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A REVIEW OF THE MECHANISM OF ACTION, SAFETY AND EFFICACY OF SELINEXOR IN MULTIPLE MYELOMA

Introduction

In recent years, the armamentarium of routinely available treatments for relapsed and/or refractory multiple myeloma (RRMM) in Canada has dramatically expanded, but treatment gaps still exist. In early relapse (1-3 prior lines), monoclonal antibody (mAb) combinations on a backbone of lenalidomide or bortezomib (e.g. DRd, DVd) have been the mainstay, with combinations building on second generation backbones such as pomalidomide and carfilzomib (e.g. PCd, PVd, Kd) largely reserved for later relapse (after 2 prior lines). However, the increasing use of multi-class drug combinations in the frontline (e.g. DRd, RVd) and a shift towards ongoing therapy until progression, renders patients heavily drug-exposed and refractory at time of early relapse, needful of treatments with novel mechanisms of action. Selinexor is poised to fill an unmet need with a unique, non-overlapping mechanism of action to other available agents. XPOVIO® (selinexor) is indicated in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.[1] SVd received Health Canada approval May 31, 2022. This review will present data on selinexor's mechanism of action, efficacy in combination with dexamethasone and bortezomib (Sd, SVd), dosing and scheduling, as well as the management of its common and distinct toxicities.

Mechanism of action (MOA)

Selinexor is an oral, first-in-class, selective inhibitor of a nuclear export protein also known as exportin (XPO1) and represents a new class of therapy for patients with MM. By binding reversibly to Cys528 in the cargo-binding pocket of XPO1, selinexor blocks XPO1 function without affecting other nuclear transporters.[2] XPO1 is responsible for the transport of more than 200 targets including tumor suppressor proteins (TSPs) and oncoprotein mRNAs from the nucleus to the cytoplasm. Many of these proteins are tumor suppressors and cell cycle negative regulators such as p53, RB1, p21, amongst others. Treatment of cancer cells with selinexor induces nuclear retention of TSPs and blocks the export of eIF4E-bound oncoprotein mRNAs, leading to apoptosis, reduced levels of proto-oncoproteins and impaired osteoclastogenesis.[2,3] Altered nuclear export signaling is recognized as a driver of oncogenesis. As such most hematologic

Regimen Abbreviations: DVd – daratumumab, bortezomib, dexamethasone, DRd – daratumumab, lenalidomide, dexamethasone, PCd – pomalidomide, cyclophosphamide, dexamethasone, PVd – pomalidomide, bortezomib, dexamethasone, Kd – carfilzomib, dexamethasone, RVd – lenalidomide, bortezomib, dexamethasone, Sd – selinexor, dexamethasone, SVd – selinexor, bortezomib, dexamethasone,

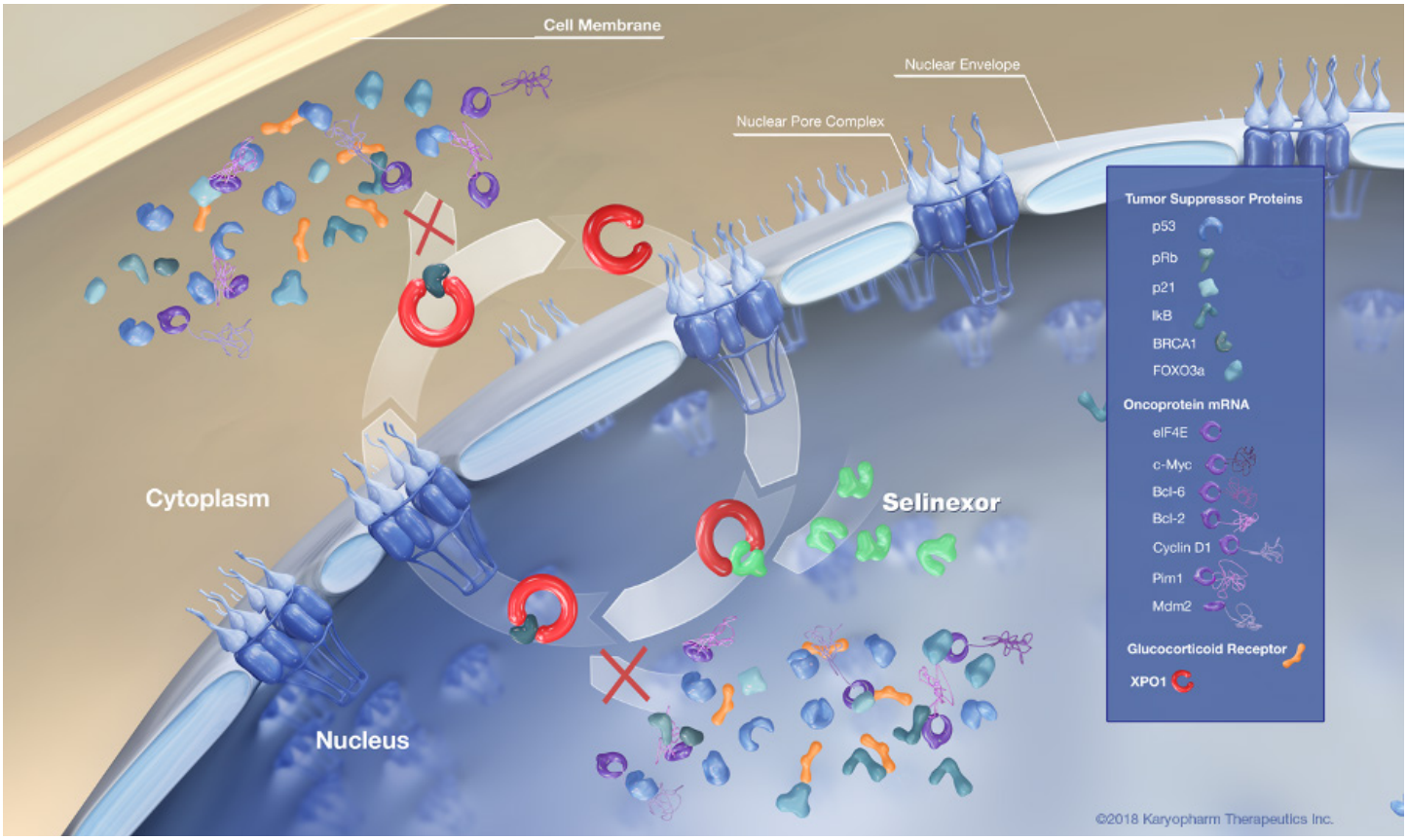

Figure 1: *Selinexor mechanism of action; courtesy of Karyopharm*

and solid tumor malignancies, including MM, overexpress XPO1 and its over-expression often correlates with aggressive disease and poor prognosis.[2,3] In addition, a genome-wide RNA interference screen has identified XPO1 as an essential gene required for MM survival and proliferation[4], highlighting its potential as a therapeutic target (**Figure 1**).

Preclinical studies have demonstrated selinexor's anti-MM activity as monotherapy and a synergistic interaction was observed when combined with glucocorticoids, proteasome inhibitors, and immunomodulatory drugs.[5,6] These findings lead to the evaluation of XPO1 inhibitors for the treatment of MM and several prospective clinical trials have been conducted to investigate the safety and efficacy of selinexor-based treatment in patients with RRMM.[7]

In particular, when combined with proteasome inhibitors (PIs), selinexor has shown synergistic activity in PI-resistant MM cells and in a MM xenograft mouse model through suppression of NF-κB transcriptional activity and induction of ribosomal stress response.[5,6,8,9] This synergistic activity with PIs has provided the rationale for the development of the BOSTON trial in which selinexor was combined with bortezomib and dexamethasone (SVd) in patients with MM.

The BOSTON Trial

The BOSTON (NCT03110562) study[10] was a prospective, open-label, multicenter, phase III trial that enrolled 402 patients at 123 sites in 21 countries globally, including 12 Canadian sites (**Figure 2**). An open-label design was necessary due to the differences in selinexor and bortezomib dosing and the efficacy outcomes were confirmed by an independent review committee (IRC).

This trial was the first large phase III study to compare a triplet regimen of selinexor, once-weekly bortezomib and dexamethasone (SVd) to a standard arm of twice-weekly bortezomib and dexamethasone (Vd). Of interest, the weekly dosing scheduling of bortezomib led to a 40% reduction in overall bortezomib use and a 37% decline in clinic visits when compared to twice-weekly Vd.[10] This once weekly bortezomib schedule also reflects the standard Canadian practice where bortezomib is used weekly to reduce its side effects.

The BOSTON study included 402 patients with a median age of 67 years (range 38-90) and receiving a median of two prior therapies. The key inclusion and exclusion criteria along with the study's stratification criteria are summarized in **Figure 3**. Prior treatment with a PI (alone or in combination) was allowed, provided that the patient had achieved at least a partial response (PR), discontinuation was not due to a grade ≥3 treatment-related toxicity, and ≥6 months had elapsed since last dose of the PI.[10]

Sixty-nine percent of the patients (n=279) were previously treated with bortezomib, while 38% (n=154) had prior lenalidomide exposure. High risk cytogenetic defined by the presence of deletion 17p, t(4;14), t(14;16) and gain of 1q were present in 48% (n=190) of the patients.[10]

Figure 2 reviews the dosing schedule for patients enrolled in the BOSTON study. Patients continued treatment until disease progression, physician decision, withdrawal of consent, or unacceptable side effects. After confirmed disease progression, 74 patients (36%) from the Vd arm crossed over to receive XVd or Xd in accordance with the study protocol.[10]

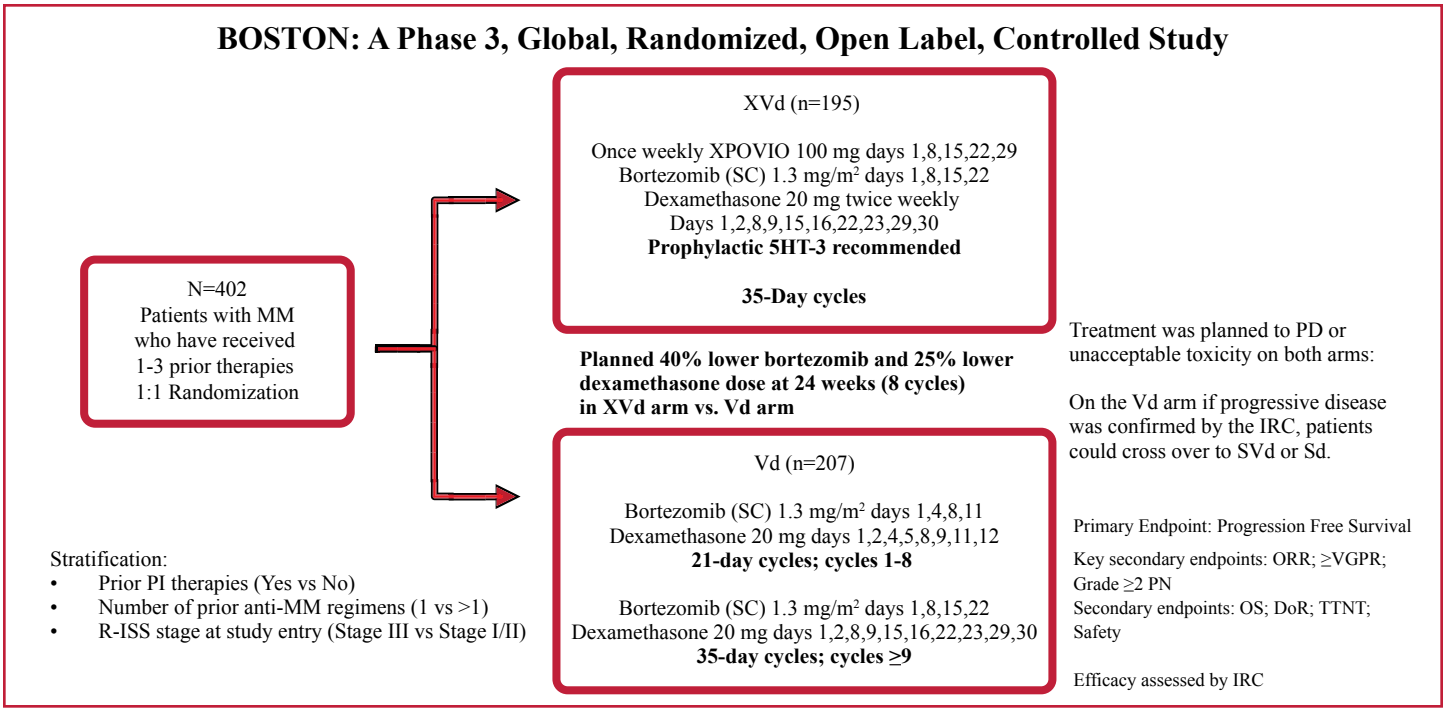

Figure 2: *BOSTON Study design; adapted from Grosicki et al., 2020*

MM = multiple myeloma, PI= proteasome inhibitors, SC= subcutaneous, PD = progressive disease, PN= peripheral neuropathy, TTNT= time to next treatment, IRC= independent review committee.

BOSTON: Efficacy (PFS, ORR, DoR, TTNT and OS)

The primary endpoint of progression free survival (PFS) was met with a significantly longer median PFS in the SVd arm than in the Vd arm (13.93 months [95% CI: 11.73 to not evaluable] vs. 9.46 months [95% CI: 8.11 to 10.78]; p = 0.0075), respectively. This corresponds to a PFS benefit of 4.47 months relative to twice-weekly Vd, a clinically significant benefit in this patient population.[10] Consistent with the improved PFS, secondary endpoints also favored SVd over Vd: ORR 76.4% vs 62.3% (p=0.0012); ≥VGPR 44.6% vs 32.4% (p=0.0082); median TTNT 16.13 vs 10.84 (p=0.0012). There was also a longer median treatment free interval for patients with new MM treatment in the SVd arm at 28.0 days (range, 1 to 447) than the Vd arm at 14.0 days (range, 1 to 419).[10] At the time of the primary analysis (February 18, 2020), the median OS had not been reached for the SVd arm and the median OS in the Vd arm was 24.97 months (95% CI: 23.49 months to not evaluable).

The incidence of peripheral neuropathy (PN) was significantly lower (p= 0.0010) in the SVd arm (32%) than in the Vd arm (47%) irrespective of the grade and there was a numerically lower incidence of grade 3–4 PN with SVd (4.6%) compared with Vd (8.8%). Of note, PN was the most common AE leading to treatment discontinuation, involving 4.6% of patients in the SVd arm vs. 7.4% in the Vd arm.[10]

Improvements in PFS, ORR and a generally manageable safety profile were observed across a variety of patient subgroups, including patients with high risk cytogenetics and elderly (aged > 65 years old) (**Figure 4**).[10]

A post hoc analysis was performed in the BOSTON and STOMP trials to evaluate the efficacy of SVd in patients with high-risk cytogenetics (HR-Cyto). The HR-Cyto group comprised patients with at least one of the following cytogenetic abnormalities at initial diagnosis or screening: del(17p), t(4;14), t(14;16), or gain(1q) (≥ 3 copies). As shown in **Figure 5**, patients with HR-Cyto had a comparable PFS and ORR to those with standard risk cytogenetics (SR-Cyto) with a median PFS of 12.9 months and 16.6 months, respectively. By comparison, the PFS reported in the HR- and SR-Cyto groups treated with the Vd control arm were 8.6 and 9.5 months, respectively.[13] Interestingly, in-vitro studies have demonstrated an increased sensitivity to selinexor of primary patient samples harbouring high-risk cytogenetics [(t 4;14) or del(17p)] and patient samples with proliferative disease (high plasma cell S Phase), suggesting a potential role for SVd in the treatment of patients with high-risk features.[14]

Key Inclusion Criteria	Key Exclusion Criteria
• Progressive measurable MM per IMWG criteria[1]	• > Grade 2 neuropathy or ≥ Grade 2 neuropathy with pain at baseline
• 1–3 prior anti-MM regimens (at least a PR to a prior PI, if received)	• Prior exposure to a SINE, including XPOVIO®
• Patients with moderate or severe renal impairment (CrCl ≥ 20mL/min) allowed, patients requiring dialysis excluded	• Prior malignancy that required treatment/had evidence of recurrence
• ECOG status score 0–2	• Concurrent medical condition/disease/active infection
• Adequate hepatic and hematopoietic function	• Active plasma cell leukemia
• ANC > 1,000/mL	• MM involving the CNS
• Platelets > 75,000/mL	

Figure 3: *BOSTON trial key inclusion/exclusion criteria and stratification criteria; adapted from Grosicki et al., 2020*

1. International Myeloma Working Group (IMWG) Criteria: Kumar S, et al. Lancet Oncology. 2016. Kumar et al. Leukemia 2017.
ANC = absolute neutrophil count, CNS = central nervous system, CrCl = creatinine clearance, ECOG = Eastern Cooperative Oncology Group.

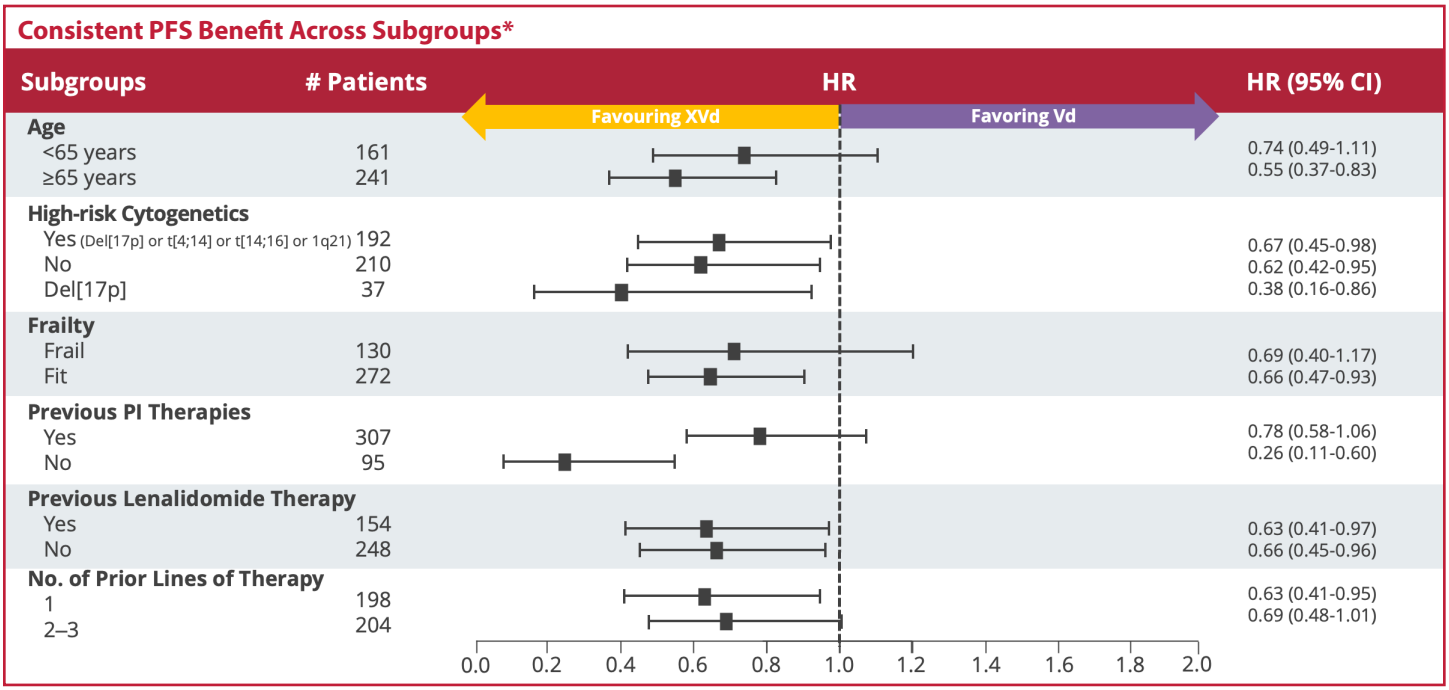

Figure 4: *Prespecified subgroup analysis for progression-free survival; adapted from Grosicki, 2020*

**These subgroup analyses were exploratory in nature, not included in the study objectives, and do not control for type 1 error. These subgroup analyses were not powered or adjusted for multiplicity to assess PFS across these prespecified subgroups.*
CI: confidence interval; d: dexamethasone; HR: hazard ratio; PI: proteasome inhibitor; V: Velcade (bortezomib); X: XPOVIO (selinexor).

	Del[17p] (N = 25)*	T[4; 14] (N = 25)*	Gain(1q) (N = 80)*	Combined High Risk (N = 106)	Standard Risk (N = 131)
PFS, months	12.22	13.24	13.93	12.91	16.62
95% CI	(5.82, NR)	(12.91, NR)	(7.95, NR)	(7.95, 17.77)	(11.76, NR)
OS, months	NR	20.44	NR	NR	NR
95% CI	(18.53, NR)	(17.77, NR)	(21.39, NR)	(18.53, NR)	(NR, NR)
ORR, n (%)	18 (72.0)	22 (88.0)	59 (73.8)	81 (76.4)	91 (69.5)
95% CI	(50.6, 87.9)	(68.8, 97.5)	(62.7, 83.0)	(67.2, 84.1)	(60.8, 77.2)

Figure 5: *High-risk cytogenetic profile of patients in BOSTON and STOMP; adapted from Bahlis et al., 2021*
**Subgroups with more than 10 patients*
CI, confidence interval; NR, not reached; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.

Regimen details and dose modifications

The dose and schedule of SVd and dose reduction levels outlined in the product monograph are shown in **Table 1**. Selinexor elimination occurs primarily through hepatic transformation and fecal excretion. Mild hepatic dysfunction does not appear to impact clearance but cautious dosing should be undertaken for moderate or severe hepatic dysfunction, as few such patients have been evaluated.[15] Dosing modifications are not required with renal dysfunction, though scant data in patients with end-stage renal failure (ESRF) or on dialysis may warrant conservative dosing at start, with careful ramp up. Selinexor is not significantly affected by CYP enzyme drug interactions, though it is prudent to avoid the concomitant use of drugs that may potentiate common toxicities of selinexor (e.g. nausea, diarrhea, cytopenias).

Toxicity and management

When used as monotherapy or in a doublet with dexamethasone in heavily pretreated MM, selinexor dosing of 80mg orally twice weekly is utilized.[16,17] This intensive dose and schedule may be necessary to gain control of rapidly progressive disease but can be challenging to tolerate. Toxicities such as nausea, vomiting, diarrhea, fatigue, and thrombocytopenia are common and frequently occur within cycle 1; hence prompt intervention is warranted to avoid early discontinuation before clinical benefit can be attained. When given in triplet combinations such as SVd in less heavily pretreated patients, selinexor can be administered at lower, once weekly dosing, leading to decreased adverse events, even in older frail patients.[10,11,18]

The most common non-hematologic toxicities observed with selinexor are gastrointestinal (GI)-related. With the SVd regimen, any grade GI toxicities include: nausea (50%), anorexia (35%), weight loss (26%), diarrhea (32%), and vomiting (21%).[10] These toxicities tend to be worse in the first cycle, frequently occurring within the first week and waning over subsequent cycles. Given selinexor's ability to cross the blood-brain barrier, nausea, vomiting and anorexia appear to be centrally mediated,

SVd dose and schedule (on a 35 day cycle)	
Selinexor 100mg PO; days 1,8,15,22,29	
Bortezomib 1.3mg/m^2 SC; days 1,8,15,22	
Dexamethasone 40mg PO; days 1,8,15,22,29 (if elderly, dose reduce to 20mg)	
SVd dose and schedule (on a 35 day cycle)	
Starting dose	100mg PO weekly
First dose reduction	80mg PO weekly
Second dose reduction	60mg PO weekly
Third dose reduction	40mg PO weekly
Fourth dose reduction	Permanently discontinue

Table 1: *SVd regimen and dose modifications; XPOVIO product monograph, 2022*

supporting the use of centrally acting anti-emetics such as olanzapine or ondansetron.[19] The routine use of both anti-emetics prior to the first dose, along with pre-emptive home hydration for the first few days of cycle 1 or in proximity to dosing days may avert the need for dose reduction. Associated toxicities include fatigue, hyponatremia, and weight loss; therefore, a holistic approach using anti-emetics, hydration, dietary counseling, nutritional supplements (including salt tablets), and close monitoring of counts, weight, and volume status, especially during the initial ramp up is critical. In the BOSTON trial, respiratory infections (pneumonia, bronchitis, upper respiratory) occurred in 12-18% of patients receiving SVd, therefore prophylactic antibiotics should be considered.[10] Although zoster reactivation is not commonly reported across selinexor trials, antiviral prophylaxis is warranted with SVd due to known risks with bortezomib. Severe neuropathy is uncommon with SVd (5%), owing to selinexor's lack of neurotoxicity and the weekly dosing schedule of bortezomib.[10,20]

The most common hematologic toxicity associated with selinexor is thrombocytopenia, although the incidence of 60% (39% grade 3-4) with SVd may also be impacted by bortezomib-related thrombocytopenia.[10] Thrombocytopenia can occur as early as 7 days after the first dose, with nadirs occurring within 1-2 months.[21] Severe thrombocytopenia is more likely in patients with baseline platelet counts of < $75x10^9$/L at the start of therapy and therefore these patients warrant weekly CBC monitoring at the start.[17] Although clinically relevant bleeding is uncommon with SVd, 6% of patients required platelet transfusions and 2% discontinued therapy due to thrombocytopenia in the BOSTON trial.[10]

Selinexor is not directly cytotoxic to megakaryocytes, but rather causes inhibition of thrombopoietin signaling; therefore, TPO receptor agonists have been used with success.[22] Neutropenia is less common with SVd (15%; 9% grades 3-4) and febrile neutropenia is rare.[10] Across selinexor trials, the use of growth factor as supportive therapy is common (75%) and once or twice weekly granulocyte colony-stimulating factor (G-CSF) use may avoid the need for selinexor dose reductions.[21] The use of adjunct growth factors to manage cytopenias may be preferred over dose reduction of selinexor in patients who have not yet attained myeloma disease control.

Table 2 outlines the incidence of common toxicities with SVd and practical suggestions in the management of selinexor-related toxicities.

Summary: The role of SVd in the Canadian treatment landscape

Given its unique mechanism of action, selinexor appears to be a promising agent for RRMM patients. As discussed, SVd is highly active in early MM relapse and has been shown to be generally tolerated with appropriate management strategies in place to address common toxicities. The optimization of dosing and supportive measures are key to maximizing response and tolerance, and, in turn, outcomes with selinexor-based therapy.

So where might the SVd triplet fit best in the Canadian treatment landscape? In first relapse, most Canadian patients are lenalidomide-refractory, having progressed on lenalidomide maintenance post-transplant or continuous Rd-based therapy if transplant-ineligible. Hence, a bortezomib-based triplet such as SVd may be a rational option over standard mAb-based triplets (e.g. DVd) in patients preferring an oral alternative or those uninterested in pursuing immunotherapies, such as CAR T-cell therapy or bispecific T-cell engagers, where early exposure to mAbs is a prerequisite. Furthermore, the shift of mAbs to the frontline in regimens such as DRd in transplant-ineligible settings may render patients antibody-refractory at the time of first relapse, widening the scope for novel regimens like SVd that are not mAb-based. SVd may also fill an unmet need in specific patient niches, such as those with renal impairment or immunomodulatory drug hypersensitivity where agents such as carfilzomib or pomalidomide are contraindicated. Once weekly SVd was also shown to be generally well-tolerated and active in MM patients with high risk features associated with poor outcome due to aggressive and resistant disease. Therefore, selinexor-based combinations such as SVd represent promising treatment options filling an unmet need for patients with advanced and refractory MM.

Non-hematologic	Incidence (%) All grades (grade 3-4)[10]	Practical management suggestions
Nausea Vomiting	50(8) 21(4)	• Initiate prophylactic ondansetron 8mg and olanzapine 2.5-5mg PO on the evening prior to dosing and repeat before and after dosing. For ongoing symptoms, continue BID x 24-48 hours or longer, as needed • Symptoms are maximal with first 1-2 cycles, therefore antiemetics can be weaned as appropriate • If not resolved, consider adding aprepitant 80-125mg PO 30 minutes prior to dosing • Other adjuncts include to consider include: benzodiazepines such as lorazepam 0.5-1.0mg PO or SL daily or cannabinoids, such as dronabinol 3.5-5mg PO BID, as needed • If severe and persistent with anti-emetics, interrupt selinexor until improved, then resume at lower dose with same anti-emetics • If poor baseline oral hydration, consider starting home hydration with intravenous saline 1-2L/day prior to first dosing and continuing as needed
Diarrhea	32(6)	• Loperamide 2mg PO with each loose bowel movement, max 16mg/day • Alternative: bismuth subsalicylate 2 tablets PO (262mg/tab) every half-hour until improved, max 16 tablets/day • If severe or recurrent, interrupt selinexor until improved and resume at lower dose
Weight loss Decreased appetite	26(2) 35(4)	• Ensure adequate control of nausea (see above) • Nutritional counseling, oral nutritional supplements • Olanzapine 5mg PO in the evenings prior to dosing may help with both appetite and nausea • For weight loss >5% body weight, consider appetite stimulants: megestrol 400mg PO daily or dronabinol 2.5mg PO daily (or other choice of cannabinoids) • If weight loss ≥10% body weight, interrupt selinexor until regained to ≥90% of baseline weight, then resume at lower dose
Fatigue	42(13)	• Often associated with diarrhea, nausea, weight loss, decreased appetite, hyponatremia; therefore follow above measures and correct electrolyte abnormalities • If associated with insomnia, mirtazapine or olanzapine can be helpful • Consider methylphenidate 10mg PO BID • If severe, interrupt until improved, then resume at lower dose
Hematologic	**Incidence (%) All grades (grade 3-4)**	**Management recommendations**
Neutropenia	15(9)	• For ANC <0.5x10^9/L or febrile neutropenia, interrupt selinexor until ANC recovers to 1.0x10^9/L or higher, then resume at lower dose • As an alternative to initial dose reduction, G-CSF 300ug SC once or twice weekly can be used to maintain ANC >1.0x10^9/L • Dose reduce for recurrent neutropenia despite G-CSF support
Thrombocytopenia	60(39)	• Monitor CBC weekly, particularly if baseline platelets <75x10^9/L, for cycle 1 at least, and as needed until platelet count is stable • Interrupt selinexor if platelets fall <25x10^9/L or any bleeding. Hold until bleeding ceases and platelets recover to ≥50x10^9/L, then resume at lower dose • Transfuse platelets for severe bleeding • For recurrent thrombocytopenia, consider TPO-mimetics: romiplostim up to 10µg/kg SC weekly or eltrombopag 50-100mg PO daily, aiming to maintain platelets >50x10^9/L

Table 2: *Common toxicities with SVd and suggested management; courtesy of Christine Chen, MD*

ANC= absolute neutrophil count, SC= subcutaneous, CBC = complete blood count, G-CSF= granulocyte colony-stimulating factor, TPO=thrombopoietin

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