still key for MM treatment by targeting not only the MM cells but also the tumor microenvironment. Until the optimal dosing and treatment combination is found, vorinostat and panobinostat in combination with bortezomib will be used in RRMM in patients who are not eligible for clinical trials and thought to be able to tolerate the treatment.

Conclusion

In this article, we discussed the use of HDAC inhibitors, specifically vorinostat and panobinostat, for the treatment of MM, which still remains incurable with current therapeutic options. Both agents, mainly in combination with a proteasome inhibitor, have demonstrated some activity in RRMM. The combination of panobinostat, bortezomib, and dexamethasone has shown promise with an improvement in PFS compared with placebo and was approved by FDA in February 2015. However, the main concern with this agent is its associated toxicities. Therefore, further research evaluating treatment combinations and different dosing schedules is needed to optimize efficacy and minimize toxicity.

References

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014; 15(12):538–48.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. *CA Cancer J Clin.* 2015; 65(1):5–29. [PubMed: 25559415]
3. Kyle R, Rajkumar S. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia.* 2009; 23(1):3–9. [PubMed: 18971951]
4. Kumar SK, Lee JH, Lahuerta JJ, 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(1):149–57. [PubMed: 21799510]
5. Esteller M. Epigenetics in Cancer. *N Engl J Med.* 2008; 358:1148–59. [PubMed: 18337604]
6. Smith EM, Boyd K, Davies FE. The potential role of epigenetic therapy in multiple myeloma. *Br J Haematol.* 2009; 148:702–13. [PubMed: 19912222]
7. Grunstein M. Histone acetylation in chromatin structure and transcription. *Nature.* 1997; 389:349–52. [PubMed: 9311776]
8. Hideshima T, Anderson KC. Histone deacetylase inhibitors in the treatment for multiple myeloma. *Int J Hematol.* 2013; 97:324–32. [PubMed: 23475757]
9. Dokumanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. *Mol Cancer Res.* 2007; 5(10):981–9. [PubMed: 17951399]
10. Kaufman JL, Fabre C, Lonial S, Richardson PG. Histone deacetylase inhibitors in multiple myeloma: rationale and evidence for their use in combination therapy. *Clin Lymphoma Myeloma Leuk.* 2013; 13(4):370–6. [PubMed: 23787122]

11. Ocio EM, San Miguel JF. The DAC system and associations with multiple myeloma. *Invest New Drugs*. 2010; 28:S28–35. [PubMed: 21120582]
12. Zain J. Role of histone deacetylase inhibitors in the treatment of lymphomas and multiple myeloma. *Hematol Oncol Clin N Am*. 2012; 26:671–704.
13. Maiso P, Carvajal-Vergara X, Ocio EM, et al. The histone deacetylase inhibitor LBH589 is a potent anti myeloma agent that overcomes drug resistance. *Cancer Res*. 2006; 66(11):5781–9. [PubMed: 16740717]
14. Urashima M, Teoh G, Chauhan D, et al. Interleukin-6 overcomes p21WAF1 upregulation and GI growth arrest induced by dexamethasone and interferon- γ in multiple myeloma cells. *Blood*. 1997; 90(1):279–89. [PubMed: 9207463]
15. Mitsiades N, Mitsiades CS, Richardson PS, et al. Molecular sequelae of histone deacetylase inhibition in human malignant B cells. *Blood*. 2003; 101:4055–62. [PubMed: 12531799]
16. Jourdan M, De Vos J, Mechti N, Klein B. Regulation of Bcl-2-family proteins in myeloma cells by three myeloma survival factors: interleukin-6, interferon- α and insulin-like growth factor 1. *Cell Death Differ*. 2000; 7:1244–52. [PubMed: 11175262]
17. Fandy TE, Shankar S, Ross DD, Sausville D, Srivastava RK. Interactive effects of HDAC inhibitors and TRAIL on apoptosis are associated with changes in mitochondrial functions and expressions of cell cycle regulatory genes in multiple myeloma. *Neoplasia*. 2005; 7(7):646–57. [PubMed: 16026644]
18. Pei XY, Dai Y, Grant S. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by proteasome inhibitor bortezomib and histone deacetylase inhibitors. *Clin Cancer Res*. 2004; 10:3839–52. [PubMed: 15173093]
19. Catley L, Weisberg E, Kizitepe T, et al. Aggresome induction by proteasome inhibitor and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood*. 2006; 108:3441–9. [PubMed: 16728695]
20. Lee A, Iwakoshi N, Anderson K, Glimcher LH. Proteasome inhibitors disrupt the unfolded protein response in myeloma cells. *Proc Natl Acad Sci USA*. 2003; 100:9946–51. [PubMed: 12902539]
21. Obeng E, Carlson L, Gutman D, Harrington WJ, Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood*. 2006; 107:4907–16. [PubMed: 16507771]
22. Hideshima T, Richardson P, Anderson K. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol Cancer Ther*. 2011; 10:2034–42. [PubMed: 22072815]
23. Patheon, Inc. Zolinza (vorinostat) package insert. Mississauga, Ontario, Canada: 2013.
24. Iwamoto M, Friedman EJ, Sandhu P, Agrawal NGB, Rubin EH, Wagner JA. Clinical pharmacology profile of vorinostat, a histone deacetylase inhibitor. *Cancer Chemother Pharmacol*. 2013; 72:493–508. [PubMed: 23820962]
25. Wong NS, Seah EZH, Wang LZ, et al. Impact of UDP-glucuronyltransferase 2B17 genotype on vorinostat metabolism and clinical information in Asian women with breast cancer. *Pharmacogenet Genomics*. 2011; 21:760–8. [PubMed: 21849928]
26. Rubin EH, Agrawal NGB, Friedman EJ, et al. A study to determine the effects of food and multiple dosing on the pharmacokinetics of vorinostat given orally to patients with advanced cancers. *Clin Cancer Res*. 2006; 12(23):7039–45. [PubMed: 17145826]
27. Mitsiades CS, Mitsiades NS, McMullan CJ, et al. Transcriptional signature of histone deacetylase inhibition in multiple myeloma: biological and clinical implications. *Proc Natl Acad Sci USA*. 2004; 101(2):540–5. [PubMed: 14695887]
28. Richardson P, Mitsiades C, Colson K, et al. Phase I trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. *Leuk Lymphoma*. 2008; 49(3):502–7. [PubMed: 18297527]
29. Siegel DS, Richardson P, Dimopoulos M, et al. Vorinostat in combination with lenalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood Cancer J*. 2014; 4:e182. [PubMed: 24562384]

30. Badros A, Burger AM, Philip S, et al. Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. *Clin Cancer Res.* 2009; 15(16):5250–7. [PubMed: 19671864]
31. Weber DM, Graef T, Hussein M, et al. Phase I trial of vorinostat combined with bortezomib for the treatment of relapsing and/or refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2012; 12(5):319–24. [PubMed: 23040438]
32. Voorhees, PM.; Gasparetto, C.; Osman, K., et al. Results of a phase I study of vorinostat in combination with pegylated liposomal doxorubicin and bortezomib in patients with relapsed/refractory multiple myeloma. [Abstract #1955]. Presented at the 53rd ASH Annual Meeting and Exposition; San Diego, CA. Dec 10–13. 2011
33. Vesole DH, Bilotti E, Richter JR, et al. Phase I study of carfilzomib, lenalidomide, vorinostat and dexamethasone in patients with relapsed and/or refractory multiple myeloma. *Br J Haematol.* 2015; 171(1):52–9. [PubMed: 26018491]
34. Siegel, DS.; Dimopoulos, MA.; Yon, SS., et al. Vantage 095: vorinostat in combination with bortezomib in salvage multiple myeloma patients: final study results of a global phase 2b trial. [Abstract #480]. Presented at the 53rd ASH Annual Meeting and Exposition; San Diego, CA. Dec 10–13. 2011
35. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomized, double-blind study. *Lancet Oncol.* 2013; 14:1129–40. [PubMed: 24055414]
36. Munster PN, Rubin EH, Van Belle S, et al. A single supratherapeutic dose of vorinostat does not prolong QTc interval in patients with advanced cancer. *Clin Cancer Res.* 2009; 15(22):7077–84. [PubMed: 19887475]
37. Anne M, Sammartino D, Barginear M, Budman D. Profile of panobinostat and its potential for treatment in solid tumors: an update. *Onco Targets Ther.* 2013; 6:1613–24. [PubMed: 24265556]
38. Novartis Pharmaceuticals Corporation. Farydak (panobinostat). East Hanover, New Jersey: p. 07936
39. Clive S, Woo M, Nydam T, Kelly L, Squier M, Kagan M. Characterizing the disposition, metabolism, and excretion of an orally active pantoic acid deacetylase inhibitor, panobinostat, via trace radiolabeled ¹⁴C material in advanced cancer patients. *Cancer Chemother Pharmacol.* 2012; 70:513–22. [PubMed: 22864948]
40. Hamberg P, Woo M, Chen L, et al. Effect of ketoconazole-mediated CYP3A4 inhibition on clinical pharmacokinetics of panobinostat (LBH589), a orally active histone deacetylase inhibitor. *Cancer Chemother Pharmacol.* 2011; 68:805–13. [PubMed: 21706316]
41. Shapiro G, Frank R, Dandamudi U, et al. The effect of food on the bioavailability of panobinostat, an orally active pan-histone deacetylase inhibitor, in patients with advanced cancer. *Cancer Chemother Pharmacol.* 2012; 68:555–62. [PubMed: 22057852]
42. Giles F, Fischer T, Cortes J, et al. A phase I study of intravenous LBH589, a novel cinnamic hydroxamic acid analogue deacetylase inhibitor, in patients with refractory hematologic malignancies. *Clin Cancer Res.* 2006; 12:4628–35. [PubMed: 16899611]
43. Sharma S, Beck J, Mita M, et al. A phase I dose-escalation study of intravenous panobinostat in patients with lymphoma and solid tumors. *Invest New Drugs.* 2013; 31:974–85. [PubMed: 23377661]
44. Prince HM, Bishton MJ, Johnstone RW. Panobinostat (LBH589): a potent pan-deacetylase inhibitor with promising activity against hematologic and solid tumors. *Future Oncol.* 2009; 5(5): 601–12. [PubMed: 19519200]
45. DeAngelo D, Spencer A, Bhatta K, 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. [PubMed: 23385375]
46. Wolf J, Siegel D, Goldschmidt H, et al. 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. [PubMed: 22288662]

47. San-Miguel J, Richardson P, Gunther A, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. *J Clin Oncol*. 2013; 31:3696–703. [PubMed: 24019544]
48. Richardson P, Schlossman R, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory patients. *Blood*. 2013; 122:1223–37.
49. San-Miguel J, Hungria V, Yoon S, 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, randomized, double-blind phase 3 trial. *Lancet Oncol*. 2014; 15:1195–206.
50. Berdeja J, Hart L, Mace J, et al. Phase I/II study of the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma. *Haematologica*. 2015; 100(5): 670–6. [PubMed: 25710456]
51. Mateos M, Spencer A, Taylor K, et al. Phase Ib study of oral panobinostat (LBH589) plus lenalidomide plus dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma. *J Clin Oncol*. 2010; 25:8030.
52. Chari, A.; Cho, H.; Parekh, S., et al. A phase II, single-center, open-label study of oral panobinostat in combination with lenalidomide and weekly dexamethasone in patients with multiple myeloma. [Abstract #3486]. Presented at the 56th ASH Annual Meeting and Exposition; San Francisco, CA. Dec 6–9. 2014
53. Offindi M, Polloni C, Cavallo F, et al. Phase II study of melphalan, thalidomide, and prednisone combined with oral panobinostat in patients with relapsed/refractory multiple myeloma. *Leuk Lymphoma*. 2012; 53:1722–7. [PubMed: 22335534]
54. Berenson J, Hilger J, Yellin O, et al. A phase I/2 study of oral panobinostat combined with melphalan for patients with relapsed or refractory multiple myeloma. *Ann Hematol*. 2014; 93:88–98.
55. Bishton M, Harrison S, Martin B, et al. deciphering the molecular and biological processes that mediate histone deacetylase inhibitor-induced thrombocytopenia. *Blood*. 2012; 117:3658–68. [PubMed: 21292776]
56. Niesvizky R, Ely S, Tomer M, et al. Phase 2 trial of the histone deacetylase inhibitor romidepsin for the treatment of refractory multiple myeloma. *Cancer*. 2011; 117:336–42. [PubMed: 20862746]
57. Harrison S, Quach H, Link E, Seymour JF, et al. A high rate of durable responses with romidepsin, bortezomib and dexamethasone in relapsed or refractory multiple myeloma. *Blood*. 2011; 118:6274–83. [PubMed: 21911830]
58. Steele NL, Plumb JA, Vidal L, et al. A phase 1, pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat (PXD101) in patients with advanced solid tumors. *Clin Cancer Res*. 2008; 14:804–10. [PubMed: 18245542]
59. Gimsing P, Hansen M, Knudsen LM, et al. A phase 1 clinical trial of the histone deacetylase inhibitor belinostat in patients with advanced hematological neoplasia. *Eur J Haematol*. 2008; 81:170–6. [PubMed: 18510700]
60. NCT00431340. A Phase II study of belinostat in combination with bortezomib in patients with relapsed, refractory multiple myeloma. Available at: <http://clinicaltrials.gov/ct2/show/NCT00431340>. [accessed 08.18.15]
61. Sullivan D, Shingal S, Chuster M, et al. A phase II study of PXD101 in advanced multiple myeloma. *Blood*. 2006; 108(1):00–000. Abstract 3583.
62. Santo L, Hideshima T, Kung A, et al. Preclinical activity, pharmacodynamic, and pharmacokinetic properties of a selective HDAC6 inhibitor; ACY-1215, in combination with bortezomib in multiple myeloma. *Blood*. 2012; 119:2579–89. [PubMed: 22262760]
63. Dimopoulos K, Gimsing P, Gronbaek K. The role of epigenetics in the biology of multiple myeloma. *Blood Cancer J*. 2014; 4:e207. [PubMed: 24786391]
64. Zhang S, Suvannasankha A, Crean C, White V, Chen C, Farag SS. The novel histone deacetylase inhibitor, AR-42, inhibits gp130/stat3 pathways and induces apoptosis and cell cycle arrest in multiple myeloma cells. *Int J Cancer*. 2011; 129:204–13. [PubMed: 20824695]

Figure 1.

Aggresome pathway and synergy with proteasome inhibitors. Unfolded and/or misfolded proteins are targeted by ubiquitin to proceed to the proteasome and aggresome pathways for degradation. Inhibiting the proteasome pathways with inhibitors such as bortezomib or carfilzomib would lead to accumulation of ubiquitin protein aggregates which are then shuttled to the lysosome to be degraded via the aggresome pathway. In the aggresome pathway, the protein aggregates are moved via microtubules by using dynein motor proteins. The protein aggregate/microtubule complex is facilitated by HDAC-6 (a histone deacetylase enzyme that belongs to class IIb). Therefore, if the histone deacetylase (HDAC) is blocked by giving an HDAC inhibitor (with a proteasome inhibitor) then further ubiquitin protein aggregates will accumulate resulting in cellular apoptosis.

Table 1Classification of HDAC Enzymes⁷⁻¹¹

HDAC Class	HDAC Enzymes	Cellular Location	Cofactor
I	1, 2, 3, 8	Nucleus	Zn ²⁺
IIa	4, 5, 7, 9	Nucleus, cytoplasm	Zn ²⁺
IIb	6, 10	Cytoplasm	Zn ²⁺
III (Sirtuins)	1, 2, 3, 4, 5, 6, 7	Nonhistone and transcription factors	NAD ⁺
IV	11	Nucleus, cytoplasm	Zn ²⁺

HDAC = histone deacetylase; NAD⁺ = nicotinamide adenine dinucleotide; Zn²⁺ = zinc.

Table 2Selected HDAC Inhibitors by Chemical Structure⁷

HDAC Chemical Structure	Potency	Drug Name	HDAC Class Selectivity
Short-chain fatty acids	Millimolar	Valproic acid Phenylbutyrate AR-42	Class I, IIa
Hydroxamic acids	Nanomolar	Vorinostat (SAHA) Belinostat Panobinostat Tubacin Rocilinostat (ACY-1215)	Class I, IIa, IIb, IV Class IIb (HDAC6)
Benzamides	Micromolar	Entinostat MGCD0103 CI-994 SK-7041	Class I
Cyclic peptides	Nanomolar	Romidepsin	HDAC 1, 2, 4, 6
Sirtuin inhibitors	Millimolar	Niacinamide Sirtinol	Class III

HDAC = histone deacetylase; SAHA = suberoylanilide hydroxamic acid.

Table 3

Summary of Oral Vorinostat Clinical Trials^{28–35}

Combination	Phase	No. of Patients	Patient Population	Schedule	Outcomes	Toxicities
Monotherapy ²⁸	I	13	RRMM (median of 3 prior treatment regimens)	Vorinostat PO BID ×5 days/wk (cohorts 1–3) 28-day cycle Vorinostat PO BID ×14 days (cohorts 4–6) 21-day cycle	MTD for vorinostat was 250 mg BID ×5 days/wk in 28 day cycle and 200 mg BID ×14 days in 21-day cycle Of 10 evaluable patients, 1 had MR and 9 had SD *Early study termination by sponsor prior to MTD determination	All grade toxicities: fatigue, anorexia, dehydration, diarrhea, nausea (most were grade 1 or 2, only one patient with grade 3 dehydration)
Vorinostat + lenalidomide + dexamethasone ²⁹	I	31 (14 dose escalation, 17 dose expansion)	RRMM	Vorinostat PO D 1–7 and D 15–21 Lenalidomide PO D 1–21 Dexamethasone 40 mg PO D 1, 8, 15, 22 28-day cycle	MTD for vorinostat was 400 mg and lenalidomide 25 mg ORR 50% (expansion) and 43% (escalation)	All grade toxicities: anemia, thrombocytopenia, diarrhea, fatigue, cough
Vorinostat + bortezomib ³⁰	I	23	RRMM (heavily pretreated with median of 7 prior treatment regimens)	Vorinostat PO D 1–8 Bortezomib IV D 1, 4, 8, 11 21-day cycle (> 2 cycles, dex PO 20 mg D 4–8 added if <PR)	MTD for vorinostat was 400 mg and bortezomib 1.3 mg/m ² ORR 42% (2 VGPRs and 7 PRs)	Grade 3/4 toxicities: myelosuppression, fatigue, diarrhea
Vorinostat + bortezomib ³¹	I	34	RRMM (median of 4 prior treatment regimens)	Vorinostat PO BID D 1–14 (cohort 1 and 2) Vorinostat PO daily D 1–14 (cohort 3–6) Bortezomib IV D 4, 8, 11, 15 (cohort 1 and 2) Bortezomib IV D 1, 4, 8, 11 (cohort 3–6) 21-day cycle (> 1 cycle or POD, dex PO 20 mg D 1–4 and D 9–12 was allowed to be added to therapy)	MTD not reached Dose recommended by authors for further testing: vorinostat 400 mg PO D 1–14 + bortezomib 1.3 mg/m ² IV D 1, 4, 8, 11 of 21 day cycle ORR of 27% (27% PR + 0% CR)	Grade 3/4 toxicities: thrombocytopenia, neutropenia, fatigue, peripheral neuropathy, nausea, vomiting, diarrhea
Vorinostat + pegylated liposomal doxorubicin (PLD) + bortezomib ³²	I	20	RRMM (median of 2 prior treatment regimens)	PLD 30 mg/m ² IV D 4 Bortezomib 1.3 mg/m ² IV D 1, 4, 8, 11 Vorinostat PO D 4–11 or D 1–14 21-day cycle	MTD of vorinostat was 400 mg on D 4–11 ORR of VGPR 38% ORR of PR 61%	Grade 3/4 Toxicities: myelosuppression, infections, diarrhea, fatigue, peripheral neuropathy, hand foot syndrome
Vorinostat + carfilzomib + lenalidomide + dexamethasone ³³	I	17	RRMM (heavily pretreated with a median of 4 prior treatment regimens)	Carfilzomib IV D 1, 2, 8, 9, 15, 16 Lenalidomide PO D 1–21 Vorinostat PO D 1–7, D 15–21 Dexamethasone PO D 1, 8, 15, 22 28-day cycle	MTD not reached Maximum dose used was carfilzomib was 20/27 mg/m ² , lenalidomide 25 mg, vorinostat 400 mg, dexamethasone 40 mg ORR 53% (12% VGPR, 41% PR) PFS of 12 mo and OS not reached	Grade 3/4 Toxicities: neutropenia, thrombocytopenia, anemia, infection, electrolyte imbalance, hyperglycemia
Vorinostat + bortezomib (VANTAGE 095) ³⁴	IIb	142	RRMM (heavily pretreated with median of 4 prior treatment regimens)	Bortezomib 1.3 mg/m ² IV D 1, 4, 8, 11 Vorinostat 400 mg PO D 1–14 21-day cycle (If no response after 4 cycles or POD after 2 cycles, dex 20 mg PO added day of and day after each bortezomib dose)	ORR 17% (4% VGPR, 12% PR, 47% SD) DOR 6.3 mo Median PFS 3.13 mo (95% CI 2.4–4.3) Median OS 11.2 mo (95% CI 8.5–14.4)	Grade 3/4 Toxicities: thrombocytopenia, anemia, neutropenia, diarrhea, fatigue

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Combination	Phase	No. of Patients	Patient Population	Schedule	Outcomes	Toxicities
Vorinostat + bortezomib (VANTAGE 088) ³⁵	III	637 (317 in vorinostat arm and 320 in placebo arm)	RRMM (median of 2 prior treatment regimens)	Bortezomib 1.3 mg/m ² IV D 1, 4, 8, 11 Vorinostat 400 mg PO or placebo PO D 1–14 21-day cycle	Median PFS 7.63 mo (95% CI 6.87–8.4) in vorinostat group Median PFS 6.83 mo (95% CI 5.67–7.73) in placebo group HR 0.77, 95% CI 0.64–0.94; p=0.0100 TTP 7.73 mo (vorinostat) vs 7.03 mo (placebo) HR 0.79, 95% CI 0.64–0.96; p=0.0184	Grade 3/4 Toxicities: Thrombocytopenia, neutropenia, anemia

CR = complete response; dex = dexamethasone; DLT = dose-limiting toxicities; IV = intravenously; MM = multiple myeloma; MR = minimal response; MTD = maximum tolerated dose; nCR = near-complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = by mouth; POD = progression of disease; PR = partial response; RRMM = relapsed refractory multiple myeloma; SD = stable disease; TTP = time to progression; VGPR = very good partial response; wk = week.

Table 4

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Combination	Phase	No. of Patients	Patient Population	Schedule	Outcomes	Toxicities
Panobinostat + lenalidomide + dexamethasone ⁵²	II	13	RRMM	Panobinostat PO 20 mg 3 times/wk, wk 1 and 3 Lenalidomide PO 25 mg/day × 21 days Dexamethasone PO 40 mg weekly 28-day cycle	OS at 24 mo 67% (95% CI 0.48–0.79) ORR 38% (3 VGPR, 2 PR, 3 MR) Median PFS not reached at 4.5 mo	Grade 3/4 toxicities: thrombocytopenia, neutropenia, anemia, infections
Panobinostat + melphalan + thalidomide + prednisone ⁵³	I/II	31	RRMM (1 previous regimen)	Panobinostat PO 10–20 mg 3 times/wk ×3 wks Melphalan PO 0.18 mg/kg D 1–4 Thalidomide PO 50 mg/day continuous Prednisone PO 1.5 mg/kg D 1–4 28-day cycle	ORR 38.5% Median TTP and PFS 14.3 mo (95% CI 12–22 mo) 1 yr OS 63% (no HR or CI reported)	DLTs: grade 3 atrial fibrillation, fatigue, grade 4 neutropenia and thrombocytopenia *Accrual stopped early secondary to toxicities

CR = complete response; D = day(s); DLT = dose-limiting toxicities; IV = intravenously; MM = multiple myeloma; MR = minimal response; MTD = maximum tolerated dose; nCR = near complete response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = by mouth; PR = partial response; RRMM = relapsed refractory multiple myeloma; TTP = time to progression; VGPR = very good partial response; wk = week.

Table 5

Ongoing Trials with HDAC Inhibitors

Phase	Regimen	Disease
I/II	VTD plus panobinostat up to 16 cycles followed by maintenance up to 1 year	Relapsed/refractory? Excludes bortezomib refractory
I	RVD plus panobinostat (pan RVD)?	Relapsed/refractory? Excludes prior tx with panobinostat
I	Carfilzomib plus panobinostat	Relapsed/refractory with failure of at least two lines, which must include IMiD and proteasome inhibitor? Excludes prior tx with valproic acid
I	Carfilzomib plus panobinostat	Relapsed/refractory at least one line of therapy? Excludes prior tx with HDACi, HSP90, valproic acid, or carfilzomib
I	Ixazomib plus panobinostat	Relapsed/refractory? Excludes prior tx with HDACi, HSP90, or valproic acid
I/II	Everolimus plus panobinostat	Relapsed/refractory?
II	Lenalidomide, dexamethasone plus panobinostat	Relapsed/refractory at least one line of therapy? Excludes prior tx with HDACi, HSP90, or valproic acid

HDACi = histone deacetylase inhibitor; IMiD = immunomodulatory agent; RVD = revlimid–velcade–dexamethasone; tx = treatment; VTD = velcade–thalidomide–dexamethasone.