Elo-VD: Elotuzumab/Bortezomib/Dexamethasone

Constituents of Regimen: elotuzumab, bortezomib, and dexamethasone

Common Names or Abbreviations for Regimen: EVd, EBd

Other Names of Regimen Constituents:

- Elotuzumab: Empliciti™, HuLuc63, BMS-901608
- Bortezomib: Velcade®, PS-341
- Dexamethasone: Aeroseb-Dex, Decaderm, Decadron®, DM, DXM

Mechanism(s) of Action:

Elotuzumab is a humanized IgG1 monoclonal antibody that targets signaling lymphocytic activation molecule family member 7 (SLAMF7), a surface protein expressed on myeloma and natural killer (NK) cells, but not normal tissue. Elotuzumab binds SLAMF7 on NK cells, initiating a signal cascade that directly activates NK cells, resulting in degranulation and release of perforin and granzyme B to initiate apoptosis in myeloma cells. Elotuzumab binds SLAMF7 on myeloma cells, tagging for recognition by NK cells and initiating antibody-dependent cellular cytotoxicity (ADCC) to cause myeloma cell death.[1, 2]

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

Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

NCCN Recommended Indication:

Elotuzumab in combination with bortezomib and dexamethasone is not currently recommended by the NCCN

NCCN Preferred regimen or other: *NA*

NCCN Category of Evidence: *NA*

Dose Schedule:

Relapsed/Refractory Disease Phase II Protocol Dose Schedule [21-day cycle (cycles 1–8) or 28-day cycle (cycles 9+)][3]

- Elotuzumab 10 mg/kg intravenous (IV) on days 1, 8, 15 q21 days for cycles 1 and 2: then days 1, 11 q21 days for cycles 3-8; then days 1, 15 q21 days for cycles 9+
- Bortezomib 1.3 mg/m^2 IV/SC on days 1, 4, 8, 11 q21 days; then days 1, 8, 15 q21 days for cycles 9+
- Dexamethasone 20 mg PO on non-elotuzumab administration days, 28 mg PO + 8 mg IV on elotuzumab administration days

Route of Administration and Drug Reconstitution for Elotuzumab[1]:

- Intravenous (IV) (300 mg vial): 13 mL sterile water for injection (25 mg/mL postreconstitution concentration)
- Intravenous (IV) (400 mg vial): 17 mL sterile water for injection (25 mg/mL postreconstitution concentration)

Primary and Secondary Efficacy Outcomes:

Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma.[4]

- Twenty-eight patients with a median of two prior therapies were enrolled in the Phase I study
- The maximum tolerated dose was 20 mg/kg and administered to 19 patients
- An objective response (a partial response or better) was observed in 13 (48%) of 27 evaluable patients and in two (67%) of three patients who were refractory to bortezomib
- Median time to progression was 9.46 months

A randomized phase II study of bortezomib (Btz)/dexamethasone (dex) with or without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).[3]

- Of the 152 patients randomized, 77 received EBd and 75 received Bd
- At data cutoff (9/12/2014), the following efficacy endpoints were reached for EBd vs. Bd, respectively:
  - Median progression-free survival (PFS) was 9.7 months (EBd) vs. 6.9 months (Bd) (hazard ratio (HR) 0.71; 70% confidence interval (CI) 0.58, 0.87; *P*=.08)
  - Adjusting for prognostic factors, the PFS HR was 0.58 (70% CI 0.47, 0.72; *P*=.01)

- Overall survival HR was 0.61 (70% CI 0.43, 0.85); 40 deaths (17 EBd, 23 Bd) were observed
- Overall response rate (ORR) was 66% (EBd) vs. 63% (Bd)

Elotuzumab Plus Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: 2-Year Follow-up[5]

- At data cut-off (4/16/2015), the following efficacy endpoints were reached for EBd vs. Bd, respectively:
  - 2-year PFS rate (95% CI) was 18% (10%, 28%) and 10% (4%, 18%)
  - Adjusting for prognostic factors, PFS HR (EBd vs. Bd) was 0.60 (70% CI 0.48, 0.74; *P*=.0116)
  - Median PFS was 9.9 months vs. 6.8 months
  - ORR was 65% vs. 63%

Safety:

Elotuzumab General Safety[1]

- Infusion reactions: administer premedication consisting of dexamethasone, antihistamines (H1 and H2 blockers) and acetaminophen prior to infusion
- Infections: monitor patients for development of infections and treat promptly
- Second primary malignancies: monitor patients for the development of second primary malignancies
- Hepatotoxicity: monitor liver enzymes periodically; stop treatment upon ≥ Grade 3 elevation of liver enzymes; continuation of treatment may be considered after return to baseline values
- Interference with determination of complete response: elotuzumab can be detected on serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein; interference can impact the determination of complete response and possibly relapse from complete response

Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma.[4]

- Common ≥ Grade 3 adverse events (AEs) were lymphopenia (25%) and fatigue (14%)
- Most frequent AEs (any grade) were fatigue, anemia, diarrhea, and thrombocytopenia (68% to 82%)
- Two elotuzumab-related serious AEs of chest pain and gastroenteritis occurred in one patient
- Twenty (71%) experienced at least one predefined peri-infusion AE; all except one were grade 1 or 2

A randomized phase II study of bortezomib (Btz)/dexamethasone (dex) with or without elotuzumab (Elo) in patients (pts) with relapsed/refractory multiple myeloma (RRMM).[3]

- Common ≥ Grade 3 AEs (EBd vs. Bd): thrombocytopenia 7 (9%) vs. 13 (17%); infections 14 (19%) vs. 11 (15%)
- Infusion reactions (IRs); all grade 1–2, none at max 5 mL/min rate) occurred in 7% of pts with EBd

Elotuzumab Plus Bortezomib and Dexamethasone Versus Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: 2-Year Follow-up[5]

- Grade 3/4 adverse events (AEs) were reported in 53 (71%) and 45 (60%) pts in the EBd and Bd arms, respectively
- AEs ≥ Grade 3 in ≥15% of pts were thrombocytopenia (7 [9%] in EBd arm; 13 [17%] in Bd arm) and infections (17 [23%] in EBd arm; 11 [15%] in Bd arm)
- Infusion reactions (all Grade 1–2) occurred in 5% of EBd-treated pts

Bortezomib General Safety[6]

- 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: Patients on this regimen are at an increased risk for infusion reactions, pneumonia, varicella zoster virus (VZV) or shingles reactivation, and peripheral neuropathy (PN). The following recommendations should be considered:

- Premedication regimen should be administered with this regimen to reduce the risk of infusion reaction associated with elotuzumab[1]
- 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[7]
- Antiviral prophylaxis with acyclovir or valacyclovir for herpes infections is recommended for patients receiving proteasome inhibitors[8]
- 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[9]
- 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[10]
- 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, 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[11]

Tailoring of Regimen:

- If the dose of one drug in the regimen is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, if dexamethasone is delayed or discontinued, base the decision whether to administer elotuzumab based on clinical judgment (eg, risk of hypersensitivity and infusion reactions)[1]
- If a Grade 2 or higher infusion reaction occurs during infusion of elotuzumab, interrupt the infusion and institute appropriate medical and supportive measures[1]
    - Upon resolution to Grade 1 or lower, restart EMPLICITI at 0.5 mL per minute and gradually increase at a rate of 0.5 mL/min every 30 minutes as tolerated to the rate at which the infusion reaction occurred. Resume the escalation regimen if there is no recurrence of the infusion reaction
    - In patients who experience an infusion reaction, monitor vital signs every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the infusion reaction recurs, stop the infusion and do not restart on that day
    - Severe infusion reactions may require permanent discontinuation of elotuzumab therapy and emergency treatment
- Bortezomib should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematologic 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)[6]
- In patients who experience bortezomib-related neuropathic pain and/or peripheral neuropathy, the following dose-modifications should be implemented[6]:
    - 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

- Patients with moderate or severe hepatic impairment should be started on 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[6]:
    - 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

Strategies to Reduce Treatment-associated Side Effects:

- To reduce the risk of infusion reaction of elotuzumab, administer the following premedication regimen **45 to 90 minutes prior to infusion**, in addition to dexamethasone as outlined in the 'Dose Schedule'[1]: diphenhydramine 25-50 mg PO or IV, or equivalent H1 blocker; ranitidine 50 mg IV or 150 mg PO, or equivalent H2 blocker; acetaminophen 650-1000 mg PO
- To reduce the risk of neuropathy, bortezomib should be given SC. Patients should be monitored closely for the onset of PN[9]

Monitoring Recommendations and Notes:

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

- Nurses who infuse elotuzumab should monitor vital signs and assess for signs of hypersensitivity or infusion reactions before, during, and after elotuzumab administration
- Regular CBC/diff and chemistry monitoring to assess for hepato/renal abnormalities, myelosuppression is suggested
- 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
- Patients should be educated regarding the side effects of medications as listed above (primarily PN, gastrointestinal, insomnia, and mood swings) and urged to report side effects to the treatment team. Adherence to therapy can be improved by intervening side effects in a timely manner
- Objective monitoring of responses to the regimen should be performed on a monthly basis (by IMWG Uniform Response Criteria) and recorded

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