Regimen Protocols

CyBorD: Primary Therapy for Newly Diagnosed, Transplant Eligible/ Ineligible and Relapsed/Refractory MM Patients[1]

Constituents of Regimen: Cyclophosphamide (Cy), bortezomib (Bor), dexamethasone (D)

Common Names or Abbreviations for Regimen: CyBorD, CVD, VCD, CBD

Other Names of Regimen Constituents:

- Cyclophosphamide: Cytoxan®, Neosar®, UNII: 8N3DW7272P
- 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.[2] Cyclophosphamide is a nitrogen mustard alkylating agent from the oxazaphosphorine group.[3] The mechanism by which the glucocorticoid dexamethasone induces apoptosis in multiple myeloma cells has not been fully elucidated, although studies suggest 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]

Bortezomib-based combination approaches with another alkylating agent, melphalan, have proven successful in newly diagnosed patients not eligible for transplant, while cyclophosphamide holds the advantage of allowing for peripheral blood stem cell collection.[16] The bortezomib, cyclophosphamide, dexamethasone (CyBorD) regimen has been clinically explored and translated into community practice for newly diagnosed (transplant eligible and ineligible) and relapsed/refractory multiple myeloma patients.[17] There are several variations of the dose-scheduling that have been used for this regimen in the newly diagnosed and relapsed and/or refractory setting.[18-21]

NCCN Recommended Indication: Recommended as primary therapy for newly diagnosed transplant candidates and non-transplant candidates, and recommended for previously treated multiple myeloma (MM).[17] ***NCCN Preferred Regimen or Other: Yes, preferred regimen for primary therapy for transplant candidates, preferred regimen for primary therapy for non-transplant candidates, and preferred therapy for previously treated multiple myeloma***[22] ***NCCN Category of Evidence and Evidence Blocks™ (See NCCN Guidelines Multiple Myeloma EB-1 for Evidence Blocks definitions):***

- Primary therapy for transplant candidates (category 2A)
  - Evidence Blocks: Efficacy of regimen/agent: 4/5, safety of regimen/agent: 3/5, quality of evidence: 4/5, consistency of evidence: 4/5, affordability of regimen/agent: 2/5

- Primary therapy for non-transplant candidates (category 2A)
    - o Evidence Blocks: Efficacy of regimen/agent: 4/5, safety of regimen/agent: 3/5, quality of evidence: 4/5, consistency of evidence: 4/5, affordability of regimen/agent: 2/5
- Therapy for previously treated multiple myeloma (category 2A)
    - o Evidence Blocks: Efficacy of regimen/agent: 4/5, safety of regimen/agent: 3/5, quality of evidence: 4/5, consistency of evidence: 4/5, affordability of regimen/agent: 2/5

Dose Schedules:

Relapsed/Refractory Disease Phase II Protocol Dose Schedule [28-day cycle][18]:

Cyclophosphamide 300 mg/m^2 by mouth once weekly; bortezomib 1.5 mg/m^2 by IV or SQ on days 1, 8, 15, 22; and dexamethasone by mouth once-weekly 40 mg on a 28-day cycle.

Note: *Bortezomib was tested at a 1.0 mg/m^2 dose in 2% of patients and at the familiar 1.3 mg/m^2 dose in 22% of patients. The remaining 76% of patients received the higher dose. The majority of patients, 87%, were treated with a once-weekly bortezomib schedule, with the remaining patients treated on a twice-weekly schedule.*

Newly Diagnosed, Transplant-eligible Patients, Phase II Protocol: **Once-weekly bortezomib dose schedule [28-day cycle][19]:**

Cyclophosphamide 300 mg/m^2 by mouth on days 1, 8, 15, 22; 1.5 mg/m^2 of bortezomib intravenously on days 1, 8, 15, 22, and dexamethasone by mouth on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle for cycles 1 and 2, then 40 mg once weekly for cycles 3 and 4.

Transplant-eligible Patients, Phase II Protocol: **Twice-weekly bortezomib dose schedule [28-day cycle]: Cyclophosphamide 300 mg/m^2 by mouth on days 1, 8, 15, 22; bortezomib administered by IV (or SQ) 1.3 mg/m^2 on days 1, 4, 8, and 11; and 40 mg of dexamethasone by mouth on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle.[19]**

Note: *SQ administration of bortezomib was not reported in this trial.*[19]

***Newly Diagnosed, Transplant-eligible and Ineligible EVOLUTION Trial Protocol [21-day cycle]*[20]:**

Cyclophosphamide by mouth 500 mg/m^2 on days 1, 8, and 15; bortezomib by IV or SQ 1.3 mg/m^2 on days 1, 4, 8, 11; and dexamethasone by mouth 40 mg on days 1, 8 and 15 on a 21-day cycle.

Note: *The EVOLUTION trial authors noted a lower than anticipated response in patients treated with the original VCD protocol which included two doses of cyclophosphamide per 21-day cycle (days 1 and 8) compared to those observed by Reeder, et al., which led to a modification of the EVOLUTION protocol for VCD to include three dose per 21-day cycle (days 1, 8, and 15) designated VCD-M (M for modified).*

Newly Diagnosed, Transplant-eligible IFM 2013-04 Trial [21-day cycle][21]:

Cyclophosphamide 500 mg/m² per day, by mouth on days 1, 8, and 15; bortezomib SQ 1.3 mg/m² on days 1, 4, 8, and 11; and dexamethasone 40 mg by mouth on days 1 to 4, days 9 to 12 for four 21-day cycles.

Note: *Using this version of the VCD regimen, the IFM 2013-04 trialists concluded that bortezomib/thalidomide/dexamethasone (BTD) was superior to VCD. This protocol is more similar to that Kumar, et al., used in the EVOLUTION trial.20 The EVOLUTION trial authors noted a lower than anticipated response based on those observed by Reeder, et al., which led to a modification of the EVOLUTION protocol for VCD. The IFM 2013-04 trial is one of the only phase III trials to date to explore VCD as induction therapy prior to transplant. Physicians should rely on their institutional protocols and experience in selecting a dose-schedule for this regimen in their practice. There are several notable differences between the dose schedules.*

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:

CyBorD for Relapsed and/or Refractory Disease Study[18]

- 55 patients with relapsed/refractory MM were treated with CyBorD on a 28-day cycle.
- Mean age was 65.6 years and 56% were male. Of the 55 patients, 64% had progressed while on therapy, and 56% had a previous autologous stem cell transplant (ASCT).
- Mean number of previous treatment lines was 3.3, and 36% and 82% were proteasome inhibitor (PI) and CyBorD naïve.
- Median follow-up time was 24.1 months, and mean number of cycles was 5 (4.4).

- Overall response rate (ORR): 71%.
    - Complete response (CR): 13%
    - Very good partial response (VGPR): 26%
- PI-naïve patients had an ORR of 95%, while patients who had previously received a PI had an ORR of 57%.
- Median progression-free survival (PFS) was 9.2 months.
- Median overall survival (OS) was 29 months.
- After a mean of 6 cycles, 22% of patients underwent subsequent ASCT.
- Increase in PFS in PI-naïve patients (14.8 vs. 5.2 months, HR 0.4, 95% CI 0.2-0.7), patients that underwent subsequent ASCT (19.7 vs. 6.3 months, HR 0.3, 95% CI 0.2-0.7) and patients that had 3 prior treatment lines (12.1 vs. 6.1 months, HR 0.5, 95% CI 0.2-0.8); no difference was found by mSMART risk or prior ASCT.
- An increase in OS was found only in PI-naïve patients (35.4 vs. 21.2 months, HR 0.5, 95% CI: 0.3-0.98) and those that underwent subsequent ASCT (53.1 vs. 26.7 months, HR 0.3, 95% CI 0.2-0.8); no difference was found by number of previous treatment lines, mSMART risk, or prior ASCT.

CyBorD for Newly Diagnosed, Transplant Eligible Patients (once-weekly, and twice-weekly bortezomib dose schedules)[19]

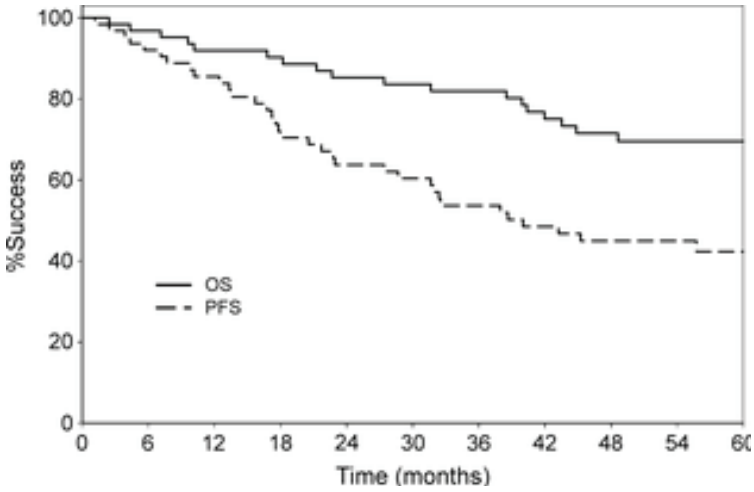
ITT	Cohort 1 [Twice-weekly Bortezomib Dosing] (n = 33)	Cohort 2 [Once-weekly Bortezomib Dosing] (n = 30)	All (n = 63)
ORR	88%	93%	90%
CR/nCR	39%	43%	41%
VGPR or better	61%	60%	60%
After 4 cycles	(n = 28)	(n = 27)	(n = 55)
ORR	96%	93%	95%
CR/nCR	46%	48%	47%
VGPR or better	71%	63%	67%

ITT=intention to treat; ORR=overall response; CR=complete response; nCR=near complete response; VGPR=very good partial response

Note: *Cohort 1 had more International Staging System stages II/III than cohort 2 (67% vs. 44%), but cohorts were otherwise comparable.*

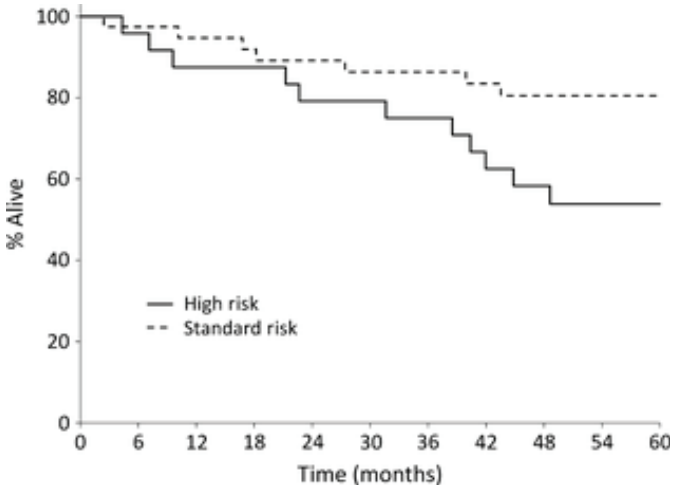
- ***The median PFS was 40.0 months.***
- ***The 5-year PFS and OS rates were 42% (95% confidence interval [CI]: 31–57) and 70% (95% CI: 59–82) for the entire group).***

Long-term Survival with Cyclophosphamide, Bortezomib and Dexamethasone Induction Therapy in Patients with Newly Diagnosed Multiple Myeloma[19]



Kaplan-Meier survival curves for all patients. OS=overall survival; PFS=progression-free survival

Long-term Survival with Cyclophosphamide, Bortezomib, and Dexamethasone Induction Therapy in Patients with Newly Diagnosed Multiple Myeloma[19]



Kaplan-Meier overall survival curves by mSMART risk

- *Analysis by risk:*
  - *Twenty-four of the 63 patients were considered high risk (38%) and had responses equal to standard-risk patients (88% vs. 90%, P = 1.0).*
  - *The median PFS was shorter in high-risk patients at 27.6 months vs. 55.7 months in the standard-risk patients.*
  - *High-risk patients had a 5-year PFS of 33% (95% CI: 19–59) vs. 48% (95% CI: 33–69) in the standard-risk group. Likewise, a lower OS rate (54% (95% CI: 37–78) vs. 81% (95% CI: 69–95) (P = ·04) was seen compared to standard-risk patients.*

Newly Diagnosed, Transplant-eligible and Ineligible EVOLUTION Trial[20]

	VDCR n = 48	VDR n = 42	VDC n = 33 Cyclophosphamide 500 mg/m^2 PO on days 1 and 8 of 21-day cycle	VDC-mod n = 17 Cyclophosphamide 500 mg/m^2 PO on days 1, 8, and 15 of 21-day cycle
Patient experience on study				
Median follow-up, months	20	20	22	15
Median cycles, n (range)	5 (1-12)	6 (1-12)	6 (3-12)	6 (3-12)
Completed induction, n (%)	16 (33)	17 (40)	15 (45)	7 (41)
Completed maintenance, n (%)	12 (25)	8 (19)	10 (30)	5 (29)
Confirmed response at cycle 4*	n = 41	n = 41	n = 32	n = 17
Complete response	2 (5)	3 (7)	1 (3)	2 (12)
sCR	1 (3)	1 (2)	0	2 (12)
VGPR or better	13 (33)	13 (32)	4 (13)	7 (41)
ORR (PR or better)	32 (80)	30 (73)	20 (63)	14 (82)
Progression	0	0	0	0
Best response across all cycles				
Complete response	10 (25)	10 (24)	7 (22)	8 (47)
sCR	6 (15)	7 (17)	3 (9)	5 (29)
VGPR or better	23 (58)	21 (51)	13 (41)	9 (53)
ORR (PR or better)	35 (88)	35 (85)	24 (75)	17 (100)
Progression	1 (3)	1 (2)	1 (3)	0

	VDCR n = 48	VDR n = 42	VDC n = 33 Cyclophosphamide 500 mg/m^2 PO on days 1 and 8 of 21-day cycle	VDC-mod n = 17 Cyclophosphamide 500 mg/m^2 PO on days 1, 8, and 15 of 21-day cycle
Best response across all cycles among patients ≤65 years	n = 28	n = 28	n = 21	n = 12
Complete response	6 (21)	6 (21)	2 (10)	7 (58)
VGPR or better	15 (54)	17 (61)	5 (24)	8 (67)
ORR (PR or better)	24 (86)	26 (93)	14 (67)	12 (100)
Survival estimates				
1-year progression-free survival (PFS)	86%	83%	93%	100%
1-year PFS without transplant	83%	68%	97%	100%
1-year PFS for patients who proceeded to transplant after 4-8 cycles of therapy	100%	100%	88%	100%
1-year overall survival (OS) estimate	92%	100%	100%	100%
1-year OS for patients who proceeded to transplant after 4-8 cycles of therapy	100%	100%	100%	100%

As the EVOLUTION trial was a comparator trial, results of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide (VDCR), and bortezomib, dexamethasone, and lenalidomide (VDR) are provided in this table. The protocol was modified to include two different dose-schedules of VDC as noted in the table.

- The 1-year PFS for the high-risk patients (n = 24) was 100% and 85% for the standard-risk patients, and was similar across the study arms.

Newly Diagnosed, Transplant-eligible IFM 2013-04 Trial [21-day cycle] NCT01564537[21]:

- Patients were stratified according to International Staging System (ISS) (1-2 versus 3) and cytogenetics (high-risk defined by 17p deletion and t(4;14) versus other).
- The primary endpoint was very good partial response (VGPR) rate following 4 cycles.
- 358 patients were enrolled into the study; 18 were screening failures, and 170 were randomized each to arm A (VTD) and arm B (VCD); the median age was 60 years (range, 26-65), 62% of the patients were male, and overall, the patient characteristics were well-balanced across the 2 arms of the study.
- The median number of induction cycles administered in both arms was 4 (1-4).

Responses to Treatment VTD vs VCD IFM-2013-04 Trial[21]

- Response to treatment:

Intent-to-treat Analysis	VTD (n=169)	VCD (n=169)	*P*-value
Overall response rate (ORR; ≥PR)	92.3%	83.4%	0.01
Complete response or better (≥CR)	13.0%	8.9%	0.22
Very good partial response or better (≥VGPR)	66.3%	56.2%	0.05
Per Protocol Analysis	**VTD (n=157)**	**VCD (n=154)**	***P*-value**
Overall response rate (ORR; ≥PR)	98.7%	90.3%	0.001
Complete response or better (≥CR)	14%	9.1%	0.17
Very good partial response or better (≥VGPR)	70.7%	60.4%	0.05

Safety

- Relapsed/Refractory Disease Phase II Protocol Dose Schedule [28-day cycle][18]:
  - Reported safety data was limited to new onset grade 1, neuropathy was present in 16% of patients, while only 2% had grade 2 and none had grade 3 neuropathy.
- Newly Diagnosed, Transplant-eligible patients, Phase II Protocol Once-Weekly Bortezomib Dose Schedule [28-day cycle][19]:
  - No formal reporting of safety data was made beyond the observation that CyBorD employed in a once-weekly schedule is not associated with thrombosis or severe neuropathy.

- Newly Diagnosed, Transplant-eligible and Ineligible EVOLUTION trial[20]
  - At least one grade ≥3 AE was seen in ~80% of patients in each arm.
  - AEs leading to discontinuation were seen in 12% and 6% of patients in the VDC and VDC-mod arms, respectively.
  - The median time-to-study discontinuation because of any toxicity was 3 months across the entire study, with 4 and 1 patients discontinuing because of AEs in the VDC and VDC-mod arms, respectively.
  - Hematologic toxicity was frequent, with neutropenia being the most common in the cyclophosphamide-containing arms.
  - The most common nonhematologic toxicities included peripheral neuropathy, fatigue, nausea, constipation, and diarrhea.
  - Grade 1/2 peripheral neuropathy was seen in 21 and 8 patients in VDC and VDC-mod arms, respectively.
  - No secondary malignancies were reported.

o Major Adverse Events of Grade 3 or Above[20]

	VDC n = 33	VDC-mod n = 17
Hematologic AEs, n (%)		
Neutropenia	10 (30)	4 (24)
Febrile neutropenia	2 (6)	0
Thrombocytopenia	4 (12)	0
Leukopenia	3 (9)	1 (6)
Anemia	0	2 (12)
Lymphopenia	4 (12)	0
Nonhematologic AEs		
Pneumonia	0	1 (6)
Neuropathy	3 (9)	3 (18)
Fatigue	1 (3)	0
Diarrhea	1 (3)	1 (6)
Nausea	0	0
Thromboembolism	0	0
Constipation	0	0
Hyperglycemia	0	0
Summary		
At least one grade 3 or above AE	26 (79)	15 (88)
At least one drug-related grade 3 or above AE		12 (71)
At least one grade 3 or above hematological AE	17 (52)	5 (29)
AE resulting in discontinuation	4 (12)	1 (6)

V=bortezomib; D=dexamethasone; C=cyclophosphamide; VDC-mod=VDC plus a day 15 dose of C; AE=adverse event

- Newly Diagnosed, Transplant-eligible IFM 2013-04 Trial [21-day cycle][21]:
    - Toxicity Grade 3-4

	VTD, n = 169 Grade 3-4%	VCD, n = 169 Grade 3-4%	*P*-value
Any AEs	63.9	68.2	0.40
Anemia	4.1	9.5	0.05
Neutropenia	18.9	33.1	0.003
Infection	7.7	10.1	0.45
Thrombocytopenia	4.7	10.6	0.04
Thrombosis	1.8	1.8	0.99
Cardiac disorders	1.2	0	0.16
Cystitis	0	0.6	0.32
GI symptoms	5.3	3.5	0.42
Peripheral neuropathy	7.7	2.9	0.05
PN grade 2-4	21.9	12.9	0.008

Required Supportive Care/Prophylaxis: Patients on this regimen are at an increased risk for pneumonia, varicella zoster virus (VZV) or shingles reactivation, myelosuppression, and peripheral neuropathy (PN). The following recommendations should be considered:

- 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).*
- Indefinite antiviral prophylaxis with acyclovir or valacyclovir for herpes zoster infections is recommended for patients receiving proteasome inhibitors such as bortezomib.
- Patients who receive bortezomib are at risk to develop PN. All patients should be educated as to the signs/symptoms of PN and to report the onset or worsening of PN symptoms immediately.
- 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.

- 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.

Tailoring of Regimen: To maximize dose delivery and reduce toxicity (primarily from PN), investigators in the original CyBorD trial modified the original schedule and accrued 30 additional patients. A second cohort received the same weekly cyclophosphamide schedule, but bortezomib was changed to a dose of 1.5 mg/m^2 of bortezomib intravenously on days 1, 8, 15, 22, and dexamethasone as in cohort 1 for cycles 1 and 2, then reduced to 40 mg orally once weekly for cycles 3 and 4.[23] It is important to note that the current recommended starting dose of bortezomib is 1.3 mg/m^2 SC/IV days 1, 4, 8, and 11 of a 21-day schedule.

- Patients with moderate-to-severe hepatic impairment should be started at a lower dose of bortezomib.
- Bortezomib should be given SC to all patients to minimize the risk of severe PN.

Safety: Warnings for bortezomib and cyclophosphamide are outlined below:

- Hypotension: Hypotension can occur with bortezomib. Caution should be exercised in patients receiving hypertensive agents, those who are dehydrated, or in those with history of syncope.
- Cardiac: Although rare, patients can develop cardiac toxicity from bortezomib and cyclophosphamide. Patients with risk factors such as pre-existing heart disease should be monitored.
- Pulmonary: Bortezomib can cause pulmonary toxicity of unknown etiology. In the event of new or worsening cardiopulmonary symptoms, bortezomib should be interrupted and a thorough diagnostic evaluation should be conducted.

- Posterior reversible encephalopathy syndrome (PRES): Bortezomib can cause a rare yet reversible neurological disorder. Monitor for seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances.
- Thrombocytopenia can occur with bortezomib and should be managed with dose modifications or platelet transfusions.
- Gastrointestinal distress can occur (nausea, vomiting, diarrhea) and can be managed by preventative antiemetic agents.
- Embryo-fetal risk: Women should not become pregnant if taking bortezomib.

In the clinical trial,[1] among patients receiving high-dose dexamethasone and twice-weekly IV bortezomib, the most common serious adverse events (grade 3 and above) were:

- Thrombocytopenia (25%), anemia (12%), neutropenia (13%), hyperglycemia (13%), diarrhea (6%), hypokalemia (9%), neuropathy (7%), and thrombosis (7%).
- Nausea and GI upset occurred but were generally mild.

Strategies to Reduce Treatment-associated Side Effects:

- To reduce the risk of neuropathy, bortezomib should be given SC.
- Dietary considerations and strategies to minimize nausea and gastrointestinal upset (use of prophylactic antiemetic agents, avoid greasy, fried heavy meals) should also be discussed.
- Electrolyte monitoring (eg, potassium) to identify and correct electrolyte abnormalities should be performed.
- A CBC with differential should be obtained prior to each bortezomib dose to monitor neutropenia and thrombocytopenia.

Monitoring Recommendations and Notes:

- Adverse events (as listed above under “safety”) should be monitored for and addressed at each visit. Regular CBC/diff and chemistry monitoring to assess for myelosuppression and hepato/renal abnormalities is suggested.
- Patients should be educated regarding the side effects of medications as listed above (primarily PN) and monitored closely. All patients should be 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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