POM-VD: Pomalidomide/Bortezomib/Dexamethasone

Constituents of Regimen: pomalidomide, bortezomib, dexamethasone

Common Names or Abbreviations for Regimen: POM-VD, PVD

Other Names of Regimen Constituents:
- Pomalidomide: Pomalyst®, POM, CC-4047
- Bortezomib: Velcade®
- Dexamethasone: Decadron®, DM, DXM

Mechanism of Action:

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (eg, TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.[1]

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

Pomalidomide, in combination with dexamethasone, is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on or within 60 days of completion of the last therapy.[1]

NCCN Recommended Indication:

Previously treated multiple myeloma, in combination with dexamethasone. Consider single-agent pomalidomide for steroid-intolerant indivudals.[2]

NCCN Preferred regimen or other: Preferred, for previously treated multiple myeloma, in combination with dexamethasone.[2]

NCCN Category of Evidence: Category 1

Dose Schedule:

Relapsed, Lenalidomide-Refractory Multiple Myeloma Phase I/II Dose Schedule [28-day cycle][3]:

- Pomalidomide 4 mg PO on Days 1-21 q28-days
- Bortezomib 1.0 or 1.3 mg/m^2 IV or SC on Days 1, 8, 15 and 22 q28-days
- Dexamethasone 40 mg PO on Days 1, 8, 15 and 22 q28-days

Relapsed, PI-Exposed and Lenalidomide-Refractory Multiple Myeloma Phase 1 Low-Dose Dexamethasone [21-day cycle][4]:

- Pomalidomide 1-4 mg PO on Days 1-14 q21 days
- Bortezomib 1.0 or 1.3 mg/m^2 IV or SC on Days 1, 4, 8 and 11 q21 days; for cycles 9+, bortezomib administered on Days 1 and 8 q21 days
- Dexamethasone 20 mg (10 mg for patients aged >75 years) PO on Days 1, 2, 4, 5, 8, 9, 11 and 12 q21 days; for cycles 9+, dexamethasone administered on Days 1, 2, 8 and 9 q21 days

Primary and Secondary Efficacy Outcomes:

Pomalidomide, bortezomib, and dexamethasone (PVD) for patients with relapsed lenalidomide refractory multiple myeloma (MM).[3]

- With a median follow-up of 9 months for a total of 47 patients, 72% remained progression free, 96% were alive and 66% remained on treatment.
- Among the 42 patients who were evaluable, confirmed responses (PR, VGPR, or CR) were seen in 34 (81%) including 3 stringent complete responses (sCR), 5 CRs, 8 very good partial responses (VGPR) and 17 partial responses (PRs).
- Median progression-free survival was 17.7 months (95% CI: 9.5, NA).

A phase 1, multicenter study of pomalidomide, bortezomib, and low-dose dexamethasone in patients with proteasome inhibitor exposed and lenalidomide-refractory myeloma (trial MM-005).[4]

- The overall response rate (ORR) for all patients (n=34) was 65%, with 2 CRs, 1 sCR, 10 VGPRs and 9 PRs; all patients achieved at least stable disease (SD).
- The median duration of response (DOR) for the 22 responders was 7.4 months.

Safety:

Pomalidomide, bortezomib, and dexamethasone (PVD) for patients with relapsed lenalidomide refractory multiple myeloma (MM)[3]

- The most common adverse events (AEs) at least possibly attributable to the combination were anemia, fatigue, leukopenia and thrombocytopenia; however, the majority of these were grade 1-2.

- Grade ≥3 AEs (regardless of attribution) that occurred in at least 3 patients included neutropenia (29), leukopenia (15), lung infection (6), lymphopenia (8), dyspnea (3), and syncope (3).
- Deep vein thrombosis/pulmonary embolism (DVT/PE) occurred in one patient.

A phase 1, multicenter study of pomalidomide, bortezomib, and low-dose dexamethasone in patients with proteasome inhibitor exposed and lenalidomide-refractory myeloma (trial MM-005)[4]

- Commonly reported grade 3/4 AEs were more frequent with bortezomib IV vs. SC (90% vs. 75%), including neutropenia (60% vs. 17%), thrombocytopenia (40% vs. 8%) and pneumonia (30% vs. 8%).
- There were no reports of grade 3/4 peripheral neuropathy (PN) or deep vein thrombosis (DVT) in any of the cohorts.

Pomalidomide General Safety[1]:

Black Box Warnings

- Embryo-Fetal Toxicity: Pomalidomide is a thalidomide analogue and contraindicated in pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death.
- Venous and Arterial Thromboembolism: Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with pomalidomide.

- Hematologic Toxicity: Neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia.
- Hepatic Toxicity: Hepatic failure, including fatal cases, have occurred in patients.
- Hypersensitivity Reactions: Angioedema and severe dermatologic reactions have been reported.
- Dizziness and Confusional State: 14% of patients experienced dizziness and 7% of patients experienced a confusional state; 1% of patients experienced Grade 3 or 4 dizziness, and 3% of patients experienced Grade 3 or 4 confusional state.[4]
- Neuropathy: 18% of patients experienced neuropathy, with approximately 12% of the patients experiencing peripheral neuropathy.[4]
- Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported.
- Tumor Lysis Syndrome (TLS): Patients with higher tumor burden are at increased risk for TLS.

Bortezomib General Safety[5]:

- 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.[6]
- Antiviral prophylaxis with acyclovir or valacyclovir for herpes infections is recommended for patients receiving proteasome inhibitors.[7]
- 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.[8]

- 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.[9]
- 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.[10]
- Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.[11]
    - Low-risk: Aspirin 81-325 mg with consideration of bleeding risks, other platelet inhibiting drugs
    - Higher-risk (≥2 risk factors): Full anti-coagulation with consideration of bleeding risks, other platelet inhibiting drugs
    - Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

Tailoring of Regimen:

Pomalidomide[1]:

- Thrombocytopenia: In patients who experience reduced platelet count, the following dose-modifications should be implemented:
    - Platelets <25,000 per mcL: interrupt pomalidomide, follow complete blood count (CBC) weekly.
        - Platelets return to >50,000 per mcL: resume at 3 mg daily.
    - For each subsequent drop in platelets <25,000 per mcL: interrupt pomalidomide.
        - Platelets return to ≥50,000 per mcL: resume at 1 mg less than previous dose.

- Neutropenia: In patients who experience reduced absolute neutrophil count (ANC), the following dose-modifications should be implemented:
    - ANC <500 per mcL or febrile neutropenia: interrupt pomalidomide, follow CBC weekly.
        - ANC return to ≥500 per mcL: resume at 3 mg daily
    - For each subsequent drop in ANC <500 per mcL: interrupt pomalidomide.
        - ANC returns ≥500 per mcL: resume at 1 mg less than previous dose.
- Dermatologic Reaction (Severe): Permanently discontinue pomalidomide for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction.
- Hepatotoxicity: Stop pomalidomide upon elevation of liver enzymes and evaluate. After return to baseline values, treatment at a lower dose may be considered.
- Co-Administration with Strong CYP1A2 Inhibitors in the Presence of Strong CYP3A4 and P-gp Inhibitors: Avoid co-administration of strong inhibitors of CYP1A2. If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce pomalidomide dose by 50%.

Bortezomib[5]:

- Thrombocytopenia: Withhold 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).
- Hepatic Impairment: 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.
- Peripheral Neuropathy: In patients who experience neuropathic pain and/or peripheral neuropathy, the following dose-modifications should be implemented:
    - 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:

- Advise patients to adhere to thromboprophylaxis regimen and to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.[11]
- 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.[10]
    - Periodic monitoring of blood glucose levels (to assess for hyperglycemia), mood disturbance and sleep patterns related to corticosteroids is recommended.
- Regular physical activity should be encouraged to combat muscle weakness, fatigue, and to reduce the incidence of venous thromboembolisms (VTEs).[11]
- Adherence to therapy can be improved by providing patients and their caregivers with drug information, the treatment plan, prevention strategies, reportable signs and symptoms, and strategies for management. Prompt identification of adverse effects with early intervention may reduce the severity of AEs.

Monitoring Recommendations and Notes:

- Hematologic Toxicity: Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.[1]
- Hepatic Toxicity: Monitor liver function tests monthly.[1]
- Monitor patients at risk of TLS (ie, those with high tumor burden) and take appropriate precautions.[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.[5]
- Objective monitoring of responses to the regimen should be performed on a monthly basis (by IMWG Uniform Response Criteria) and recorded.[2]

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