RVD: Primary (induction) and Consolidation Therapy in Transplant Eligible Patients

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.

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).*[26]

- Primary therapy for transplant eligible candidates – Category 1 - preferred
- Primary therapy for non-transplant candidates – Category 2A - preferred
- Other recommended uses for RVD:
    - Therapy for previously treated multiple myeloma – preferred

Dose Schedule:

Transplant Eligible: IFM 2008 phase II/III study patients age <65 years IFM/DFCI2009 (NCT01191060).[27]

Primary Induction Therapy: Treatment comprised three 3-week cycles of intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; oral lenalidomide 25 mg on days 1 to 14; and oral dexamethasone 40 mg on days 1, 8, and 15.

Stem-cell Harvest: After high-dose cyclophosphamide 3 g/m^2 plus granulocyte colony-stimulating factor (G-CSF) 5 mcg/kg (according to local practice), with a goal of at least 5 × 10^6 CD34 cells/kg for two potential autologous stem cell transplants (ASCTs) [with minimum required of 2 × 10^6 CD34 cells/kg for one ASCT].

High-dose Chemotherapy (HDT)-ASCT: Melphalan 200 mg/m^2 as conditioning.

Consolidation [RVD] (post ASCT, two months after hematologic recovery, nonprogressive patients): Two 3-week cycles of RVD, in an identical schedule as induction, at the last tolerated dose.

Maintenance Therapy with Continuous Oral Lenalidomide: Starting dose 10 mg/d escalated to 15 mg/d after 3 months according to blood cell counts and safety for 1 year [IFM trial].

Note: Results for this trial are anticipated to be reported in December 2015.

Randomized Trial of Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT in MM Patients up to Age 65 (DFCI 10-106) Phase III (NCT01208662) DETERMINATION STUDY

Primary Induction Therapy: Treatment comprised a total of five 3-week cycles of intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11; oral lenalidomide 25 mg on days 1 to 14; and oral dexamethasone 20 mg/day for first 3 cycles and 10 mg/day for remaining cycles on days 1, 2, 4, 5, 8, 9, 11 and 12.

Stem-cell harvest: After high-dose cyclophosphamide 3 g/m^2 plus granulocyte-colony stimulating factor (G-CSF) 5 mcg/kg (according to local practice), with a goal of at least 5 × 10^6 CD34 cells/kg for two potential ASCTs [with minimum required of 2 × 10^6 CD34 cells/kg for one ASCT].

High Dose Chemotherapy (HDT)-ASCT: Melphalan 200 mg/m^2 as conditioning.

Consolidation [RVD] (post ASCT, two months after hematologic recovery, nonprogressive patients): Two 3-week cycles of RVD, in an identical schedule as induction, at the last tolerated dose.

Maintenance Therapy: Continuous oral lenalidomide: starting dose 10 mg/d escalated to 15 mg/d after 3 months according to blood cell counts and safety until disease progression.

Note: Results of the DETERMINATION Study have not yet been reported. This trial is being held jointly with the IFM study noted above; results are anticipated to be reported after those of the IFM in 2016.

Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma: Phase I/II Regimen[28] [NCT00378105]

Primary Induction Therapy: Treatment comprised five 3-week cycles of intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; oral lenalidomide 25 mg/d on days 1-14; and oral dexamethasone 20 mg/d on days 1, 2, 4, 5, 8, 9, 11, 12.

Responding patients proceeded to maintenance or transplantation.

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:

- Phase I/II: NCT00378105: Dana-Farber Cancer Institute (DFCI) Trial: Overall response rate (ORR) for all patients with or without hematopoietic stem cell transplantation (HSCT) = 100% with 67% very good partial response (VGPR) or better and 39% complete response (CR) or near CR (Table 1).[28]

- **Table 1. Best Response to Treatment for the Treated Population and the Phase 2 Population.**

Table 1. Best Response to Treatment for the Treated Population and the Phase 2 Population[28]

	All Patients (N=66)			Phase 2 Population (N=35)		
Response*	**n**	**%**	**90% CI**	**n**	**%**	**90% CI**
ORR (≥PR)	66	100	96-100	35	100	92-100
≥VGPR	44	67	56-76	26	74	59-86
CR + nCR	26	39	29-50	20	57	42-71
CR	19	29	20-39	13	37	24-52
nCR	7	11	5-19	7	20	10-34
VGPR	18	27	18-38	6	17	8-31
PR	22	33	24-44	9	26	14-41

CI=confidence interval; CR=complete response; nCR=near-complete response; PR=partial response; VGPR=very good partial response.
*According to European Group for Blood and Marrow Transplant (EBMT) criteria, all response categories, including VGPR, required a confirmatory assessment at 6 weeks.

  - Estimated 18 month progression-free survival (PFS) at a median follow-up of 21 months: 75% with or without HSCT.
    - PFS rate appeared lower among patients with advanced International Staging System (ISS) stage II/III) disease, although the proportion of patients with ISS stage III disease at treatment initiation was relatively low, at 9%.
    - All patients achieved at least a PR, with high rates of CR, nCR, and VGPR or better despite a number of patients with adverse cytogenetic findings: 13/13q by fluorescence in situ hybridization (FISH) (75%, n=18); Del 17p by FISH (60%, n=3); t(4;14) by FISH (100%, n=2); t(11;14) by FISH (64%, n=7), Del 17p and/or t(4;14) by FISH (67%, n=4).

- Estimated overall response (OR) at 21 months of follow-up: 97% with or without HSCT.
- For patients in the maintenance arm, a continued response by at least one response category was observed in 75% of the patients.
- Duration of response (DOR) had not been reached at the close of study with 68% of patients having a continued response (95% CI, 55-79%).

- Phase II: IFM 2008: Overall response rate (ORR) for all patients was 94%, 93%, 97% and 100% after primary induction therapy, after ASCT, after consolidation therapy and best response any time, respectively (See Table 2).[27]
  - Median follow-up from start of therapy was 39 months (range, 36 to 42 months). At data cutoff, all patients were alive, and seven patients had relapsed.
  - Estimated 3-year PFS was 77% (95% CI, 57% to 88%).
  - Estimated 3-year overall survival (OS) was 100%.
  - Among the 10 patients who never achieved minimal residual disease (MRD) negativity, 70% progressed, with an estimated 3-year PFS of 23% (95% CI, 4% to 53%) [Figure 1].
  - None of the 21 patients who achieved MRD negativity relapsed [Figure 1].
  - Survival outcomes among the patients with high-risk cytogenetics were similar to the group as a whole, with an estimated 3-year PFS of 86% (95% CI, 33% to 98%). For patients in the maintenance arm, a continued response by at least 1 response category was observed in 10 patients, and was observed in 17 patients in the transplant arm.
  - Responses.

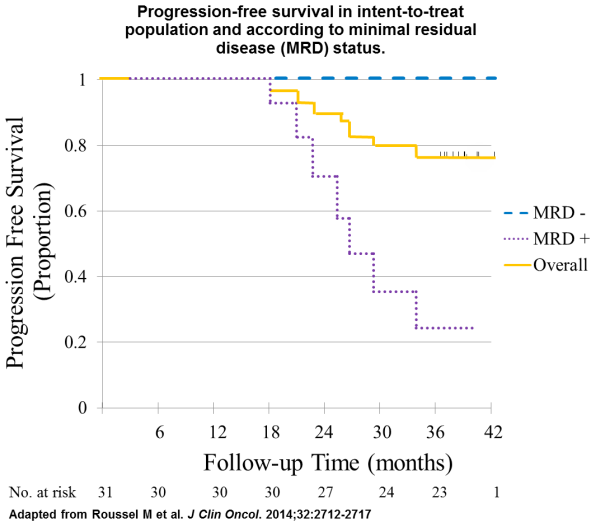
Table 2. Summary of Responses IMF 2008 Phase II[27]

Response	After Primary Induction Therapy (N=31)		After ASCT (N=30)*		After Consolidation Therapy (N=30)*		Best Response at Any Time (N=31)	
	No.	%	No.	%	No.	%	No.	%
ORR (≥PR)	29	94	28	93	29	97	31	100
sCR	3	10	8	27	12	40	15	48
CR	4	13	6	20	3	10	3	10
VGPR	11†	35	7	23	11†	37	8	26
PR	11	35	7	23	3	10	5	16
SD	2	6	2	7	1	3	0	0
PD	0	0	0	0	0	0		
MRD negative by flow cytometry**	4/25	16	14/26	54	15/26	58	21/31	68
sCR + CR	7	23	14	47	15	50	18	58
≥VGPR	18	58	21	70	26	87	31	100

ASCT=autologous stem-cell transplantation; CR=complete response; MRD=minimal residual disease; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

*One patient, who had achieved PR after induction therapy, did not receive planned ASCT because of mobilization failure. †One patient with negative serum and urine immunofixation but without bone marrow evaluation was assessed as having achieved VGPR. **Irrespective of other response criteria.

Figure 1. Progression-free Survival in Intent-to-Treat Population and According to MRD Status.[27]



Adapted from Roussel M et al. *J Clin Oncol.* 2014;32:2712-2717

This trial in combination with the IFM 2008 trial provide the basis for the current DFCI/IFM international trial: Randomized Trial of Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment with SCT in MM Patients up to Age 65 (DFCI 10-106).

Regimen Safety:

- As reported for the DFCI Phase I/II study Richardson PG, 2010.[28]
- At least one dose modification was required in 73% (48) of patients: 44% (29) bortezomib; 35% (23) lenalidomide; and 48% (32) dexamethasone.
    - Most common reasons for dose modification:
        - Bortezomib: neuropathic pain (15%, n=10), sensory neuropathy (14%, n=9), and fatigue (8%, n=5).
        - Lenalidomide: fatigue (6%, n=4, neuropathic pain (5%, n=3), sensory neuropathy (5%, n=3), and rash (5%, n=3).
- Dexamethasone: lower extremity edema (6%, n=4), mental status (5%, n=3), and tremor (5%, n=3).
- Most common terminology criteria for adverse event (CTCAE) grade ≥3 adverse events (AEs) included sensory neuropathy (80%, n=53), motor neuropathy (18%, n=12), and neuropathic pain (32%, n=21).
- Grade 3 or 4 AEs reported in at least 5% of patients included: lymphopenia (14%), neutropenia (9%), thrombocytopenia (6%), hypokalemia (5%) and hypophosphatemia (5%).

Table 3. Adverse Events Reported in at Least 15% of Patients in the Lenalidomide/Bortezomib/Dexamethasone Treated Population (N=68) Plus All Other Events Reported at Grade 3 or 4 Severity DFCI Phase I/II Study[28]

Event	Total, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neuropathy, sensory	53 (80)*	1 (2)	0
Fatigue	42 (64)	2 (3)	0
Constipation	40 (61)	0	0
Edema limb	30 (45)	0	0
Muscle pain	29 (44)	1 (2)	0
Rash/desquamation	24 (36)	1 (2)	0
Diarrhea	23 (35)	0	0
Nausea	21 (32)	0	0
Neuropathic pain	21 (32)	2 (3)	0
Extremity, limb pain	20 (30)	2 (3)	0
Insomnia	20 (30)	1 (2)	0
Hyperglycemia	18 (27)	1 (2)†	0
Dizziness	17 (26)	2 (3)	0
Constitutional, other	12 (18)	0	0
Dyspnea	12 (18)	0	0
Neuropathy, motor	12 (18)	1 (2)	0
Platelets	12 (18)	1 (2)	3 (5)
Pruritus/itching	12 (18)	0	0
Neutrophils	10 (15)	5 (8)	1 (2)
Anxiety	9 (14)	1 (2)	0
Dry skin	9 (14)	1 (2)	0
Lymphopenia	9(14)	7 (11)	2 (3)
Vision, blurred	9 (14)	1 (2)	0
Alanine transaminase	8 (12)	2 (3)†	0
Hypokalemia	7 (11)	3 (5)	0
Mental status	7 (11)	1 (2)	0
Hyperkalemia	6 (9)	1 (2)	0
Hyponatremia	6 (9)	1 (2)	0
Hypophosphatemia	6 (9)	3 (5)	0
Pulmonary/upper respiratory, other	6 (9)	2 (3)	0
Agitation	4 (6)	1 (2)	0
Hearing	4 (6)	1 (2)	0
Hemoglobin	4 (6)	1 (2)	0
QTc interval	4 (6)	2 (3)	0
Thrombosis/thrombus/embolism	4 (6)	2 (3)	1 (2)
Creatinine	2 (3)	1 (2)	0
Leukocytes	2 (3)	2 (3)	0
Atrial fibrillation	1 (2)	1 (2)	0
Infection, other	1 (2)	1 (2)	0
Stomach hemorrhage	1 (2)	1 (2)	0

*Including 34 (52%) patients with grade 1 and 18 (27%) with grade 2 neuropathy, sensory.
†One dose-limiting toxicity.

Table 4. Grade 3 to 4 AEs in Treated Population IFM 2008 Phase II Trial.[27]						
AE	**At Any Time (N = 31)**		**RVD Induction or Consolidation (N = 31)**		**Lenalidomide Maintenance (n = 30)**	
	No.	**%**	**No.**	**%**	**No.**	**%**
Any AE	28	90	15	50	20	67
Bone or lymphatic system disorder						
Neutropenia	20	65	11	35	18	60
Thrombocytopenia	6	19	4	13	1	3
Anemia	1	3	1	3		
Pancytopenia					1	3
Infection						
Enterocolitis infectious	2	6				
General disorder						
Fatigue	2	6			2	6
Skin disorder						
Rash	1	3	1	3		
Vascular disorder						
Deep vein thrombosis	1	3			1	3
Pulmonary embolism	1	3			1	3
Other						
Bone pain	1	3	1	3		
Dose reduction because of AEs	23	74	12	39	19	63
Discontinuation because of AEs	7	23	1	3	6	20

Drug-specific Safety:

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

- Lenalidomide[30]:
  - 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[30]

- 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[31]

- 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[32-34]:
    - 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)[35,36]:
    - 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[37]:
    - 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/*[30]
    - *Renal dose adjustments: Dose modification for lenalidomide is required in the presence of renal impairment.*[29,30]

Table 5. 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*[30]
    - *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/*[31]
    - *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 6. 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 7. 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***[38]
  - ***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 (NCCN); 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[35,36,38-40]***:***

- 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.[35,40]
  - 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.[38]
  - 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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Primary Author: Sandra E. Kurtin, RN, MS, AOCN©, ANP-C, Clinical Assistant Professor of Medicine, Adjunct Clinical Assistant Professor of Nursing. The University of Arizona Cancer Center, Tucson, Arizona
External Reviewer: Chris Fausel, PharmD, MHA, BCOP
Internal Reviewer: Eugene R. Tombler, PhD, Medical Director for MediCom Oncology and *Managing Myeloma*
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