



Selinexor—A Drug Review

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Abstract

Selinexor developed by Karyopharm Therapeutics is the first orally available small-molecule inhibitor of *exportin-1* (*XPO1*). *XPO1* is a protein transporter responsible for the export of macromolecules such as tumor suppressor proteins and oncoprotein mRNAs from the nucleus to the cytoplasm; its inhibition results in blocking of multiple oncogenic pathways. Overexpression of *XPO1* is seen in multiple myeloma and various other malignancies and is a poor prognostic marker. Pivotal positive trials have resulted in the approval of selinexor for use in refractory or relapsed diffuse large B cell lymphoma and multiple myeloma. In this review, we briefly cover the drug development, mechanism of action, indications, and toxicities of the drug, and the major pivotal trials.

Keywords

- ▶ selinexor
- ▶ XPO-1
- ▶ oncoprotein
- ▶ multiple myeloma

Introduction

Therapeutic intervention for hematological malignancies has made rapid advancement in recent years, thanks to discoveries at the molecular level. Selinexor, an orally active exportin-1 (*XPO1*) inhibitor, is the latest to join the armamentarium directed against recurrent refractory or relapsed multiple myeloma (MM) and diffuse large B cell lymphoma (DLBCL).¹ Combinations of proteasome inhibitors, immunomodulatory drugs (IMiDs), and monoclonal antibodies (MABs) produce excellent outcomes, but ultimately patients turn resistant to these drugs and are termed “triple-class refractory.”² Selinexor is a welcome weapon against this group. Similarly, it has also been approved in patients of DLBCL who progressed on at least two lines of chemotherapy.³ The compound is also being tested in hard to treat cancers such as soft tissue sarcomas and glioblastoma.⁴

Development

The first *XPO1* inhibitor, leptomyacin B, is a natural compound derived from bacteria, *Streptomyces*. It was initially studied for its antifungal properties, and it was only later that its anticancer properties were discovered. Studies showed that it works by complete *XPO1* inhibition, which is toxic to organisms. Many semisynthetic *XPO1* inhibitors were studied after that in the preclinical setting, but none of them proved effective. Further modifications led to the development of the next-generation compounds called selective inhibitor of nuclear export (SINE) compounds, which included KPT-185, KPT-249, KPT-251, KPT-276, and KPT-330. These compounds cause a temporary deterioration of *XPO1* that was reversible on discontinuation of the SINE compound. Selinexor is the lead compound of this class.⁵

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Mechanism of Action⁶

XPO1 is one of the eight nucleocytoplasmic shuttling proteins involved in the export of proteins from the nucleus to the cytoplasm. It is a member of the karyopherin B family and has two main activities.

- It acts as a carrier for tumor suppressor proteins (TSPs) from the nucleus to the cytoplasm. These include p53, p21, p73, FOXO1, NPM1, BCR-ABL, BRCA 1 & 2, and IκB-α. This builds up the activity of TSPs in the nucleus.
- It plays a major role in the transport of the eukaryotic translation initiation factor (eIF4E). This factor is responsible for the transport of oncoprotein mRNA like c-Myc, Pim1, and cyclins. The blockade of XPO1 prevents these oncoprotein mRNAs from exiting the nucleus. Hence, the translation of oncoprotein is prevented.

XPO1 is overexpressed in multiple cancers, and the activity of XPO1 results in the functional inactivation of multiple TSPs; XPO1 blockade ensures their nuclear retention. Oncoprotein translation is inhibited, providing additional benefit. Selinexor thus induces nuclear accumulation and activation of TSPs while simultaneously reducing levels of oncoproteins. This leads to transient cell cycle arrest, suppression of growth of the tumor, and induction of apoptosis with minimal effects on normal lymphocytes.⁶

Indications

Currently, there is U.S. Food and Drug Administration (FDA) approval for relapsed or refractory MM and DLBCL.

Contraindications

There are no absolute contraindications for this drug.

Pivotal Trials

Selinexor and Backbone Treatment of MM Patients (STOMP) (NCT02343042)

A phase I/II, multicentric, open-label study in MM patients was conducted to determine the maximum tolerated dose, efficacy, and the safety profile of eight combination therapies in nine different arms. The population comprised of newly diagnosed multiple myeloma patients and patients who were relapsed from their treatment. The enrollment eligibility was that the patient should have received ≥ 1 therapy prior to the trial. The dose of selinexor was escalated in three regimens: 80 mg once weekly, 60 mg twice weekly, and 60 mg once weekly, along with low-dose dexamethasone and novel anti-MM drugs. The novel anti-MM drugs included were pomalidomide (Arm 1), bortezomib (Arm 2), lenalidomide in RRMM (Arm 3), pomalidomide+ bortezomib (Arm 4), daratumumab (Arm 5), carfilzomib (Arm 6), lenalidomide in newly diagnosed multiple myeloma (NDMM) (Arm 7), ixazomib (Arm 8), and pomalidomide + elotuzumab (Arm 9). This study showed that all the regimens produced good response rates; for instance, the selinexor-pomalidomide- dexamethasone

arm showed a 55% overall response rate (ORR) and 11.6 months median progression-free survival (PFS).⁷ The selinexor-Velcade-dexamethasone arm showed an 83% ORR with a 17.8-month median PFS.⁸ The study is still ongoing.

Selinexor Treatment for Refractory Myeloma (STORM) (NCT02336815)

STORM was a phase 2b, multicentric, open-label study that recruited refractory MM patients who had received ≥ 4 lines of treatment (i.e., who were refractory to ≥ 2 IMiD, ≥ 2 proteasome inhibitors, and an anti-CD38 monoclonal antibody).⁹ The single arm study used a combination of selinexor (80 mg) and dexamethasone (20 mg) dosed twice weekly for a 4-week cycle. The response rate was 26%. The major adverse events included thrombocytopenia, neutropenia, and hyponatremia. FDA approval was granted for the use of selinexor in this group. The results of the STORM study were compared with a matched group treated with standard of care (MAMMOTH study)¹⁰ and those treated with selinexor in the STORM study had clear overall survival benefit.

(BOSTON) (NCT03110562)

BOSTON was phase 3, multicentric open-label double arm study, which studied the safety, efficacy, and the health-related quality of life in RRMM patients. The two arms were selinexor with bortezomib with low dose of dexamethasone (Arm 1) versus bortezomib and with low dose dexamethasone (Arm 2). The results showed that the selinexor containing arm had superior PFS (13.3 vs. 9.46 months). There was a 30% reduction in disease progression or death (hazard ratio [HR], 0.70; $p = 0.0066$). FDA approval for using this combination in patients progressing on at least one line of chemotherapy is awaited.¹¹

Selinexor in Relapsed or Refractory Diffuse Large Cell Lymphoma (DLBCL) (SADAL) (NCT02227251)

In a phase 2 trial called SADAL, 127 patients were enrolled in this study who were either relapsed or refractory DLBCL patients, who were not eligible for transplant or either progressed after a transplant was administered with monotherapy of selinexor.¹⁰ The trial showed a response rate of 28% with 12% CR and 17% PR. The response rate was comparatively better in the germinal center B (GCB) cell type (33.9%) than in non-GCB (20.6%) type. The median overall survival and PFS of the study were 9.1 and 3.6 months, respectively. And it was based on the trial FDA approved the drug for use in relapsed or refractory DLBCL who had received at least 2 lines of therapy.³

Selinexor in Advanced Liposarcoma (SEAL) (NCT02606461)

Selinexor in advanced liposarcoma (SEAL) is a randomized, double-blind, placebo-controlled, multicenter phase 2/3 trial. The drug was administered twice a week, with a fixed dose of 60 mg. The study population was patients who were on at least two lines of systemic treatment for liposarcoma. When compared with the placebo, an improved PFS was observed with a 30% reduction in the disease progression risk

Table 1 Ongoing clinical trials

Trial name	Year of starting the trial	Phase	Treatment	Study population
XPORT-DLBCL-030 (NCT04442022)	2020	2 3	Arm 1 – selinexor + R-GDP Arm 2 – placebo Arm 1 – selinexor + R-GDP Arm 2 – R-GDP + placebo	DLBCL
SIENDO (NCT03555422)	2018	3	Arm 1–selinexor Arm 2 – placebo	Endometrial carcinoma
SPRINT (NCT04256707)	2020	1	Arm 1 – selinexor Arm 2 – selinexor + docetaxel + pembrolizumab	Nonsmall cell lung carcinoma, colorectal cancer

Abbreviation: DLBCL, diffuse large B cell lymphoma.

or death (HR, 0.70; $p=0.023$). FDA approval is awaited for this indication.¹²

Pharmacokinetics

Selinexor reaches the maximum concentration (C_{max}) within 4 hours of administration, and the absorption of the drug is not affected by the presence of food. Selinexor undergoes hepatic metabolism by CYP3A4, UDP-glucuronosyltransferases, and glutathione S transferases.⁶

Dosage and Administration

The recommended dose for relapsed or refractory multiple myeloma is 80 mg once daily on day 1 and 3 of every week along with 20 mg dexamethasone until disease progression or unacceptable toxicity.¹ However, in DLBCL, the dose is 60 mg on day 1 and day 3 every week until disease progression or unacceptable toxicity.³ It can be taken with or without food.

Adverse Events

Other than hematological toxicities common with anticancer medicines (especially thrombocytopenia), selinexor can cause hyponatremia,³ gastrointestinal, and neurological toxicities (such as altered sensorium). Most of the side effects were grade 1/2 and reversible.

Dose Modifications

According to the manufacturer label, there is no dosage modification for renal and hepatic impairment. There was no significant difference observed in the pharmacokinetics of the drug in this impairment.

Special Considerations

Like any chemotherapy drug, selinexor can be teratogenic and impair fertility. Contraceptive measures are recommended for women of reproductive age as long as they are on this drug and for a week after that.¹

Cost-Effectiveness

The drug is not available in the Indian market.

Ongoing Clinical Trials

There are three ongoing clinical trials–XPORT-DLBCL-030 (NCT04442022), SIENDO (NCT03555422), and SPRINT (NCT04256707), the details of which are given in ► **Table 1**.

Take-Home Points

- Selinexor is an orally active XPO1 inhibitor.
- It is approved in RRMM at a dose of 80 mg biweekly till progression or toxicity.
- It is approved in RRDLBCL at a dose of 60 mg biweekly till progression or toxicity.
- Side effects to watch for include thrombocytopenia and hyponatremia.

Conclusions

Selinexor is a welcome addition for the treatment of relapsed or refractory multiple myeloma and diffuse large cell lymphoma as an orally active drug with reasonable toxicities. The good safety profile allows it to be combined with other classes of drugs, and it is expected that ongoing trials in other refractory cancers such as gynecological malignancies and glioblastoma will reveal its true potential. Interestingly, it is even being investigated as a treatment for COVID-19 infection.

Conflict of Interest

None.

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