Published in final edited form as:

Ann Pharmacother. 2020 June ; 54(6): 577–582. doi:10.1177/1060028019892643.

Selinexor: A First-in-Class Nuclear Export Inhibitor for Management of Multiply Relapsed Multiple Myeloma

Tim J Peterson, PharmD, BCOP[1], **Jennifer Orozco, PharmD**[1], **Michael Buege, PharmD, BCOP**[1]

[1]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Objective: To review the pharmacology, pharmacokinetics, efficacy, and safety of selinexor for management of relapsed multiple myeloma (MM).

Data Sources: A literature search was performed of PubMed and Medline databases (January 1, 2000 to November 14, 2019), abstracts from the American Society of Hematology and the American Society of Clinical Oncology, and ongoing studies from U.S. National Institutes of Health clinicaltrials.gov. Queries were performed using key words *selinexor, SINE, XPO1, and Xpovio*.

Study Selection/Data Extraction: Human and animal studies related to the pharmacology, pharmacokinetics, efficacy, and safety of selinexor were identified.

Data Synthesis: Although numerous advances have been made in MM management, there remains an unmet need for treatment of heavily relapsed/refractory disease. Selinexor is a first-in-class selective inhibitor of nuclear export which, through inhibition of exportin-1, causes accumulation of tumor suppressor proteins, reduction in oncoproteins, and apoptosis of plasma cells. Selinexor exhibited an overall response in 26% of patients with multiply relapsed MM. Median progression free survival was 3.7 months and overall survival was 8.6 months. Common adverse effects include thrombocytopenia, neutropenia, fatigue, and nausea. Ongoing studies are investigating combination therapies utilizing selinexor.

Relevance to Patient Care and Clinical Practice: This review describes the efficacy, safety, and clinical applicability of selinexor, a novel agent with potential to meet an unmet need in refractory MM.

Conclusion: Selinexor has demonstrated activity in a heavily refractory patient population. Given the adverse effect profile and associated costs, additional studies are needed to further elucidate the appropriate clinical scenario and combinations for selinexor use.

Keywords

Clinical pharmacy; multiple myeloma; hematology; oncology; pharmacology

Corresponding author: Tim J Peterson, PharmD, BCOP, Clinical Pharmacy Specialist – Multiple Myeloma, Department of Pharmacy, Memorial Sloan Kettering Cancer Center, 1250 1st Avenue, Schwartz 710, New York, NY 10065, Phone: 212-639-3755, Fax: 212-639-2171, petersot@mskcc.org.

All authors report no relevant conflicts of interest to disclose.

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy characterized by uncontrolled proliferation of clonal plasma cells. MM primarily affects the elderly with a median age at diagnosis of 69 years and an estimated 32,000 new diagnoses in 2019.[1,2] In recent years, numerous additions to the MM armamentarium have significantly improved depth and duration of responses and progression free survival (PFS). Despite these improvements, relapse is largely unavoidable. As such, the need for novel agents and optimization of combination therapies remains unmet.

Treatment of relapsed MM may include re-challenging with initial induction regimen if more than 6 months have passed following treatment, or an alternative combination therapy.[3] Regimens in the relapsed setting may include a proteasome inhibitor (bortezomib, carfilzomib, ixazomib), immunomodulatory agent (thalidomide, lenalidomide, pomalidomide), alkylating agent (cyclophosphamide, bendamustine), and/or a monoclonal antibody (daratumumab, elotuzumab). The addition of monoclonal antibodies targeting CD38 and SLAMF7 as well as optimization of combination therapies have improved response rates in the relapsed setting; however, the risk of resistance development remains. Selinexor (Xpovio, Karyopharm Therapeutics Inc., Newton, MA) is a small molecule, first-in-class, selective inhibitor of nuclear export (SINE) which acts through blockade of exportin-1 (XPO1).[4] Selinexor was granted accelerated approval by the Food and Drug Administration (FDA) in July 2019 for penta-refractory MM and is now a Category 2A recommendation from the National Comprehensive Cancer Network (NCCN). In this article, we describe the pharmacology, pharmacokinetics, clinical efficacy, and safety of selinexor for the management of multiply relapsed MM.

Data Sources

Sources were identified through queries of PubMed and Medline databases (January 1, 2000 to November 14, 2019) using key terms *selinexor, SINE, XPO1, and Xpovio*. Additional abstracts were acquired from the American Society of Hematology and the American Society of Clinical Oncology. Further information was acquired through the National Institutes of Health, FDA, clinicaltrials.gov, and product prescribing information.

Pharmacology and Pharmacodynamics

Nucleated cells are dependent upon numerous processes mediated by myriad macromolecules. Participation of these macromolecules in intra- and extranuclear processes necessitates active transport across the nuclear envelope. Large nuclear pore complexes mediate exchange between the nucleus and cytoplasm, facilitated by shuttling proteins collectively referred to as importins or exportins.[5,6]

The chromosome region maintenance 1 (CRM1) protein, also known as exportin-1 (XPO1), participates in transport of more than 200 proteins across the nuclear envelope.[7] These include tumor suppressor proteins (e.g., p53, retinoblastoma protein), growth regulating proteins (e.g., p21, survivin), and proto-oncogenic mRNAs.[8] Preclinical and clinical data

indicate several malignancies overexpress XPO1, increasing export of regulatory proteins and leading to aberrant proliferation, drug resistance, and poorer outcomes in some cases.[9] In MM, XPO1 is overexpressed compared to normal plasma cells, and preclinical models indicate XPO1 is vital for MM cell survival.[10] Clinical data in MM indicate XPO1 overexpression is associated with reduced survival and lytic bone disease, presenting XPO1 as a potential therapeutic target.[11]

Early preclinical attempts to inhibit XPO1 yielded promising clinical pursuits, but agents tested *in vivo* were fraught with toxicity.[12] This prompted development of newer-generation XPO1-selective inhibitors of nuclear export (SINE) which bind irreversibly to XPO1's nuclear export signaling (NES) binding groove. Selinexor (KPT-330), initially identified through virtual screening of compounds for NES binding groove affinity, was the first SINE used in clinical trials.[13] In MM cells, selinexor induces apoptosis through nuclear accumulation of tumor suppressor proteins and inhibition of proto-oncogenic mRNA translation.[9,11] Additionally, it impairs receptor activator of nuclear factor kappa-B ligand (RANK-L) mediated osteoclast differentiation, potentially mitigating myelomatous bone disease. A screening panel of 112 receptors and enzymes with functional assays suggested no appreciable off-target activity.[9] Pharmacodynamic analysis in a phase 1 trial of solid tumors indicated induction of XPO1 mRNA via positive feedback loop in circulating leukocytes and suggested a pharmacodynamic half-life of at least 48 hours, although this analysis has not been reported in plasma cells.[14]

Pharmacokinetics

Oral bioavailability of selinexor has not been reported in humans; in rat and monkey studies, bioavailability was approximately 60 to 70%.[9] Administration in fed and fasted states did not appear to influence peak plasma concentrations or cumulative exposure. Estimated apparent volume of distribution is 125 liters with 95% protein-bound in the plasma, and animal models suggest brain penetration.[15] Selinexor undergoes oxidation by cytochrome P450 (CYP) 3A4 to the minimally-active (less than 5% of parent drug) metabolite KPT-375, followed by glucuronide and glutathione conjugation. While it has been suggested that enzyme- and transporter-mediated drug-drug interaction potential is minimal based on population pharmacokinetics, there are no *in vivo* interaction studies to support this.[16] Elimination has not undergone definitive study in humans; hepatobiliary secretion into feces appears to be the primary route of excretion based on radiolabeled mass studies in rats, with minimal urinary excretion. The mean half-life is 6 to 8 hours.[9]

Clinical Trial Efficacy: Selinexor and Dexamethasone

Following extrapolation from animal toxicology studies, numerous doses and schedules were tested in the phase 1 multicenter study of selinexor with dexamethasone in advanced hematologic malignancies.[17] Of the 285 patients, 81 had MM and 3 had Waldenström macroglobulinemia. Included patients were adults with progressive disease and ≥ 3 prior lines of therapy comprised of ≥ 1 immunomodulatory agent, proteasome inhibitor, alkylating agent, and steroid. Median number of prior therapies was 6 with 54% of patients having previously received an autologous hematopoietic cell transplantation (HCT).

While the maximum tolerated dose (MTD) was not reached, a parallel phase 1 study in patients with solid tumors identified a MTD of 65 mg/m^2 which was subsequently established as MTD across all malignancy types.[17] Patients receiving a lower dose of 45 mg/m^2 experienced less weight loss over the first 2 weeks of therapy, required fewer dose reductions, and remained on study significantly longer. This led to a recommended phase 2 dose (RP2D) of 45 mg/m^2 twice weekly (days 1 and 3), which was found to be equivalent to 80 mg flat-dose twice weekly.

The phase 2b, multicenter, open-label STORM study utilized this dose and schedule in combination with dexamethasone. The first 51 enrollees received doses on a 3 week on/1 week off (6 doses per 28-day cycle) schedule and all subsequent enrollees received 8 doses per 28-day cycle following protocol amendment.[18,19] Patients included were required to have previous exposure to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent (‘penta-exposed’); they must have also had disease refractory to at least one proteasome inhibitor, an immunomodulatory agent, and daratumumab (triple-class refractory).

One patient was excluded from the modified intent-to-treat (mITT) population for primary efficacy analysis (n=122).[18,19] Median age of study population was 65 (range, 40-86) with a median of 6.6 years from diagnosis (range, 1.1-23.4), and over half of patients with high-risk cytogenetics. The median number of prior therapies was 7 (range, 3-18) with 84% (n=102) of patients having previously received an autologous HCT. Notably, 68% (n=83) of patients had disease refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (‘penta-refractory’). The primary endpoint of overall response (≥ partial response) was observed in 26% of patients (95% CI, 19 to 35). Of these, 2 patients experienced stringent complete response, 6 experienced a very good partial response (VGPR; 5%) and 24 experienced a partial response (PR; 20%). Median time to PR or better was 4.1 weeks (range, 1-14) and median duration of response was 4.4 months (95% CI, 3.7 to 10.8). Of note, response rates appeared to be consistent across subgroups, including patients with high-risk cytogenetics. Median PFS was 3.7 months (95% CI, 3 to 5.3) and median OS was 8.6 months (95% CI, 6.2 to 11.3); median OS in patients with a minimal response or better was 15.6 months. Based on a revised mITT analysis (including only penta-refractory patients (n=83)), FDA granted accelerated approval for penta-refractory patients who have received daratumumab and at least 2 each of proteasome inhibitors and immunomodulatory agents.[9]

Clinical Trial Efficacy: Combination Therapies

Selinexor plus carfilzomib and dexamethasone was studied in a phase 1, dose-escalation trial in which selinexor 60 mg twice weekly was selected as the RP2D.[20] Patients had received ≥ 2 prior lines, including a proteasome inhibitor and immunomodulatory agent. In patients who received the RP2D, the overall response rate (ORR) was 38% (90% CI, 0.17-0.65) with 15% achieving VGPR. Median PFS and OS were 3.7 and 22.4 months, respectively, in all patients. Importantly, activity was maintained in patients deemed carfilzomib-resistant in their last line of therapy suggesting restoration of drug sensitivity.

Selinexor plus bortezomib and dexamethasone was studied in a phase 1, dose-escalation study, which identified a RP2D of selinexor 100 mg in combination with bortezomib 1.3 mg/m^2 and dexamethasone 40 mg once weekly.[21] Patients had received a median 3 prior lines of therapy (range, 1-11), including 50% refractory to proteasome inhibitors. The ORR for all patients was 63%, including an ORR of 43% in patients refractory to prior proteasome inhibitors suggesting potential re-sensitization to proteasome inhibition. The ongoing phase 3 BOSTON trial is comparing bortezomib and dexamethasone with or without selinexor. Additional ongoing clinical trials of selinexor in relapsed MM are outlined in Table 1.

Safety

In the phase 2 STORM trial of selinexor with dexamethasone, 18% of patients discontinued therapy due to an AE related to treatment.[18,19] Dose interruption or modification occurred in 80% of patients, most during the first two cycles. Common AEs are summarized in Table 2.

Severe thrombocytopenia has occurred (61% ≥ grade 3) with a median onset of 22 days following initiation.[4] Non-clinically significant and clinically significant bleeding events occurred in 23% and 5% of patients with thrombocytopenia, respectively. During the phase 1, dose-escalation study, one patient developed grade 4 thrombocytopenia and subsequently died from an intracranial hemorrhage, deemed possibly related to therapy.[17] Platelet count should be monitored at baseline, frequently during the first 2 months, and at regular intervals throughout therapy; supportive measures such as platelet transfusions and growth factors should be utilized as appropriate.

Clinically significant neutropenia may occur, with grade ≥ 3 neutropenia occurring in 21% of patients and 3% of patients experiencing episodes of febrile neutropenia. Median onset of neutropenia was 25 days; monitoring of absolute neutrophil count (ANC) should be completed at baseline, frequently during the first 2 months, and at regular intervals throughout therapy; supportive measures such as growth factors and antibiotics should be utilized as appropriate.[4]

Gastrointestinal AEs represent a significant concern for patients receiving selinexor. Nausea and vomiting occurred in 72% and 41% (9% and 4% grade 3) of patients at a median of 3 and 5 days following initiation, respectively. Diarrhea occurred in 44% of patients (6% grade 3) at a median of 15 days. Anorexia and weight loss were reported in 53% and 47% (5% and 1% grade 3) of patients at a median of 8 and 15 days, respectively. Antiemetic premedication, as needed antiemetics, and as needed antidiarrheals should be pre-emptively prescribed. Patient weight should be monitored at baseline and throughout therapy.[4]

All-grade hyponatremia occurred in 39% of patients.[4] The mechanism of selinexor-induced hyponatremia has not been described; sodium levels should be corrected for hyperglycemia, and causes such as syndrome of inappropriate antidiuretic hormone, Fanconi syndrome, adrenal insufficiency, or other organ dysfunction should be investigated. Supplementation with oral sodium chloride or aggressive sodium repletion may be considered in the absence of an alternative cause.

Additional AEs (all grade) occurring in ≥ 10% of patients included anemia (59%), upper respiratory tract infections (21%), hypokalemia (12%), insomnia (15%), mental status changes (16%), pyrexia (16%), epistaxis (12%), hyperglycemia (15%), and blurred vision (10%). Serious AEs occurred in 63% of patients (11% pneumonia; 9% sepsis). Twenty-eight patients died while enrolled in STORM; 12 due to an AE (2 of which were deemed related to therapy, both involved infectious events) and 16 due to disease progression.[4,19]

Dosing & Administration

While 80 mg twice weekly without a week off was the ultimate FDA-approved dose, reviewers noted exposure-associated toxicity.[19] As a result, FDA approval included stipulations for characterizing safety and efficacy of 2 lower starting doses of selinexor with dexamethasone.

Selinexor elimination occurs primarily via hepatic transformation and fecal excretion and administration in the setting of mild hepatic dysfunction does not appear to impact clearance.[9] However, few patients with moderate (n=6) or severe (n=3) hepatic dysfunction were studied, and FDA approval stipulated further study in this population. Mild to severe renal dysfunction did not appear to affect clearance of selinexor; however, no patients with end-stage renal disease or requiring dialysis were included. Although population pharmacokinetics suggested no effect of CYP3A4 inhibitors or inducers on selinexor exposure, FDA approval was also contingent on post-marketing human drug interaction studies. No clinically significant effects of sex, age, or ethnicity on pharmacokinetics were identified to warrant individualized dosing in these subpopulations. Animal studies suggest risk for embryofetal toxicity, but no studies have been performed in pregnant or lactating women.

Dose reductions for toxicity were developed by the manufacturer and include specific guidance for several toxicities, in addition to general guidance (Tables 3 and 4).[4] In all cases, supportive care measures, such as transfusions, antidiarrheals, or additional antiemetics should be utilized as indicated.

As administration of selinexor in a fed or fasted state does not appear to affect pharmacokinetics, it may be taken with or without food.[9] Due to high risk of nausea and vomiting, prophylaxis with an antiemetic (e.g., ondansetron) is recommended prior to each selinexor dose.[4]

Cost

Selinexor is available exclusively in 20 mg tablets, provided in 4 blister packs for 80 mg twice weekly, 100 mg once weekly, 80 mg once weekly, and 60 mg once weekly dosing schedules. The reported average wholesale price, regardless of dosing schedule, is approximately $26,400 per 4-week cycle.[23] Based on the median duration of therapy in the STORM trial of 9 weeks, this amounts to approximately $60,000 per individual treatment course. In addition to direct costs associated with acquiring selinexor, one must consider the costs associated with laboratory monitoring and supportive medications.

Relevance to Patient Care and Clinical Practice

Depth and duration of responses to selinexor in its current setting are limited; however, it has potential to match an unmet need, particularly in providing a bridge to additional salvage therapies or clinical trials. Given the significant toxicity profile and modest activity of selinexor plus dexamethasone, its current use should be reserved for heavily refractory patients with good performance status, minimal cytopenias, and without significant comorbidities. Initiation of selinexor should be undertaken with close attention to supportive care medications, including antiemetics, antidiarrheals, and growth factors. As formal cost effectiveness analyses have not been performed for selinexor, careful consideration of direct and indirect financial burden is essential.

Conclusion

Based on the results reported in the STORM study, selinexor has modest activity in a heavily refractory patient population. Responses in this heavily relapsed population with current standard of care options are known to be dismal, as such it is important to identify novel treatments and combinations. Notably, combination studies of selinexor with bortezomib or carfilzomib suggest activity in MM refractory to these agents, representing potential re-sensitization to proteasome inhibition. Optimization of combination therapies and sequencing of novel agents is necessary to further elucidate the role of selinexor in the management of MM.

References

1. National Cancer Institute. SEER Stat Fact Sheets: Multiple Myeloma https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed October 14, 2019.
2. American Cancer Society. Cancer Facts and Figures 2019. Atlanta, GA: American Cancer Society; 2019.
3. National Comprehensive Cancer Network. Multiple Myeloma (v1.2020). Available online: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed October 14, 2019.
4. Karyopharm Therapeutics Inc. XPOVIO (selinexor) [prescribing information]. 7 2019. Available online: https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=f6dd2682-75a6-4863-90a8-a3197f6f78a8.
5. Gorlich D et al. Nucleocytoplasmic transport. Science. 1996;271:1513–18. [PubMed: 8599106]
6. Nguyen KT et al. The CRM1 nuclear export protein in normal development and disease. Int J Biochem Mol Biol. 2012;3:137–51. [PubMed: 22773955]
7. Xu D et al. NESdb: a database of NES-containing CRM1 cargoes. Mol Biol Cell. 2012;23:3673–76. doi: 10.1091/mbc.E12-01-0045 [PubMed: 22833564]
8. Center for Drug Evaluation and Research. Application Number 212306Orig1s000 Multi-Discipline Review. 7 1, 2019. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MutidisciplineR.pdf. Accessed October 14, 2019.
9. Turner JG et al. Inhibition of CRM1-dependent nuclear export sensitizes malignant cells to cytotoxic and targeted agents. Semin Cancer Biol. 2014;27:62–73. doi: 10.1016/j.semcancer.2014.03.001 [PubMed: 24631834]
10. Schmidt J et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. Leukemia. 2013;27:2357–65. doi: 10.1038/leu.2013.172 [PubMed: 23752175]

11. Tai YT et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28:155–65. doi: 10.1038/leu.2013.115 [PubMed: 23588715]
12. Turner JG et al. Nuclear export of proteins and drug resistance in cancer. Biochem Pharmacol. 2012;83:1021–32. doi: 10.1016/j.bcp.2011.12.016 [PubMed: 22209898]
13. Etchin J et al. Antileukemic activity of nuclear export inhibitors that spare normal hematopoietic cells. Leukemia. 2013;27:66–74. doi: 10.1038/leu.2012.219 [PubMed: 22847027]
14. Abdul Razak AR et al. First-in-class, first-in-human phase 1 study of selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors. J Clin Oncol. 2016;34:4142–50. doi: 10.1200/JCO.2015.65.3949 [PubMed: 26926685]
15. Hing ZA et al. Next-generation XPO1 inhibitor shows improved efficacy and in vivo tolerability in hematological malignancies. Leukemia. 2016;30:2364–72. doi: 10.1038/leu.2016.136 [PubMed: 27323910]
16. Center for Drug Evaluation and Research. Application Number 212306Orig1s000 Other Review(s). 1 7 2019. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000OtherR.pdf. Accessed October 14, 2019.
17. Chen C et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. Blood. 2018;131:855–63. doi: 10.1182/blood-2017-08-797886 [PubMed: 29203585]
18. Vogl DT et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. J Clin Oncol. 2016;36(9):859–866.
19. Chari A Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med. 2019;381(8):727–38. doi: 10.1056/NEJMoa1903455 [PubMed: 31433920]
20. Jakubowiak AJ et al. Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. Br J Cancer. 2019;186:549–60. doi: 10.1111/bjh.15969
21. Bahlis NJ et al. Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. Blood. 2018;132(24):2546–54. doi: 10.1182/blood-2018-06-858852 [PubMed: 30352784]
22. Clinicaltrials.gov. http://clinicaltrials.gov. Accessed October 14, 2019.
23. Lexicomp. Selinexor. http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6837563. Accessed October 14, 2019.

Table 1.

Ongoing Selinexor Studies in Multiple Myeloma.[22]

Phase (NCT Identifier)	Selinexor Dosing	Additional Therapeutic Agents	Prior Lines of Therapy
1/2 (NCT02199665)	60 mg twice/week	Carfilzomib Dexamethasone	2 (must include PI and IMiD)
1 (NCT02831686)	Twice/week for 3 weeks, 1 week off	Ixazomib Dexamethasone	≥ 1 (must include PI and IMiD)
½ (NCT02186834)	80 mg loading dose followed by 60 mg once/week to 80 mg twice/week	Liposomal doxorubicin Dexamethasone	≥ 2 (must include PI and lenalidomide)
½ (NCT02780609)	Dose escalation starting with 40 mg 2-3 hours prior to melphalan for autologous HCT (day −3 and −2)	High dose melphalan Dexamethasone	< 4
2 (NCT03589222)	100 mg once/week	Bortezomib Daratumumab Dexamethasone	≥ 3 (must include PI and IMiD)
3 (NCT03110562)	100 mg once/week	Bortezomib Dexamethasone	1-3

Abbreviations: PI, proteasome inhibitor; IMiD, immunomodulatory agent; HCT, hematopoietic cell transplantation.

Table 2.

Adverse Events Reported with Selinexor and Dexamethasone.[4]

Adverse Event	Any Grade n (%)	Grade 3-4 n (%)
Thrombocytopenia	149 (74)	124 (61)
Anemia	119 (59)	81 (40)
Neutropenia	68 (34)	43 (21)
Fatigue	147 (73)	44 (22)
Nausea	146 (72)	18 (9)
Diarrhea	89 (44)	13 (6)
Hyponatremia	78 (39)	44 (22)
Upper respiratory infection	42 (21)	6 (3)
Mental status changes	33 (16)	14 (7)
Pneumonia	26 (13)	18 (9)

Table 3.

Dose Levels for Adjustment of Selinexor.[4]

Dose Level	Dose (mg)
0	80 mg twice weekly
−1	100 mg once weekly
−2	80 mg once weekly
−3	60 mg once weekly
−4	Discontinue

Table 4.

Dose Adjustments of Selinexor for Toxicity.[4]

Parameter or Toxicity	Threshold	Interrupt Therapy?	Threshold for Restart	Dose Reduction
Absolute neutrophil count	500 – 1000 cells/mm^3	No	N/A	1 level
	< 500 cells/mm^3 or neutropenic fever	Yes	≥ 1000 cells/mm^3	1 level
Hemoglobin	< 8 g/dL	No	N/A	1 level
	Life-threatening requiring urgent intervention	Yes	≥ 8 g/dL	1 level
Platelets	25,000 – 75,000 cells/mm^3, no bleeding	No	N/A	1 level
	25,000 – 75,000 cells/mm^3, bleeding	Yes	Bleeding resolved	1 level
	< 25,000 cells/mm^3	Yes	≥ 50,000 cells/mm^3	1 level
Diarrhea	Initial grade 2	No	N/A	None
	Recurrent grade 2	No	N/A	1 level
	Grade ≥ 3	Yes	Grade ≤ 2	1 level
Fatigue	Grade 2 > 7 days	Yes	Grade ≤ 1	1 level
	Grade ≥ 3			
Nausea or vomiting	Grade 1 or 2	No	N/A	None
	Grade ≥ 3	Yes	Grade ≤ 2	1 level
Sodium	≤ 130 mmol/L	Yes	≥ 130 mmol/L	1 level
Weight loss	≥ 10% or associated with anorexia or malnutrition	Yes	> 90% of baseline weight	1 level
Other	Grade ≥ 3	Yes	Grade ≤ 2	1 level