RVD: Post-consolidation Maintenance Therapy in High-risk Myeloma

Constituents of Regimen: Lenalidomide, bortezomib, dexamethasone

Common Names or Abbreviations for Regimen: RVD, VRD, VRd, LBD, BLD

Other Names of Regimen Constituents:

- Lenalidomide: CC-5013, CC5013, CDC 501, IMID-2, Revlimid®, UNII: F0P408N6V4
- Bortezomib: PS-341, Bort, Btz, Velcade®, UNII: 69G8BD63PP
- Dexamethasone: Decadron®, Dex, DXM, DM, UNII: 7S5I7G3JQL

Mechanism(s) of Action:

The proteasome inhibitor bortezomib is a dipeptide boronic acid analog that reversibly inhibits the chymotryptic activity of the 20S subunit of the proteasome.[1] Lenalidomide is an immunomodulatory drug that exerts its effects through multiple pathways, both directly on multiple myeloma tumor cells and indirectly through activation of T-cells as well as lowering the threshold of natural killer (NK) cell activation and augmenting stimulated NK cell responses as described below.[2,3] The mechanism by which the glucocorticoid dexamethasone induces apoptosis in multiple myeloma (MM) cells has not been fully elucidated, although studies suggests that either transactivation through the glucocorticoid response element (GRE) resulting in activation of proapoptotic genes[4-7] transrepression of NF-κB, phosphorylation of RAFTK (Pyk2), or induction of Bim is important in exerting its therapeutic activity.[8-15]

Supporting the combination of bortezomib and lenalidomide is that these two drugs have different but overlapping mechanisms of anti-MM activity in preclinical studies.[16-18] Bortezomib-induced tumor cell death has been associated with activation of both the mitochondrial, caspase-9–mediated and Fas/caspase-8–mediated apoptotic pathways, as well as the induction of endoplasmic reticulum stress and inhibition of nuclear factor κ-B signaling.[16,17] Lenalidomide primarily triggers the caspase-8–mediated apoptotic pathway and also down-regulates nuclear factor κ-B activity via a mechanism distinct from that of bortezomib.[18] Lenalidomide binding to cereblon has been show to result in the interaction of Ikaros and Aiolos to CRL4(CRBN), leading to their ubiquitination, subsequent proteasomal degradation and T-cell activation.[2] Lenalidomide has also been recently shown to lower the threshold for NK-cell activation, allowing NK cells to respond to lower doses of ligand. In addition, lenalidomide augments NK-cell responses, but does not trigger interferon gamma (IFN-γ) production in unstimulated NK cells.[3] Both bortezomib[16] and the immunomodulatory drugs enhance the activity of dexamethasone, and synergy has been demonstrated between bortezomib and

lenalidomide.[18] These preclinical findings have been translated into clinical efficacy; bortezomib plus dexamethasone[19-21] as well as lenalidomide plus dexamethasone[22-25] have both demonstrated substantial activity in the frontline treatment of MM.

Rationale for Extended-time RVD Maintenance Therapy Post HDT-ASCT Consolidation

Despite the significant survival improvement achieved by most myeloma patients over the past decade, patients with genetically defined high-risk disease continue to have poor outcomes.[26] Current treatment approaches with the goal of achieving a complete response (CR) among these patients typically fail owing to inadequate maintenance therapy.[27] It is now known that the negative impact on progression free survival (PFS) and overall survival (OS) associated with t(4;14) can be eliminated by the use of proteasome inhibition and immunomodulatory therapy at the time of primary induction therapy[28] and in consolidation[29] and maintenance[27] phases. A mitigation of the negative impact of p53 deletion has been shown in a single trial using bortezomib maintenance which provided a 3-year OS 69% vs 17%.[30] However, in this trial, bortezomib did not completely overcome the adverse prognosis of del 17p compared with patients lacking del 17p where it provided a 3-year OS 69% vs 85%. Among patients that present with plasma cell leukemia (PCL), there have also been significant improvements in survival with 64% patients alive at 3 years in the era of novel agents[31] compared with a median OS of 15 months using older therapeutic approaches.[32] However, these results are often short-lived as well, and PCL patients also relapse rapidly post-autologous stem cell transplant. Alternative prolonged post-transplant combination maintenance therapy may be a solution for better disease control in high-risk patients. The safety and efficacy of the RVD maintenance strategy after immediate high-dose therapy with melphalan and autologous stem cell transplantation support has been demonstrated in one phase II trial and represents the source of the RVD maintenance protocol.[33]

National Comprehensive Cancer Network (NCCN) Recommendations with Level of Evidence: *(Category 1 implies a preferred regimen based on a high level of evidence and uniform NCCN consensus; category 2A implies a lower level of evidence, but uniform NCCN consensus that the intervention is appropriate).*[34]

- RVD maintenance therapy: This regimen is not recommended outside of clinical trial by the NCCN Guidelines committee at this time.
- No drug has been approved by the US FDA for use as maintenance therapy for the treatment of multiple myeloma at this time.
- Both lenalidomide (category 1), and bortezomib (category 2a) are listed individually as preferred maintenance agents by the NCCN.

Dose Schedule:

RVD Consolidation/Maintenance Therapy: Consists of oral lenalidomide given 10 mg/day on days 1–21 of a 28-day cycle in combination with bortezomib given 1.3 mg/m^2 per week either subcutaneously or intravenously and low-dose dexamethasone given orally 40 mg per week.

This consolidation/maintenance approach follows upfront high-dose therapy-autologous stem cell transplantation (HDT-ASCT). *In clinical study, RVD was administered for up to 3 years, followed by single-agent lenalidomide maintenance thereafter.*[33]

Note: In clinical study evaluating the safety and efficacy of RVD as consolidation/ maintenance therapy, high-risk myeloma was defined by the presence of either deletion of p53 (locus 17p13); deletion of 1p; immunoglobulin heavy chain translocations (t(4;14) or t(14;16)) by fluorescence in situ hybridization (FISH) or by metaphase cytogenetics; or presentation as PCL (X20% circulating plasma cells in peripheral blood).[33]

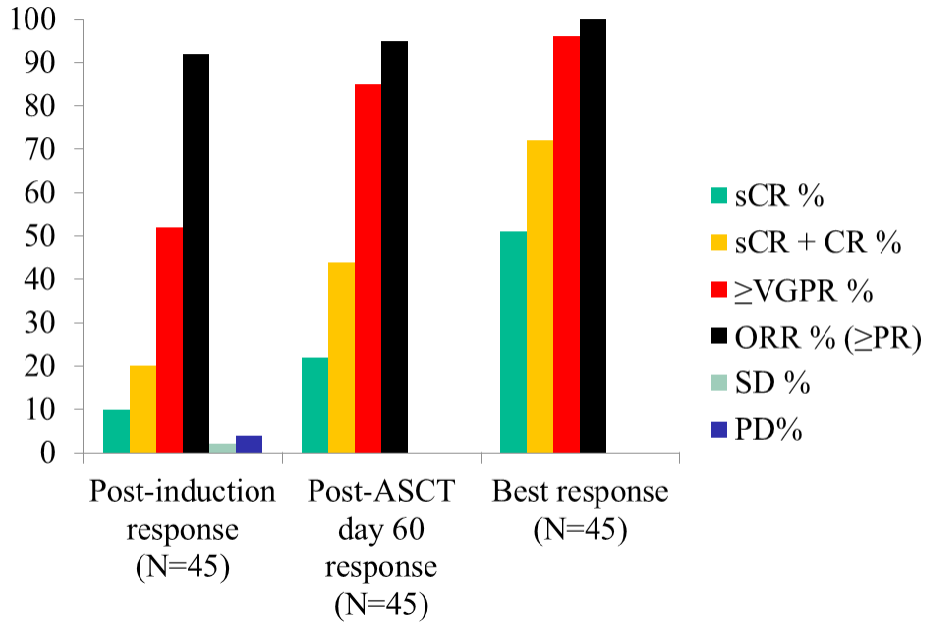
Route of Administration and Drug Reconstitution for Bortezomib:

- Intravenous (IV): 3.5 mL 0.9% sodium chloride, 1 mg/mL bortezomib.
- Subcutaneous (SC): 1.4 mL 0.9 % sodium chloride, 2.5 mg/mL bortezomib – recommended to reduce incidence of peripheral neuropathy and gastrointestinal toxicities.

Primary and Secondary Efficacy Outcomes:

- A total of 45 high-risk patients were evaluated with a median follow-up of 26 months (range 6–48 months); 42% had del 17p and 75% had more than one cytogenetic abnormality[33]
- Best responses with the RVD maintenance strategy following melphalan high-dose therapy were stringent complete response (sCR) among 51%, ≥ very good partial response (VGPR) among 96%, with all patients achieving ≥ partial response (PR) (overall response rate (ORR): 100%) ([Figure 1)

Figure 1. Response Rates in Patients with High-risk Disease[33]



Adapted from Nooka AJ, et al. *Leukemia*. 2014;28:690-693.

- Median time from diagnosis to the best response was 11 months (range 4–25 months)
- The median PFS for all patients was 32 months
- The 3-year OS rate was 93%
- A median PFS of 20 months was observed among patients achieving < PR before transplant, and 36 months among patients ≥ PR
- The median time from progression to death among the four patients who died was 2 months (1–5 months)
- The survival among all high-risk patients vs patients with del 17p was not different (median PFS of 32 months vs 28 months; *P*=.86; 3-year OS of 93% vs 94%, *P*=.51, respectively. Analysis of the plasma cell leukemia (PCL) high-risk group showed that the 3-year PFS and OS were 57% and 100%, respectively

Regimen Safety:

- **No patient developed Grade 3 or 4 neuropathy and no patient discontinued maintenance therapy owing to adverse events**
- **Dose modifications were required in 18 (40%) patients**

Note: No other safety information was provided in this study report.[33]

- **The most common toxicities during maintenance schedule were: peripheral neuropathy (PN) 40% (G1: 26%; G2:14%); G1 rash 10%, and G1 fatigue in 78% patients. Cytopenias were seen in 25% patients**[35]

Drug-specific Safety:

Black Box Warnings: (Celgene Corporation, www.celgene.com US-REV140064)

- Lenalidomide[36]:
  - Embryo-fetal toxicity:
    - Lenalidomide is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death.
    - In females of reproductive potential, obtain two negative pregnancy tests before starting lenalidomide treatment.
    - Females of reproductive potential must use two forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after lenalidomide treatment.
    - To avoid embryo-fetal exposure to lenalidomide, lenalidomide is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the "RevAssist®" program).
  - Hematological toxicity: Neutropenia, thrombocytopenia.
  - Venous and arterial thromboembolism:
    - Deep vein thrombosis, pulmonary embolism, and arterial thrombosis as well as risk of myocardial infarction and stroke have been reported in patients with MM who were treated with lenalidomide and dexamethasone therapy.

Additional Warnings and Precautions: Lenalidomide[36]

- Allergic reactions: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis. If these occur, lenalidomide should be discontinued.
- Tumor lysis syndrome (TLS): Cases of TLS have been reported, although rare in MM.
- Hepatotoxicity: Hepatic failure (including fatalities) has occurred. Liver function should be monitored at baseline and regularly while on treatment. If drug-related hepatotoxicity is suspected, lenalidomide should be stopped.
- Second primary malignancies (SPMs): A higher incidences of SPMs were observed in controlled trials of patients with multiple myeloma receiving lenalidomide.
- Embryo-fetal toxicity: Patients should avoid pregnancy for at least 4 weeks before starting lenalidomide and should not become pregnant when taking lenalidomide. For more information see below ***Recommended Supportive Care/ Prophylaxis*** and package insert for full prescribing information.

Warnings and Precautions: Bortezomib[37]

- Peripheral neuropathy, including severe cases, may occur. Patients should be monitored for symptoms and managed with dose modification or discontinuation. Patients with preexisting symptoms may experience worsening peripheral neuropathy (including ≥ Grade 3). Starting with bortezomib subcutaneously may be considered for patients who either have preexisting or are at high risk for peripheral neuropathy.
- Hypotension: Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated.
- Cardiac toxicity, including acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction has occurred. Isolated cases of QT-interval prolongation have been reported. Patients with risk factors for, or existing, heart disease should be closely monitored.
- Pulmonary toxicity: Acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology have occurred (sometimes fatal). Pulmonary hypertension, in the absence of left heart failure or significant pulmonary disease, has been reported. In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.
- Posterior reversible encephalopathy syndrome has occurred. Consider magnetic resonance imaging (MRI) for onset of visual or neurological symptoms; discontinue bortezomib if suspected.
- Gastrointestinal toxicity, including nausea, diarrhea, constipation, and vomiting, has occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. Interrupt bortezomib for severe symptoms.
- Thrombocytopenia/neutropenia: Manage with dose and/or schedule modifications. Complete blood counts should be monitored frequently during treatment. There have been reports of gastrointestinal and intracerebral hemorrhage. Support with transfusions and supportive care, according to published guidelines.
- Tumor lysis syndrome: Closely monitor patients with high tumor burden and take appropriate precautions.
- Hepatic toxicity: Monitor hepatic enzymes during treatment. Upon occurrence, interrupt therapy with bortezomib to assess reversibility.
- Embryo-fetal risk: Women should avoid breast feeding or becoming pregnant while on bortezomib.
- Patients with diabetes may require close monitoring and adjustment of the antidiabetic medications.

Recommended Supportive Care/Prophylaxis: Patients on this regimen are at an increased risk for infection, venous or arterial thromboembolic events, and embryo-fetal toxicity.

- Embryo-fetal toxicity: **REVLIMID REMS™** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.
    - Females: Must obtain two negative pregnancy tests prior to initiating therapy, avoid pregnancy (abstinence or two forms of birth control) for at least 4 weeks before starting lenalidomide, during treatment with lenalidomide, and for at least 4 weeks after completing therapy with lenalidomide.
    - Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 28 days after discontinuing lenalidomide, even if they have undergone a successful vasectomy. Male patients taking lenalidomide must not donate sperm.
    - Blood donation: Patients must not donate blood during treatment with lenalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to lenalidomide.
- Infections[38-40]:
    - 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 (link to CDC guidelines http://www.cdc.gov/vaccines/vpd-vac/pneumo/vacc-in-short.htm).
    - Shingles prophylaxis is recommended for all patients receiving bortezomib.
- Venous thromboembolic events (VTEs)[41,42]:
    - Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.
- General supportive care[43]:
    - 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.

- Drug-drug interactions:
    - Lenalidomide: Digoxin levels may be reduced. Concurrent administration with erythropoiesis-stimulating agents (ESAs) or estrogen compounds may increase the risk of thrombosis.

Tailoring of Regimen:

- Lenalidomide - http://www.revlimid.com/[36]
    - Renal dose adjustments: Dose modification for lenalidomide is required in the presence of renal impairment.[36,44]

Table 1. Lenalidomide Dose Modification for Renal Impairment

Category	Renal Function (Cockcroft-Gault creatinine clearance [CLcr])	Dose Adjustment for Multiple Myeloma Patients
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg every 24 hours
Severe Renal Impairment	CLcr <30 mL/min (not requiring dialysis)	15 mg every 48 hours
End Stage Renal Disease	CLcr <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.

- ***Lenalidomide (Revlimid®) Package Insert. RevPlyPI.020/MG.020 02/15***[36]
    - Hepatic dose adjustments: Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
    - Neutropenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
    - Thrombocytopenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
    - Harvesting of peripheral blood stem cells is recommended prior to prolonged exposure to lenalidomide.
- ***Bortezomib - http://www.velcade.com/***[37]
    - Patients with moderate or severe hepatic impairment should be started on 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.

Table 2. Recommended Starting Dose Modification for Bortezomib (VELCADE) in Patients with Hepatic Impairment			
	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	≤1.0x ULN	More than ULN	None
	More than 1.0x – 1.5x ULN	Any	None
Moderate	More than 1.5x – 3x ULN	Any	Reduce bortezomib to 0.7 mg/m^2 in the first cycle. Consider dose escalation 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	More than 3x ULN	Any	
SGOT=serum glutamic oxaloacetic transaminase; AST=aspartate aminotransferase; ULN=upper limit of the normal range			

- ***Dose modification is recommended in the presence of peripheral neuropathy. Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.***

Table 3. Recommended Dose Modification for Bortezomib (VELCADE)-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of peripheral neuropathy signs and symptoms	Modification of dose and regimen
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 (ADL)**)	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. When toxicity resolves, 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
*Grading based on NCI Common Terminology Criteria CTCAE v4.0. **Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc. ***Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

- Neutropenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.
- Thrombocytopenia: Guidelines for dose delay, dose reduction, or discontinuation of treatment are included in the package insert.

- ***Dexamethasone***[45]
    - Patients with diabetes: adjustment of the dexamethasone dose and/or anti-diabetic medications may be required. Insulin administration may be required for some patients.
    - Steroid intolerance: consider single agent lenalidomide, pomalidomide, or thalidomide in steroid intolerant individuals; Titration of the dexamethasone over time to improve tolerance and reduce adverse events/late effects may also be considered.

Strategies to Reduce Treatment-associated Side Effects[41,42,45-47]***:***

- Monitoring recommendations and notes: Adverse events (as listed above under "safety") should be monitored for and addressed at each visit.
- Complete blood counts (CBCs) with differential should be monitored routinely in patients receiving bortezomib. Should cytopenias occur, intervene with dose reduction, treatment interruption or discontinuation of the causative agent; transfusion (platelets) and/or growth factor support (neutropenia) should be provided as required.
- Thromboprophylaxis: Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.[41,47]
    - Low-risk: Aspirin 81-325 mg with consideration of bleeding risks, other platelet inhibiting drugs.
    - Higher-risk (≥2 risk factors): Full anticoagulation 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.
- 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.[45]
    - 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 VTEs.
- 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.

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