VD-Pan: Bortezomib/Dexamethasone/Panobinostat

Constituents of Regimen: bortezomib, dexamethasone, panobinostat

Common Names or Abbreviations for Regimen: VD-Pan

Other Names of Regimen Constituents:
- Bortezomib: Velcade®, PS-341
- Dexamethasone: Aeroseb-Dex, Decaderm, Decadron®, DM, DXM
- Panobinostat: Farydak®, LBH589

Mechanism(s) of Action:

Panobinostat is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs, which normally catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, subsequent relaxation of chromatin, and transcriptional activation. HDAC inhibitors may increase transcription of genes that regulate proliferation and induce normal cell death. In vitro, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells.[1, 2]

U.S. FDA-Approved Indication(s):

Panobinostat in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma (MM) who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent (IMiD).[1]

NCCN Recommended Indication:

Indicated for previously treated myeloma patients who have received two prior regimens including bortezomib and an IMiD.[3]

NCCN Preferred Regimen or Other: Preferred, for previously treated multiple myeloma[3]

NCCN Category of Evidence: Category 1[3]

Dose Schedule[1]:

- Panobinostat 20 mg PO once every other day for 3 doses per week in Weeks 1 and 2 of each 21-day cycle for up to 8 cycles (days 1, 3, 5, 8, 10 and 12 q21 days); total duration of treatment may be up to 16 cycles (48 weeks)
  - Consider continuing treatment for an additional 8 cycles for patients with clinical benefit who do not experience unresolved severe or medically significant toxicity
- Bortezomib 1.3 mg/m^2 SC/IV on days 1, 4, 8 and 11 q21 days for cycles 1-8
  - For cycles 9-16, administer on days 1 and 8 q21 days
- Dexamethasone 20 mg PO on days 1, 2, 4, 5, 8, 9, 11 and 12 q21 days for cycles 1-8
  - For cycles 9-16, administer on days 1, 2, 8 and 9 q21 days

Primary and Secondary Efficacy Outcomes:

In the pivotal study,[1] patients who received the combination of bortezomib and dexamethasone plus panobinostat (VD-Pan) (n=387) or placebo (VD-PBO) (n=381) demonstrated the following efficacy outcomes, respectively (VD-Pan vs. VD-PBO):

- Median progression-free survival (PFS) of the overall trial population was 12 months (95% CI: 10.3, 12.9) vs. 8.1 months (95% CI: 7.6, 9.2) [HR: 0.63 (95% CI: 0.52, 0.76)]
- Median progression-free survival (PFS) of patients who received prior therapy with a proteasome inhibitor (PI) and IMiD (n=94 in VD-Pan, n=99 in VD-PBO) was 10.6 months (95% CI: 7.6, 13.8) vs. 5.8 months (95% CI: 4.4, 7.1) [HR: 0.52 (95% CI: 0.36, 0.76)]
- Overall response rate (ORR) in previously treated patients (n=94 in VD-Pan, n=99 in VD-PBO) was 58.5% (95% CI: 47.9, 68.6) vs. 41.4% (95% CI: 31.6, 51.8), with a complete response (CR) of 8.5% vs. 2.0%, near CR of 13.8% vs. 7.1% and partial response (PR) of 36.2% vs. 32.3%

Safety:

In the pivotal study[1], patients who received the combination of bortezomib and dexamethasone plus panobinostat (VD-Pan) (n=387) or placebo (VD-PBO) (n=381) demonstrated the following safety outcomes:

- Serious adverse events (SAEs) occurred in 60% of patients who received bortezomib, dexamethasone, and panobinostat compared to 42% of patients in the control arm. The most frequent (≥5%) treatment-emergent SAEs reported for patients treated with panobinostat were pneumonia (18%), diarrhea, (11%), thrombocytopenia (7%), fatigue (6%), and sepsis (6%).
- Cardiac arrhythmias occurred in 12% panobinostat arm vs 5% control arm.

- Panobinostat may prolong cardiac ventricular repolarization (QT interval), so it should be administered with caution in patients with cardiac dysfunction.
  - Avoid concomitant use of anti-arrhythmic/QT-prolonging drugs
- Adverse reactions that led to discontinuation of panobinostat occurred in 36% of patients and included diarrhea, fatigue, and pneumonia.
- Deaths occurred in 8% of patients in the panobinostat arm versus 5% on the control arm, with the most common causes of death being infection and hemorrhage.
- Hepatic dysfunction (elevated levels of aminotransferases and total bilirubin) occurred in patients treated with panobinostat; liver function should be monitored prior to treatment and regularly during treatment.

Panobinostat General Safety[1]

Black Box Warnings

- Severe Diarrhea: occurred in 25% of patients treated with panobinostat; monitor for symptoms, institute antidiarrheal treatment, interrupt panobinostat and then reduce dose or discontinue
- Cardiac Toxicity: severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred; obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated
- Warnings and precautions, as determined from the pivotal trial, include diarrhea, cardiac toxicity, hemorrhage, myelosuppression, infections, hepatotoxicity, and embryo-fetal toxicity

Bortezomib General Safety[4]

- Peripheral Neuropathy (PN): in the Phase 3 relapsed multiple myeloma trial comparing bortezomib SC vs. IV, the incidence of Grade ≥2 PN was 24% vs. 39%; Grade ≥3 PN occurred in 6% vs. 15% of patients, respectively
- Hypotension: incidence of hypotension (postural, orthostatic, and hypotension not otherwise specified [NOS]) was 8%
- Cardiac Toxicity: in the relapsed multiple myeloma study of bortezomib vs. dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5%, respectively
- Pulmonary Toxicity: acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, and lung infiltration has occurred
- Posterior Reversible Encephalopathy Syndrome (PRES): in patients developing PRES, discontinue bortezomib
- Gastrointestinal Toxicity: bortezomib can cause nausea, diarrhea, constipation, and vomiting

- Thrombocytopenia/Neutropenia: in the single-agent, relapsed multiple myeloma study of bortezomib vs. dexamethasone (n=331), 3% of patients experienced thrombocytopenia with a platelet count <10,000/mcL and 16% with a platelet count between 10,000-25,000/mcL
- Tumor Lysis Syndrome: patients with high tumor burden are at risk; monitor closely
- Hepatic Toxicity: hepatitis, increases in liver enzymes, hyperbilirubinemia and acute liver failure; if it occurs, interrupt therapy to assess reversibility
- Embryo-fetal Risk: bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses

Required Supportive Care/Prophylaxis:

- Pneumococcal infections are common in patients with multiple myeloma. Pneumococcal vaccination should be completed at the time of diagnosis and repeated in 5 years to minimize preventable illness.[5]
- Antiviral prophylaxis with acyclovir or valacyclovir for herpes infections is recommended for patients receiving proteasome inhibitors.[6]
- Patients who receive bortezomib are at risk to develop PN. All patients should be educated as to the signs and symptoms of PN and report the onset or worsening of PN symptoms immediately.[7]
- Bisphosphonates (zoledronic acid or pamidronate) are intended to decrease the risk of skeletal related events and should be considered in all patients with MM receiving first-line therapy, regardless of presence of osteolytic bone lesions on conventional radiography. Dental health should be evaluated at baseline and an ongoing basis to assess for osteonecrosis of the jaw. Serum creatinine levels should be obtained prior to each bisphosphonate dose. Periodic 24-hour urine monitoring should be performed to assess for renal damage secondary to bisphosphonate use long-term.[8]
- Corticosteroids such as dexamethasone can lead to many side effects such as hyperglycemia, mood swings, insomnia, and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders, and psychiatric illnesses. Periodic monitoring of blood glucose levels for mood disturbance and sleep patterns is recommended. Sleep hygiene (avoid excessive exercise and caffeine before sleep, limit daytime napping) and over-the-counter interventions for insomnia (such as melatonin and diphenhydramine) are generally safe and recommended.[9]

Tailoring of Regimen:

- Thrombocytopenia
  - Panobinostat should be dose-adjusted based on the severity of thrombocytopenia[1]:
    - Grade 3 (Platelets <50 x 10^9/L): maintain dose; monitor platelet counts at least weekly

        - Grade 3 with Bleeding or Grade 4: interrupt dose; monitor platelet counts at least weekly until ≥50 x 10^9/L, then restart at reduced dose
    - Bortezomib should be withheld at the onset of any Grade 4 hematological toxicities, excluding neuropathy. Once the symptoms of the toxicity have resolved, bortezomib may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose)[4]
- Neutropenia
    - Panobinostat should be dose-adjusted based on the severity of neutropenia[1]:
        - Grade 3 (ANC 0.75 to 1.0 x 10^9/L): maintain dose
        - Grade 3 (ANC 0.5 to 0.75 x 10^9/L with ≥2 Occurrences): interrupt dose until ANC ≥1.0 x 10^9/L, then restart at same dose
        - Grade 3 (ANC <1.0 x 10^9/L with Febrile Neutropenia): interrupt dose until febrile neutropenia resolves and ANC ≥1.0 x 10^9/L, then restart at reduced dose
        - Grade 4 (ANC <0.5 x 10^9/L): interrupt dose until febrile neutropenia resolves and ANC ≥1.0 x 10^9/L, then restart at reduced dose
    - Bortezomib should be interrupted until febrile neutropenia resolves and ANC ≥1.0 x 10^9/L for Grade 3 or 4 neutropenia[1]
        - If only 1 dose was omitted prior to correction to these levels, restart at same dose
        - If 2 or more doses were omitted consecutively, or within the same cycle, restart at a reduced dose
- Anemia
    - Grade 3 (Hb <8 g/dL): interrupt panobinostat until Hb ≥10 g/dL; restart at reduced dose[1]
- Diarrhea
    - Panobinostat and bortezomib should be dose-adjusted based on the severity of diarrhea[1]:
        - Grade 2 (4 to 6 stools/day): interrupt doses; restart at same doses
        - Grade 3 (≥7 stools/day): interrupt doses; restart at reduced doses
        - Grade 4 (life-threatening): permanently discontinue both drugs
- Nausea or Vomiting
    - Grade 3 or 4: interrupt panobinostat until resolved; restart at reduced dose[1]
- Hepatic Impairment
    - In patients with mild hepatic impairment, start panobinostat at 15 mg; if moderate hepatic impairment, start at 10 mg. Avoid use in patients with severe hepatic impairment[1]

- In patients with moderate or severe hepatic impairment, start bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance[4]
    - If bilirubin level ≥1.5x ULN, reduce bortezomib to 0.7 mg/m^2 in the first cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability

- Peripheral Neuropathy
    - In patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy, the following dose-modifications should be implemented[4]:
        - Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function: no action
        - Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADLs)): reduce bortezomib to 1 mg/m^2
        - Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL): withhold bortezomib therapy until toxicity resolves, then reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
        - Grade 4 (life-threatening consequences; urgent intervention indicated): discontinue bortezomib

Strategies to Reduce Treatment-associated Side Effects:

- Important safety considerations include management of diarrhea (25% severe), correction of blood electrolyte abnormalities, and assessment of cardiac abnormalities with electrocardiogram (ECG). Baseline and ongoing monitoring should be employed on at least a monthly basis with CBC (including platelets and absolute neutrophil count) and chemistry panel (including potassium and magnesium). ECG monitoring should be performed periodically in all patients.[1]
- To reduce the risk of neuropathy, bortezomib should be given SC. Patients should be monitored closely for the onset of PN. All patients should be educated as to the signs and symptoms of PN and report the onset or worsening of PN symptoms immediately.[7]
- Corticosteroids such as dexamethasone can lead to many side effects such as hyperglycemia, mood swings, insomnia, and proximal muscle weakness. Prior to starting a corticosteroid-containing regimen, patients should be screened for a history of diabetes, mood disorders, and psychiatric illnesses. Periodic monitoring of blood glucose levels, for mood disturbance and sleep patterns is recommended.[9]

- Dietary considerations and strategies to minimize nausea and gastrointestinal upset (avoid greasy, fried heavy meals, use of prophylactic antiemetic agents) should also be discussed.[1]

Monitoring Recommendations and Notes:

Adverse events [as listed above under "***Safety***"] should be monitored for and addressed at each visit.

- Obtain a CBC before initiating treatment. Verify that the baseline platelet count is at least 100 x 10^9/L and the baseline absolute neutrophil count (ANC) is at least 1.5 x 10^9/L. Monitor the CBC weekly (or more often as clinically indicated) during treatment.[1]
- Perform an ECG prior to the start of therapy and repeat periodically during treatment as clinically indicated. Verify that the QTcF is less than 450 msec prior to initiation of treatment. If during treatment, the QTcF increases to ≥480 msec, interrupt treatment. Correct any electrolyte abnormalities. If QT prolongation does not resolve, permanently discontinue treatment.[1]
- Obtain electrolytes, including potassium and magnesium, at baseline and monitor during therapy. Correct abnormal electrolyte values before treatment. During the trial, monitoring was conducted prior to the start of each cycle, at Day 11 of cycles 1 to 8, and at the start of each cycle for cycles 9 to 16.[1]
- Patients on oral anti-diabetic agents receiving bortezomib may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medication.[4]
- Monitor patients for signs and symptoms of infections during treatment. Initiate the appropriate anti-infective treatment promptly if infection is suspected and consider interruption or discontinuation of panobinostat.[1]
- Objective monitoring of responses to the regimen should be performed on a monthly basis (by IMWG Uniform Response Criteria) and recorded.[3]

References:

1. FARYDAK® [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
2. Xu WS, Parmigiani RB, Marks PA. Histone deacetylase inhibitors: molecular mechanisms of action. *Oncogene*. 2007;26(37):5541-5552.
3. National Comprehensive Cancer Network [NCCN]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple Myeloma. Version 3.2016.
4. Velcade® [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2015.
5. Prevention of pneumococcal disease: Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2014;46:1-24.
6. Kim SJ, Kim K, Do YR, et al. Low-dose acyclovir is effective for prevention of herpes zoster in myeloma patients treated with bortezomib: a report from the Korean Multiple Myeloma Working Party (KMMWP) Retrospective Study. *Jpn J Clin Oncol*. 2011;41(3):353-357.
7. Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. *Leukemia*. 2012;26(4):595-608.
8. Terpos E, Roodman GD, et al. Optimal use of bisphosphonates in patients with multiple myeloma. *Blood*. 2013;121(17):3325-3328.
9. Faiman B, Bilotti E, Mangan P, et al. Steroid-Associated Side Effects in Patients With Multiple Myeloma: Consensus Statement of the IMF Nurse Leadership Board. *Clin J Oncol Nurs*. 2008;12(0):53-62.

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