

Panobinostat: a novel mechanism of action shows promise in multiple myeloma

Following an initial “no” vote from the Oncologic Drugs Advisory Committee (ODAC) in late 2014, the US Food and Drug Administration eventually awarded accelerated approval in February 2015 to the histone deacetylase (HDAC) inhibitor panobinostat for use in select patients with relapsed multiple myeloma. Panobinostat has a novel mechanism of action that demonstrates synergy with the proteasome inhibitor bortezomib and the immunomodulatory agent dexamethasone, which translated into improved progression-free survival (PFS) for patients with multiple myeloma who had received at least 2 prior therapies, according to data from a prespecified subgroup analysis from the Panorama-1 trial.

Data from an overall analysis of the Panorama-1 trial was initially submitted to the FDA for approval of panobinostat in patients with relapsed multiple myeloma. That multicenter, randomized, placebo-controlled, double-blind phase 3 trial enrolled 768 patients at 215 centers across 34 countries from January 21, 2010 to February 29, 2012. Patients were randomized 1:1 to a combination of panobinostat, bortezomib, and dexamethasone or a combination of placebo, bortezomib, and dexamethasone. They were stratified by previous treatment strategies and previous use of bortezomib. No crossover was permitted.

Patients aged 18 years or older, with measurable relapsed or relapsed and refractory multiple myeloma, who had received 1-3 previous treatments, with an Eastern Cooperative Oncology Group Performance Status of ≤ 2 , creatinine clearance of ≥ 60 mL/min, absolute neutrophil count of $\geq 1.5 \times 10^9$ cells/L, platelet count of $\geq 100 \times 10^9$ cells/L or higher, normal electrolytes and liver function, and serum creatinine no higher than 1.5 times the upper limit of normal, were eligible for enrollment. Ineligible patients included those with primary refractory or bortezomib-refractory myeloma; who received previous HDAC inhibitor therapy; who received previous antimyeloma treatment within 3 weeks of the start of the study; who received experimental treatment, immunotherapy, or radiation therapy within 4 weeks of the start of the study; who had grade 2 or higher peripheral neuropathy or unresolved diarrhea; or who had impaired cardiac function or clinically significant heart or vascular disease. Demographics and baseline

What's new, what's important

Early this year, the US Food and Drug Administration gave accelerated approval to panobinostat, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

The approval was based on the progression-free survival (PFS) results in a subgroup of patients from a randomized, international, two-arm, placebo-controlled trial that was evaluating panobinostat (or placebo) in combination with bortezomib and dexamethasone. The median PFS values were 10.6 and 5.8 months, respectively, in the panobinostat-containing arm (panobinostat-bortezomib-dexamethasone) and control (placebo-bortezomib-dexamethasone), with a hazard ratio of 0.52 (95% CI, 0.36, 0.76). Overall response rates were 58.5% (95% CI, 47.9, 68.6) in the panobinostat arm and 41.4% (95% CI, 31.6, 51.8) in the placebo arm.

The most common side effects were diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting. Serious adverse reactions included pneumonia, diarrhea, thrombocytopenia, fatigue, and sepsis. There was an increased incidence of deaths that were not due to progressive disease (7% vs 3.2%) among patients in the panobinostat-containing arm.

The recommended dose of the medication is panobinostat, 20 mg, taken orally once every other day for 3 doses per week (on days 1, 3, 5, 8, 10, and 12) of weeks 1 and 2 of each 21-day cycle for 8 cycles. Consider continuing treatment for an additional 8 cycles for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity.

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disease characteristics were well balanced between arms.

Patients were treated in 2 phases with a maximum duration of 12 cycles. In phase 1, patients received 8 3-week cycles of oral panobinostat (20 mg) or placebo 3 times a week for the first 2 weeks, in combination with intravenous bortezomib (1.3 mg/m²) on days 1, 4, 8, and 11, and oral dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12. Patients who experienced clinical benefit, defined as at

How I treat relapsed and refractory multiple myeloma

Patients with relapsed/refractory multiple myeloma have clearly benefited from the significant increase in the number of available agents over the past decade. With several new options available, physicians must consider several variables in making an informed treatment decision including the type, duration and number of prior therapeutic regimens the patient has received, the patient's response to these previous regimens, the intervals to progression and the existence of any comorbidities.

Typically, patients who are newly diagnosed with multiple myeloma receive combinations of proteasome inhibitors (specifically bortezomib) and immunomodulatory drugs (thalidomide or lenalidomide) as part of their primary therapeutic regimen. For patients who relapse >6 months after completion of primary therapy and while on maintenance, retreatment with the previous regimen is a reasonable course of action. For example, a patient induced with lenalidomide, bortezomib, and dexamethasone and maintained on low-dose lenalidomide, but then progressed, could be re-challenged with bortezomib-based therapy. However, in patients who relapse quickly from primary therapy and/or prove refractory to agents used as part of the primary regimen, novel combinations should be introduced. These include second-generation proteasome inhibitors (carfilzomib) and/or immunomodulatory drugs (pomalidomide) or a combination using an agent with a novel mechanism of action, such as the histone deacetylase inhibitor, panobinostat. Recent results with pomalidomide and carfilzomib have led to striking durable and deep responses particularly in patients with high-risk genetics.

The judicious use of conventional cytotoxic therapies with novel agents can be helpful, such as liposomal doxorubicin, cyclophosphamide, and bendamustine. Intensive chemotherapeutic regimens may also help, especially when combined with novel agents, but responses can be short and toxicities may be challenging.

Underlying comorbidities or complications emerging from previous therapies are important factors when deciding on a course of action for patients with relapsed/refractory multiple myeloma, especially because of the need for continuous treatment. Supportive care for common complications, including use of growth factors, bisphosphonate, antithrombotic agents, and intravenous immunoglobulin are relevant considerations. Moreover, management of adverse events is critical to increase time on therapy, and thus maximize clinical benefit.

In addition, the clinical development of novel agents shows enormous promise and includes monoclonal antibodies (eg, elotuzumab and daratumumab) and the first orally bioavailable proteasome inhibitor, ixazomib; thus enrollment in a clinical trial remains a real and often desirable option for relapsed/refractory multiple myeloma patients who are resistant to currently available therapies. Unfortunately, relapse remains inevitable, which highlights the continuing need for agents with unique mechanisms of action, including immune-oncologic and targeted therapies to overcome resistance.

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least no change on day 1 of cycle 8 as assessed by modified European Group for Blood and Marrow Transplantation (EBMT) criteria, were subsequently treated in phase 2, consisting of 4 6-week cycles. The same schedule for panobinostat and placebo was used in phase 2, but bortezomib was administered once a week during weeks 1, 2, 4, and 5 and dexamethasone on the same and subsequent days to bortezomib.

Response assessments, based on EBMT criteria and performed by the investigators and an independent review committee, were carried out at screening, on day 1 of each cycle during phase 1, on days 1 and 22 of each cycle during phase 2, at the end of treatment, and for the following 6 weeks until disease progression or relapse, and responses were confirmed after 6 weeks. Adverse events, serious AEs, and laboratory assessments were reported throughout the study and electrocardiogram monitoring was performed on days 1 and 5 of cycle 1 and day 1 of cycles 2-8.

At the time of data cut-off in September 2013, the median duration of treatment was 5 months in the panobinostat arm and 6.1 months in the placebo arm and the

median duration of follow-up was 6.47 months and 5.59 months, respectively. Median PFS was 11.99 and 8.08 months, and two-year PFS was 20.6% and 8.4%. Median overall survival data was not yet mature, but at the time of reporting, it was 33.64 and 30.39 months, respectively. The proportion of patients achieving overall response was similar in both groups; however, a greater proportion of patients achieved near complete or complete response with panobinostat treatment.

The approval of panobinostat is based on efficacy analyses from a prespecified subgroup analysis of patients who received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, as the ODAC judged that the benefit-to-risk ratio seemed greater in this heavily pretreated population. Among 193 patients, 76% of whom had received 2 or more prior lines of therapy, the median PFS was 10.6 months in the panobinostat arm, compared with 5.8 months in the placebo arm. The tumor shrinkage rate was 59% versus 41% and overall response rates were 55% and 41%, respectively.

Among the study population as a whole, grade 3-4 AEs

Mechanism of action – panobinostat Synergistic impact on proteasomal degradation

In eukaryotic cells, DNA is packaged into structural units called nucleosomes, in which the DNA, in the form of chromatin, is wrapped around histone proteins like thread on a spool. Two groups of enzymes, known as histone acetyl transferases (HATs) and histone deacetylases (HDACs), mediate the transfer and removal, respectively, of acetyl groups from histone proteins, as well as some nonhistone proteins. In the context of histone proteins, acetylation changes the conformation of the chromatin-histone spool; increased acetylation, mediated by HATs, leads to “loosening” of the thread on the spool, rendering the chromatin more transcriptionally active, while, conversely, deacetylation “tightens” the thread and represses gene transcription.

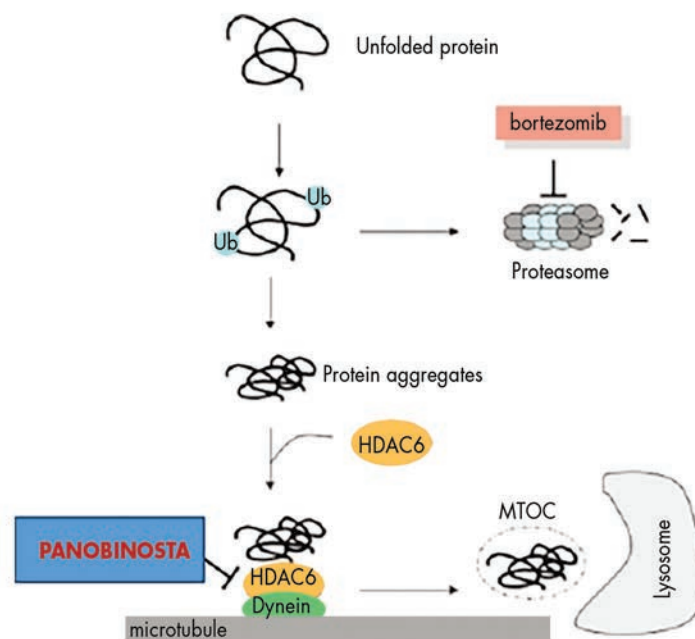
Higher levels of HDAC activity have been shown to be associated with the silencing of tumor suppressor genes, leading to the development of cancer, and increased HDAC levels have been reported in several tumor types, including multiple myeloma. Thus, drugs designed to inhibit HDAC activity are hypothesized to be a potentially important therapeutic option for these cancer types.

There are numerous HDACs found within the cell and panobinostat is a potent pan-HDAC inhibitor, with proven antitumor activity in multiple myeloma. In the PANORAMA-1 trial, panobinostat was evaluated in combination with bortezomib, a proteasome inhibitor, and dexamethasone, an immunomodulatory agent, both established therapies for patients with multiple myeloma, based on the observation that panobinostat seems to have synergistic activity with proteasome inhibitors. Although the activity of panobinostat in multiple myeloma is likely the result of a number of different mechanisms of action, including its effects on histone deacetylation and the bone marrow micro-environment, which have been demonstrated in preclinical trials, it has been hypothesized that the mechanism behind its synergy with proteasome inhibitors may be a nonhistone-related effect involving the ubiquitin-proteasome system (UBS).

The UBS is responsible for the degradation of the majority of regulatory proteins in the eukaryotic cell, which helps to keep the cell healthy. Proteins within the cell that need to be degraded (such as those that are damaged or are no longer needed) are “tagged” for destruction by the proteasome by the addition of multiple ubiquitin molecules.

Defects in this process lead to the accumulation of these proteins and can trigger programmed cell death.

Proteasome inhibitors like bortezomib have been developed to target this process, with the aim of inducing cancer cell death. There has been a particular focus on the treatment of hematologic malignancies such as multiple myeloma because these cancer cells are malignant plasma cells that produce large amounts of immunoglobulin. This overabundance of protein eventually needs to be disposed of, so proteasome activity is increased



in multiple myeloma cells, and they are exquisitely sensitive to proteasome inhibition.

This class of agent has become an important treatment option in multiple myeloma in the past decade, but many patients don't respond and those who do almost invariably relapse. One of the proposed reasons for resistance or relapse is that the cell adapts to proteasome inhibition by activating the unfolded protein response, in which the undegraded proteins are organized at a single location in the cell, forming what is known as an aggresome. This induces an alternative degradation pathway called autophagy in which the proteins are disposed of in degradative organelles called lysosomes.

HDAC6 plays an important role in this adaptive response because it binds both polyubiquitinated proteins and cellular motors and therefore helps to recruit protein cargo to the motors that will transport them to the aggresome. Therefore, combining HDAC inhibitors with proteasome inhibitors has the potential to inhibit both the proteasome and aggresome/lysosome pathways of protein degradation, resulting in greater induction of tumor cell death.

occurred in 96% of panobinostat-treated patients compared with 82% of placebo-treated patients, and serious AEs in 60% and 42% of patients, respectively. The most common nonhematologic AEs in patients treated with panobinostat were diarrhea (68%), peripheral neuropathy (61%), and asthenia/fatigue (57%), whereas common hematologic laboratory abnormalities were related to platelet and absolute lymphocyte count (98% and 83%, respectively). At least 1 dose change for panobinostat was required in 51% of patients, and the discontinuation rate as a result of AEs was 36%, of which 24% were suspected to be related to the study drug.

The recommended dose of panobinostat is 20 mg once every other day for 3 doses a week on days 1, 3, 5, 8, 10, and 12 of weeks 1 and 2 of each 21-day cycle for 8 cycles. Continuation of treatment for up to 16 cycles can be considered in patients who achieve clinical benefit and do not experience unresolved severe or medically significant toxicity. The starting dose should be reduced to 15 mg in patients with mild hepatic impairment and to 10 mg for moderate hepatic toxicity and in those being coadministered strong cytochrome P450 3A inhibitors.

Panobinostat is marketed as Farydak by Novartis. It carries a boxed warning alerting patients and health care providers about the risk of severe diarrhea and severe and

fatal cardiac events, arrhythmias, and ECG changes that have occurred in patients taking this drug in clinical trials. As a result of these risks, it has also been approved with a risk evaluation and mitigation strategy that details how to inform health care providers of these risks and how to minimize them.

The prescribing information also details warnings and precautions on hemorrhage, hepatotoxicity, and myelosuppression. It is also recommended that toxicity be monitored more frequently in patients who are 65 years or older, especially for gastrointestinal toxicity, myelosuppression, and cardiac toxicity. Panobinostat can cause fetal harm and patients should be advised to avoid pregnancy during treatment.

References

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