

REVIEW

Refining the role of selinexor in multiple myeloma: strategic use in a shifting treatment landscape

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The treatment landscape of multiple myeloma (MM) has been revolutionized over the past two decades, leading to unprecedented deep and durable responses, prolonged survival, and improved quality of life. Nonetheless, MM is still an incurable disease, and many patients, especially those with high-risk cytogenetics, renal impairment, or early drug resistance, continue to face poor outcomes. Selinexor, the first-in-class, orally bioavailable selective inhibitor of exportin 1 (XPO1), has shown encouraging results in combination with other agents, and selinexor-based therapy has been approved for the treatment of relapsed/refractory MM, with selinexor–bortezomib–dexamethasone approved for patients with at least one prior line of therapy and selinexor–dexamethasone approved in the later-relapse setting. Notably, selinexor-based combinations have demonstrated consistent efficacy across different subgroups of patients, including those with triple-class refractory disease, renal dysfunction, high-risk cytogenetics, and prior anti-CD38 therapy. We herein provide an overview of selinexor, by describing its mechanism of action, potential interaction with other classes of drugs, novel combinations under investigation, and its role in treatment sequencing, by discussing latest results and potential strategies to mitigate toxicities, increase efficacy, and implement treatment adherence in MM. Overall, selinexor continues to represent a valuable option, especially for patients who are ineligible to receive T-cell-redirecting therapies, or difficult-to-treat patient subgroups, where alternative strategies remain limited. Meanwhile, further data on the use of selinexor-based combinations in different settings are eagerly awaited, to help clarify its role and address persistent unmet clinical needs.

Key words: multiple myeloma, relapsed/refractory multiple myeloma, selinexor, exportin 1 inhibition, selinexor-based therapies

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INTRODUCTION

The last two decades remarkably revolutionized the treatment landscape of multiple myeloma (MM), leading to unprecedented deep and sustained responses, prolonged survival, and substantially improved quality of life (QoL).

Specifically, proteasome inhibitors (PIs), immuno-modulatory agents (IMiDs), monoclonal antibodies (mAbs), and, more recently, antibody–drug conjugates (ADCs), chimeric antigen receptor T-cell (CAR-T), bispecific antibodies (BsAbs), and selective inhibitors of nuclear export (SINEs) molecules, have progressively expanded the MM treatment scenario.

In this article, we provide a comprehensive overview of selinexor, the first-in-class, orally bioavailable SINE compound, describing its mechanisms of action (MoA), interaction with other drugs, and its role in treatment sequencing, and discussing potential strategies to mitigate toxicities, increase efficacy, and implement treatment adherence.

SELINEXOR MoA AND SYNERGY WITH OTHER ANTI-MM DRUGS

Exportin 1 (XPO1), also known as chromosomal region maintenance 1 (CRM1), plays a critical role in the nuclear export of a wide range of cargo proteins, including tumor suppressor proteins (TSPs) like retinoblastoma and p53, through the nuclear pore complexes.¹ XPO1 also exports key immune response regulators like the inhibitor of nuclear factor- κ B (NF- κ B) I κ B, whose cytoplasmic relocation contributes to NF- κ B activation, inhibition of apoptosis, and dysregulation of cellular growth signaling. Notably, XPO1 is overexpressed in several cancers, including MM, and its overexpression is associated with poor prognosis.² Indeed, elevated XPO1 expression leads to aberrant cytoplasmic accumulation of common regulatory proteins, like p53, impairing their nuclear tumor-suppressive functions while promoting the cytoplasmic accumulation of pro-survival proteins, ultimately promoting dysregulated growth and resistance to apoptosis.³

SINEs are small molecules designed with N-azolylacrylate derivatives that selectively inhibit XPO1-mediated nuclear

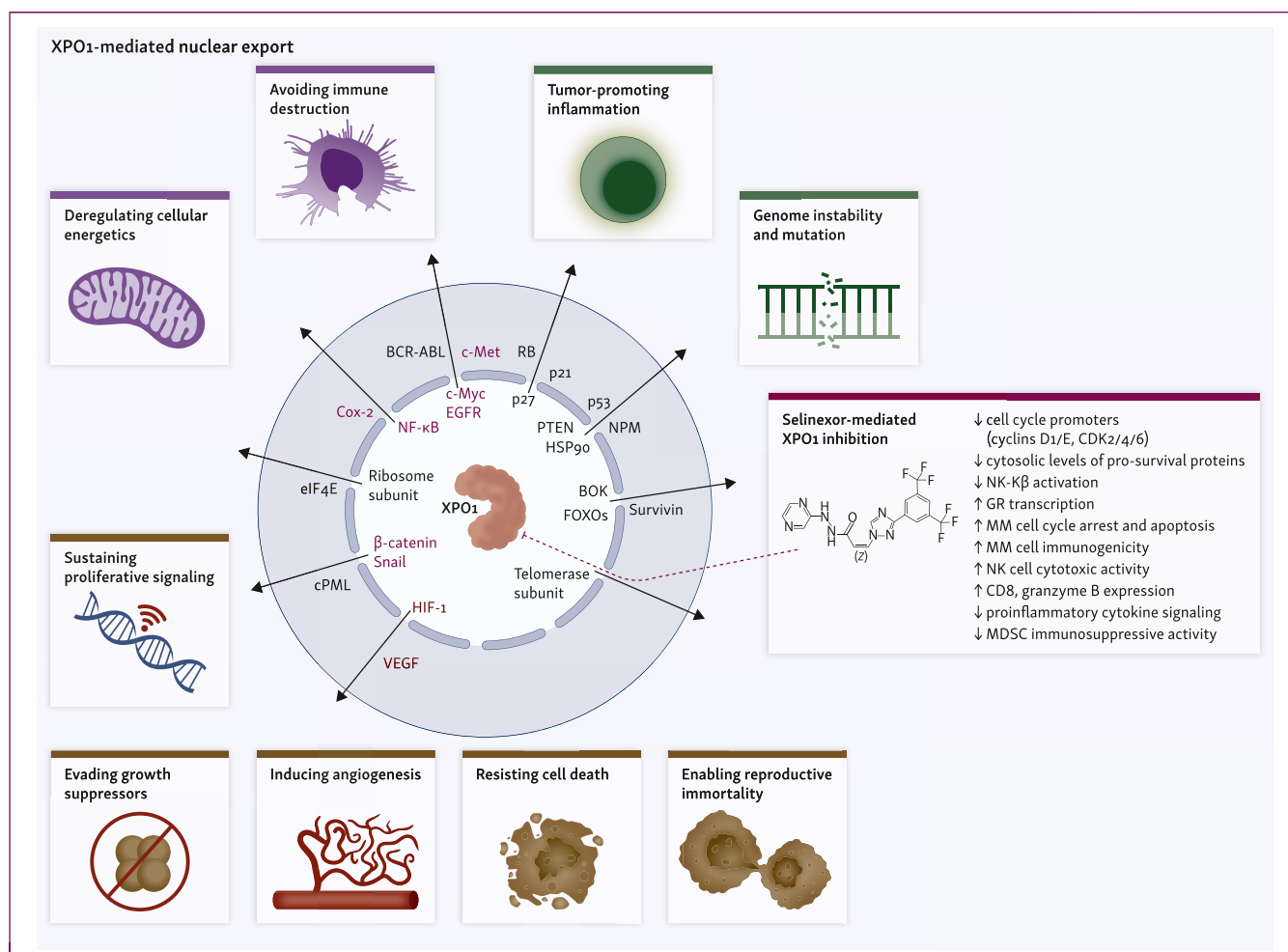


Figure 1. Mechanism of action of selinexor.

BCR-ABL, Breakpoint Cluster Region and Abelson murine leukemia viral oncogene homolog genes; BOK, Bcl-2 related ovarian killer; CDK, cyclin-dependent kinase; cMET, mesenchymal-epithelial transition factor tyrosine kinase; cMyc, myelocytomatosis viral oncogene homolog oncoprotein; cPML, cytoplasmic promyelocytic leukemia protein; EGFR, epidermal growth factor receptor; eIF4E, eukaryotic translation initiation factor 4E; FOXO, Forkhead Box O3; GR, glucocorticoid receptor; HIF, hypoxia-inducible factor; HSP, heat shock protein; MDSC, myeloid-derived suppressor cell; MM, multiple myeloma; NF- κ B, nuclear factor- κ B; NK, natural killer; NPM, nucleophosmin, also known as nucleolar phosphoprotein B23; PTEN, phosphatase and tensin homolog tumor suppressor gene; RB, retinoblastoma; VEGF, vascular endothelial growth factor; XPO1, exportin 1.

export of cargo proteins.⁴ Selinexor binds covalently and reversibly to cysteine-528 within the hydrophobic cargo-binding pocket of XPO1, preventing nuclear export of TSPs and other regulatory proteins.^{5,6} This restores nuclear levels of TSPs, traps oncoprotein messenger RNA in the nucleus, and retains activated glucocorticoid receptors (GRs) in the nucleus, which may interfere with tumor-supportive mechanisms like neutrophil extracellular trap formation^{3,7} (Figure 1, Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2025.106054>).

Notably, selinexor acts as a slow reversible inhibitor. Structural and kinetic studies have shown that after drug withdrawal selinexor gradually disengages from XPO1, allowing resumption of normal nuclear export processes.^{8,9} Consequently, this dynamic binding profile enables selinexor to maintain sufficient engagement to induce cancer cell death while reducing off-target effects by restoring nuclear export in normal cells, likely contributing to its tolerability.⁸

Pharmacokinetically, selinexor is the main circulating form in plasma; rapidly absorbed, it reaches peak levels within 4 h. It has high plasma protein binding (95%) and a volume of distribution of ~125 l. Metabolism primarily occurs via CYP3A4 oxidation, as well as conjugation by uridine diphosphate-glucuronosyltransferases (UGTs) and glutathione-S-transferases (GSTs). The drug has a plasma half-life of 4–6 h and is excreted primarily through feces, with minimal renal clearance.^{10,11}

Selinexor has demonstrated synergistic anti-myeloma activity with various anti-MM agents, both *in vitro* and *in vivo*. Specifically, it synergizes with corticosteroids, like dexamethasone, by enhancing GR expression and inhibiting the mammalian target of rapamycin (mTOR) pathway, a key contributor to myeloma progression.¹² Selinexor has also been shown to potentiate the effects of PIs, IMiDs, and chemotherapeutic agents, providing compelling rationale for subsequent clinical investigations on combination regimens.

In preclinical models, selinexor increased nuclear localization of p53 and restored sensitivity to bortezomib and carfilzomib in PI-resistant MM cells. This was largely mediated by nuclear localization of IκB and suppression of NF-κB transcriptional activity, thus overcoming resistance mechanisms^{13,14} and enhancing *in vitro* and *in vivo* cytotoxicity.^{15–18} Furthermore, the combinations stabilize TSPs such as p21, p27, and p53 by reducing their proteasomal degradation.¹³ In combination with carfilzomib, selinexor also down-regulates B-cell lymphoma 2 (BCL-2) expression, promotes serine/threonine kinase cleavage and inactivation, and induces caspase-10-dependent apoptosis.¹⁹

Interestingly, selinexor has also demonstrated preclinical synergy with pomalidomide²⁰ and lenalidomide, as well as with chemotherapeutic agents like melphalan and doxorubicin.²¹ In the case of melphalan, selinexor enhances cytotoxicity through increased DNA damage and impaired DNA repair, even in melphalan-resistant cells.¹⁷ For anthracyclines, synergy results from nuclear retention of topoisomerase II-α, intensifying doxorubicin-induced

DNA damage.¹⁶ Lastly, emerging evidence suggested that selinexor may also affect the tumor microenvironment and reduce T-cell exhaustion *in vitro*.²² Ongoing clinical trials aim to determine whether these findings translate into improved outcomes in patients treated with immunotherapies.²³

PIVOTAL REGISTRATIONAL TRIALS AND EXPERIENCE FROM REAL LIFE

In 2019, selinexor was granted Food and Drug Administration accelerated approval in combination with dexamethasone (Sd) for the treatment of adult patients with refractory/relapsed MM (RRMM) with at least four prior therapies, refractory to two or more PIs, two or more IMiDs, and an anti-CD38 mAb. The approval was based on the phase IIb STORM trial (NCT02336815) evaluating Sd in 122 heavily pretreated RRMM patients (median age 65 years, 53% with high-risk cytogenetics), all being triple-class refractory (TCR) and most ($n = 83$) penta-refractory.²⁴

The overall response rate (ORR) was 26.2% (25.3% in penta-refractory), with consistent responses across subgroups, including high-risk cytogenetics. The median duration of response (mDOR), progression-free survival (mPFS), and overall survival (mOS) were 4.4, 3.7, and 8.6 months, respectively. Among enrolled patients, 27 had baseline plasmacytomas (mainly soft tissue) and a subset analysis showed that 9/16 patients with a follow-up plasmacytoma assessment had plasmacytomas either completely resolved or decreased in size and/or metabolic activity,²⁵ showing potential benefit in this hard-to-treat subset.

Selinexor is also approved in combination with once-weekly bortezomib and low-dose dexamethasone (SVd) for MM patients with at least one prior line of therapy (LOT), based on the phase III BOSTON trial (NCT03110562), which randomized RRMM patients with one to three prior LOTs (39% lenalidomide-exposed; 27% lenalidomide-refractory) to SVd ($n = 195$) or bortezomib–dexamethasone (Vd) ($n = 207$). After a median follow-up of 13.2 (SVd) and 16.5 (Vd) months, ORR was significantly higher for SVd than Vd (76.4% versus 62.3%), with 44.6% and 32.4% of very good partial response or better ($\geq$ VGPR), respectively. SVd was also superior in terms of mPFS (13.93 versus 9.46 months), mDOR (20.3 versus 12.9 months), and time-to-next-treatment (TTNT: 16.1 versus 10.8 months). The mOS was not reached in the SVd arm (25 months with Vd). Overall, the study showed a benefit of SVd over Vd in all analyzed subgroups, including elderly, frail patients previously exposed to lenalidomide and patients with high-risk cytogenetic abnormalities.²⁶ Notably, dose modifications of selinexor in BOSTON were associated with improved outcomes, likely because they allowed patients to stay on treatment for longer.²⁷ These results were maintained across key subgroups, emphasizing the synergistic potential of selinexor plus bortezomib.²⁸

Real-world experience with selinexor-based regimens further confirmed its clinical utility. Kastritis et al. studied 44 RRMM patients (median age: 69 years) treated with

either Sd ($n = 21$) or SVd ($n = 23$) after six median prior LOTs.²⁹ All were lenalidomide-refractory and previously exposed to PIs (91% refractory to one or more PI, 70% to carfilzomib), 86% pomalidomide-refractory, 93% anti-CD38-refractory, and 34% anti-B-cell maturation antigen (BCMA)-exposed/refractory. In the intention-to-treat population, the ORR was 29.5% (35% SVd; 24% Sd), with five patients achieving $\geq$ VGPR. The mPFS was 3.4 (SVd) and 2.7 (Sd) months, while OS across the cohort exceeded 1 year. Overall, selinexor-based therapies offer meaningful clinical benefits in real-world settings, particularly for highly refractory patients.

TOXICITY PROFILE, POTENTIAL DRUG–DRUG INTERACTION, AND STRATEGIES TO MITIGATE SELINEXOR-RELATED TOXICITIES

Selinexor has a unique MoA and a well-established, predictable toxicity profile that differs from other anti-MM therapies. The most common treatment-related adverse events (TRAEs) include gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea), anorexia, weight loss, hematological toxicities (thrombocytopenia, anemia, neutropenia), hyponatremia, and fatigue. These adverse events (AEs) are dose- and schedule-dependent, preventable with prophylactic measures, and require close monitoring to maintain patient's QoL.

In the BOSTON and STORM trials, nausea was reported in 50% and 73% of patients, diarrhea in 32% and 46%, and anorexia in 35% and 53%, respectively. Loss of appetite, dehydration, and weight loss occurred in 26%–47% of patients. Also, a pooled analysis of 437 MM patients treated with selinexor across four clinical trials confirmed similar results, with nausea (68%), vomiting, diarrhea (41%), fatigue, decreased appetite (53%), and hyponatremia being the most common non-hematological TRAEs.³⁰ Data from real-life confirmed the occurrence of fatigue [66%, 14% grade (G) 3/4] and nausea (47%, 9% G3/4) as the most common non-hematological toxicities.²⁹

GI side-effects typically occur during the first treatment cycles and often improve over time, especially with adequate supportive therapy. To mitigate these events, consensus guidelines based on clinical experience and manufacturer's recommendations have been developed.^{31,32} Firstly, as nausea is best managed preventively rather than reactively, patients should undergo antiemetic prophylaxis before starting selinexor. A dual antiemetic approach with 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonists (ondansetron or equivalent) or neurokinin-1 receptor antagonists (aprepitant or rolapitant) and low-dose olanzapine for the first two cycles is recommended, plus a third agent when necessary.^{33,34} Alternatively, once-weekly oral fixed dose of netupitant plus palonosetron, or granisetron-containing transdermal patches, may be considered (Table 1). Then, one or both antiemetics may be tapered after 8 weeks, and patients should be monitored closely to assess tolerability. Dose reductions and

Table 1. Recommended antiemetic prophylaxis before starting therapy with selinexor

Option 1	Option 2
Ondansetron: 8 mg p.o. 30-60 min before each dose and continued for every 8 h for 2 days following dosing Plus olanzapine: 2.5 mg-5 mg p.o. qhs Plus aprepitant ^a : 125 mg p.o. qam day 1, and 80 mg for 2 days each week	Once-weekly oral dose of netupitant ^a 300 mg + palonosetron ^a 0.5 mg

A 5-HT₃ receptor antagonist and other antinausea agents should be provided before and during treatment with selinexor for the first two courses of treatment. One or both antiemetics may be tapered after 6-8 weeks. Maintain hydration and caloric intake.

5-HT₃, 5-hydroxytryptamine type 3; p.o., per os; qam, quaque ante meridiem (every morning); qhs, quaque hora somni (every night at bedtime).

^aUsing dexamethasone together with aprepitant and/or netupitant + palonosetron may increase the effects of dexamethasone. If using either of these agents, the dose of dexamethasone may need to be reduced.

concurrent supportive antiemetic medications should be considered on a case-by-case basis.

Standard antidiarrheal agents are recommended to manage diarrhea; based on severity, dose reduction/discontinuation may be considered. Also, proper hydration with saline-containing drinks (e.g. sport drinks) and/or intravenous fluids is recommended to contrast diarrhea-related events and minimize risk of hyponatremia, the latter generally multifactorial, asymptomatic, and correctable with sodium tablets or electrolyte-containing fluids.

Regarding hematological toxicities, thrombocytopenia was the most common in registrational studies (BOSTON: 60%; STORM: 73%, G3/4: 39% and 58%, respectively), followed by anemia (36% and 67%, G3/4: 16% and 44%), and neutropenia (15% and 40%, G3/4: 9% and 21%).^{24,26} A meta-analysis on 954 RRMM patients across 16 studies reported thrombocytopenia (9%–71%), anemia (16%–60%), and neutropenia (23%–63%) as G3/4 hematological toxicities.³⁵ In this regard, regular monitoring of platelet counts is strongly recommended. When necessary, neutropenia can be managed with granulocyte colony-stimulating-factors.

Dose adjustments based on hematological toxicity are shown in Table 2. Overall, selinexor dose reduction was required in 89% (BOSTON) and 80% (STORM) of patients within trials, and in about half of the patients in real life (57% Sd, 56.5% SVd), while toxicity-related discontinuation was required in 20%.²⁹ Further studies examining AE mitigation strategies in larger, standardized populations are warranted to optimize supportive care and develop best-practice guidelines.

Notably, RRMM patients may be carriers of existing TRAEs and comorbidities, and are frequently on multiple medications. As selinexor is metabolized by the CYP3A4, UGT, and GST pathways, potential drug–drug interactions (DDIs) with medications that inhibit or induce CYP3A4, UGT, and GST pathways may occur (Table 3). However, selinexor does not inhibit major CYP or UGT enzymes, nor the hERG K⁺ channel, at clinically relevant levels, as indicated by IC₅₀ (half-maximal inhibitory concentration) values far

Table 2. Selinexor dosage adjustment due to toxicities		
Selinexor dosage adjustment due to hematological toxicities		
Thrombocytopenia	Platelet count 25 000-75 000 cells/mm ³ Platelet count 25 000-75 000 cells/mm ³ with hemorrhagic manifestations Platelet count <25 000 cells/mm ³	One-step dose level reduction (see below) Stop the drug Restarting with one-step dose level reduction after bleeding resolution Stop the drug Restarting with one-step dose level reduction when platelet count is >50 000 cells/mm ³
Neutropenia	Neutrophil count 0.5-1.0 × 10 ⁹ /l without fever Neutrophil count below 0.5 × 10 ⁹ /l or febrile neutropenia	One-step dose level reduction (see below) Stop the drug Restarting with one-step dose level reduction when neutrophil count is >1.0 × 10 ⁹ /l
Anemia	Hemoglobin level below 8.0 g/dl	One-step dose level reduction (see below)
Selinexor recommended dose and reduction due to toxicities		
	SVd	Sd
Recommended dose	100 mg once weekly	80 mg on days 1 and 3 of each week (160 mg weekly)
First reduction	80 mg once weekly	100 mg once weekly
Second reduction	60 mg once weekly	80 mg once weekly
Third reduction	40 mg once weekly	60 mg once weekly
Discontinuation		

Sd, selinexor—dexamethasone; SVd, selinexor—bortezomib—dexamethasone.

Table 3. Potential drug–drug interactions among selinexor and other antimyeloma agents		
Potential toward CYP3A4	Drug categories and examples	Clinical impact
Strong inhibitors	- Antibiotics: clarithromycin, telithromycin - Antifungals: voriconazole, itraconazole, ketoconazole - Antivirals: delavirdine, indinavir, nelfinavir, ritonavir	Clinically significant interaction is unlikely
Moderate inhibitors	- Calcium channel blockers: verapamil, diltiazem - NK1 receptor antagonists: netupitant, aprepitant - Antibiotics: erythromycin, ciprofloxacin. Antifungals: fluconazole - Antiviral: letermovir	Clinically significant interaction is unlikely
Strong inducers	- Anticonvulsants: carbamazepine - Antibiotics: rifampin	The clinical relevance of this interaction is unknown. No a priori dose adjustment is necessary, but it is recommended to monitor for selinexor toxicity
Moderate inducers	- Anticonvulsants: phenytoin, phenobarbital, eslicarbazepine, oxcarbazepine - Antiviral: efavirenz - Hormonal agents: elagolix	Clinically significant interaction is unlikely

exceeding therapeutic plasma concentrations. Consequently, selinexor does not cause significant metabolic DDIs, nor does it prolong the QT interval. Also, food does not significantly impact selinexor pharmacokinetics.

Population pharmacokinetic analyses indicated that selinexor absorption is unaffected by co-administration with pH-altering drugs, like proton pump inhibitors or H2 receptor antagonists. Co-administration with the strong CYP3A4 inhibitor clarithromycin (500 mg twice daily for 7 days) did not significantly alter selinexor pharmacokinetics. Similarly, co-administration with paracetamol (up to 1000 mg daily) had no meaningful effect. Overall, co-administration with common drug classes including anti-hypertensives, anticoagulants, or antibiotics is considered largely safe, and clinically significant interactions are unlikely. However, caution is advised when selinexor is used with strong CYP3A4 inducers, (e.g. rifampicin, carbamazepine, St. John’s wort), as these may reduce selinexor exposure. In such cases, therapeutic monitoring and dose adjustments may be necessary, in line with product labeling and clinical judgment.

IMPACT OF SELINEXOR ON QoL

MM is the second most common hematological cancer, and its incidence is rising due to population ageing. As a largely incurable disease, long-term toxicities and QoL are of increasing importance.³⁶

Currently available anti-MM therapies, often used in combination, can be grouped according to the type of administration: oral, subcutaneous (s.c.), and intravenous (i.v.), with

inevitable advantages/disadvantages and logistical differences ultimately impacting QoL and treatment adherence (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2025.106054>). Overall, i.v. therapies ensure precise dosing and rapid drug action, despite infusion-related complications and the frequent need for central venous access. Subcutaneous administration offers ease of use and reduced systemic side-effects, while minimizing infusion-related reactions and shortening treatment times. However, both i.v. and s.c. administrations require medical supervision in hospital settings and are generally delivered on bi-weekly or monthly schedules, though comorbidities and disabling symptoms may hinder MM patients’ frequent hospital access. Conversely, oral therapies provide greater flexibility, allowing for at-home administration, ultimately resulting in robust systemic treatment while supporting patient adherence and QoL. Indeed, though oral combinations force patients to take an active role in managing their medications to avoid suboptimal administration, good treatment adherence was reported, though evidence remains limited.³⁷⁻⁴⁰

In this regard, selinexor-based therapies offer a huge advantage, as they could be administered at home, either through caregiver support or via structured home care programs, the latter supporting broader access to therapy and overall treatment continuity.⁴¹ In this context, caregivers play a pivotal role in both logistical support and treatment adherence, limiting treatment defections by non-compliant MM patients.^{42,43}

Moreover, patient and caregiver education is vital in ensuring tolerance to anti-MM therapies and avoiding related toxicities. Indeed, early incorporation of supportive

care and adherence to antiemetics are key to address selinexor-related AEs. Also, caregivers should help in controlling dietary regimens (e.g. small, frequent meals, and avoiding large, fried, or greasy meals), monitoring daily weight, hydration, and physical activity. In case of weight loss or loss of appetite, high-calorie snacks should be added and, if weight drops, the patient should be referred to nutritional counseling. Meanwhile, patients and family should be trained on the main strategies to minimize constipation risk, including optimal hydration, high-fiber diet, and potential use of laxatives, although attention should be paid to the risk of diarrhea and proactively intervene through adequate hydration. Not least, regular exercise can be effective in minimizing fatigue. Also, frequent communication with patients or caregivers to monitor tolerability and manage emergent AEs is crucial to prevent more severe reactions in this often medically fragile population.

Notably, despite the key role of caregivers in MM, very little is known about the impact that the disease (diagnosis, logistical challenges, management of complex symptoms, and prognosis) can have on them. Moreover, to date, tools to assess QoL have largely focused on patients' reporting of symptoms, with limited data on patients' caregiver burden. To fill this gap, a self-report Caregiver Burden Inventory questionnaire⁴⁴ was administered to 40 family caregivers of MM patients to assess QoL, patient symptom burden, and the impact of family caregiving. This questionnaire, based on the study by Guest,⁴⁵ was implemented with the addition of further features according to previously published scales to fit a multidimensional model.⁴⁶⁻⁴⁸ Caregivers were interviewed in hematology outpatient departments of five Italian hematology centers (one in northern Italy, three in central Italy, and one in southern Italy), using a questionnaire with open-ended and fixed-choice questions (further details and results in [Supplementary Material](#), and [results in Supplementary Figure S2](#), available at <https://doi.org/10.1016/j.esmoop.2025.106054>). As this was a preliminary pilot survey, it had several limitations, including the limited number of subjects and the variability of an unselected population, including caregivers of fit, unfit, or frail MM patients, regardless of their age, comorbidities, clinical picture and disease stage, and types/schemes of therapy. Nonetheless, the survey interestingly showed that the assistance of MM patients, mostly independent in their daily activities, had no relevant impact on the private, social, and working life of caregivers. Anyhow, as improvements in treatment raised the chance of functionally curable MM, the goal of treatment should increasingly be long-term survival with adequate QoL for MM patients and their caregivers.

TREATMENT SEQUENCING AND ROLE OF SELINEXOR IN MM

The rapid expansion of the anti-MM therapeutic armamentarium has greatly complicated the choice of treatment.⁴⁹ Ideally, therapy should provide an optimal balance between efficacy and safety, reducing the disease burden

rapidly while achieving deep and durable responses, especially in the early phases of the disease.

Treatment selection is multifactorial, depending on patient-related factors (e.g. age, frailty, comorbidities), disease characteristics, potential toxicities, logistical feasibility, and drug accessibility, including country-specific reimbursement policies. In relapsed settings, prior treatment history, response rates and durations, and the nature of relapse must be considered. More importantly, the optimal sequence of available treatments remains undefined, and several studies have shown progressive decline in the proportion of patients receiving treatments beyond the first and subsequent LOTs, underscoring the need to select the most effective treatment at each relapse.

With current data, ciltacabtagene autoleucel (cilta-cel) should be the therapy of choice at first relapse in eligible patients, though only available in accredited hub centers having the required multidisciplinary expertise to administer CAR-T therapies. In case this option may not be available, or patients are not suitable candidates, several studies suggest that changing the MoA at relapse can improve outcomes. In this context, selinexor appears to be promising, as the STORM and BOSTON trials highlighted the potential of targeting XPO1 in TCR-RRMM.^{24,26} Noteworthy, selinexor may also represent a good option in patients with extramedullary disease (EMD), a group historically resistant to conventional therapies and associated with poor outcomes.⁵⁰

Nonetheless, resistance to therapy has a critical impact, as early exposure to different classes of drugs raised new challenges at subsequent relapse(s), with lenalidomide-refractory patients still representing a significant unmet need in MM.⁵¹ Notably, updated data from the BOSTON study, with longer follow-up and analysis on the impact of prior treatments, were recently published, with better results observed in patients with no prior PI or bortezomib exposure, and after one prior LOT.²⁸ In lenalidomide-refractory patients, the SvD regimen resulted in longer mPFS than Vd (10.2 versus 7.1 months), prolonged TTNT (13.0 versus 7.6 months), and higher ORR (67.9% versus 47.2%). These results compare favorably to other standard regimens in this setting, like carfilzomib–dexamethasone (ENDEAVOR, mPFS 8.6 months) and pomalidomide–bortezomib–dexamethasone (OPTIMISMM, mPFS 9.5 months). Bortezomib-naïve patients, who are increasingly prevalent due to the upfront use of daratumumab–lenalidomide–dexamethasone in transplant-ineligible patients, experienced an even greater benefit: mPFS reached 29.5 months with SvD versus 9.7 months with Vd; ORR was 75.4%, and mTTNT 29.8 months. Similarly, in patients with only one prior LOT, mPFS was 21.0 versus 10.7 months, mTTNT was 19.0 versus 12.9 months, and $\geq$ VGPR was 52.5% versus 11.2% (SvD versus Vd). Notably, the safety profile remained consistent and manageable.²⁸

Moreover, as the increasing use of anti-CD38 mAbs in newly diagnosed MM (NDMM) or early relapsed MM may progressively increase early refractoriness to anti-CD38 mAbs, agents against novel targets or with different MoA, such as

selinexor, have the potential to circumvent resistance mechanisms. In this regard, an exploratory analysis on a small subgroup of patients with prior daratumumab exposure confirmed mPFS of 12.2 months, not significantly different from the broader population,⁵² emphasizing the role of selinexor in the expanding population of MM patients with previous treatment with anti-CD38-containing regimens.

Notably, predictive biomarkers of response could also help guide therapeutic strategies. A recent study evaluated *ex vivo* sensitivity and resistance to 37 drugs and combinations in MM, by integrating functional genomics analysis (i.e. cytogenetics, mutational profiles, transcriptomes, and clinical variables).⁵³ The footprints generated by this analysis for daratumumab and selinexor revealed a precise pattern of clinical response. Specifically, based on the different mechanisms of resistance of these drugs, sequential therapy with selinexor after daratumumab appears to be ideal for improving survivals. Moreover, a *post hoc* analysis of the STOMP and BOSTON trials found selinexor combination therapy to be efficacious in patients exposed/refractory to daratumumab or isatuximab, with mPFS ranging from 8.7 to 15.0 months.

Based on the latest European Hematology Association and European Myeloma Network guidelines,⁵⁴ SVd might be a suitable second-line option in patients ineligible to receive novel anti-BCMA therapies. Also, in patients eligible to receive anti-BCMA therapies in the following LOTs, selinexor-based regimens should be considered. Looking ahead, ongoing trials are evaluating selinexor in earlier LOTs and at lower doses to optimize efficacy while minimizing toxicity. Moreover, sequencing strategies combining selinexor with T-cell-redirecting therapies are gaining interest. In this regard, recent findings reported selinexor-containing regimens as viable bridging therapies before CAR-Ts; also, selinexor could find a place following CAR-T therapies, or among BsAbs, allowing for T-cell function recovery and mitigating T-cell exhaustion, potentially enhancing the outcomes from these therapies. Meanwhile, further data on SVd in these contexts are warranted.

Selinexor in high-risk cytogenetic MM and renal impairment

The cytogenetic asset of MM has been shown to influence disease outcomes, with high-risk anomalies such as del(17p), t(4;14), t(14;16), and gain/amp1q21 associated with shorter PFS and OS than those with standard-risk cytogenetics.

Interestingly, a subgroup analysis of the BOSTON trial compared SVd versus Vd in patients with high-risk cytogenetics (70 SVd, 71 Vd), defined by the presence of one or more among del17p, t(4;14), t(14;16), or 1q21 amplification (four or more copies).⁵⁵ Overall, SVd yielded more favorable efficacy outcomes over Vd in all patient subgroups with either high-risk or standard-risk cytogenetics, while safety profiles in both subgroups were

similar. Specifically, among high-risk patients, mPFS was 12.91 months with SVd and 8.61 months with Vd (16.62 versus 9.46 months in standard-risk patients, respectively), while ORR was 78.6% versus 57.7% and 75.2% versus 64.7% (SVd versus Vd) in high-risk and standard-risk subgroups, respectively. Notably, patients who achieved $\geq$ VGPR were twofold higher for SVd than Vd (30.0% versus 18.3%) in the high-risk subgroup. Median TTNT was prolonged with SVd in both high-risk (14.03 versus 8.61 months) and standard-risk (18.23 versus 11.73 months) subgroups. Notably, a trend toward improved ORR, PFS, and TTNT with SVd compared with Vd was also observed in patients with two or more cytogenetic abnormalities. In line with these results, a retrospective analysis examining selinexor-based regimen in TP53-altered RRMM patients showed similar outcomes among RRMM patients with del17p, other high-risk cytogenetics, and standard-risk cytogenetics, again emphasizing the use of selinexor in RRMM patients with either high-risk or standard-risk cytogenetics.⁵⁶

Recently, a new consensus classification⁵⁷ has been published that identifies high-risk myeloma patients at diagnosis if they carry *TP53* gene mutations and/or deletion of chr(17p); bi-allelic deletions of chr(1p32); t(4;14) or t(14;16) or t(14;20)—co-occurring with 1q+ and/or del(1p32); monoallelic del(1p32) along with 1q+; and high b2M (>5.5 mg/dl) with normal creatinine (<1.2 mg/dl). This new classification will hopefully help the harmonization of the definition of high-risk myeloma across clinical trials and allow the accurate assessment of drug combinations in this setting.

Besides cytogenetic abnormalities, renal impairment (RI) is frequent in MM and often associated with poorer outcomes.⁵⁸ Furthermore, in the elderly, RI may originate from diabetes and/or hypertension. Importantly, recovery from RI may not occur, even with deep hematological responses, strongly conditioning subsequent therapies. The role of bortezomib in this setting is well established, and patients with RI are strong candidates to receive bortezomib-based regimens. However, in cases of intolerance or refractoriness to bortezomib-containing regimens, alternatives are needed.

Interestingly, selinexor may be effectively used in patients with renal dysfunction, with the drug being primarily metabolized by multiple hepatic routes without significant renal metabolism. In this regard, a subgroup analysis from the BOSTON study compared SVd versus Vd in patients with RI, proving to be favorable in terms of PFS and safety, underlying a role for selinexor in this context.⁵⁹ Collectively, 126 patients (56 SVd, 70 Vd) had RI (CrCl <40 or 40–60 ml/min): mPFS was significantly improved with SVd compared with Vd (CrCl 40–60 ml/min: 16.62 versus 7.26 months; CrCl <40 ml/min: 7.62 versus 4.30 months); also, in terms of OS, patients with RI showed a trend in favor of SVd (median: not reached in both $\leq$ 40 ml/min and 40–60 ml/min) versus Vd (median: 19.06 months for <40 ml/min; 21.22 months for 40–60 ml/min).

Table 4. Results from main clinical trials investigating selinexor-based therapies in MM

Relapsed/refractory multiple myeloma					
Regimen	Clinical trial	Status of trial	SEL dosing	Clinical outcomes	Safety (G $\geq$ 3 AEs)
SKd https://doi.org/10.1038/s41416-021-01608-2	Phase I/II STOMP trial (arm 6) NCT02343042	Enrollment complete (32 patients)	80/100 mg	ORR 78% ≥VGPR 44% mPFS 15 months mDOR 22.7 months mOS NR	Thrombocytopenia (47%) Nausea (6%) Anemia (19%) Fatigue (9%) (all expected and manageable with supportive care/dose modification)
SId https://doi.org/10.1016/j.clml.2019.12.013	Phase I/II STOMP trial (arm 8) NCT02343042	Enrollment complete (18 patients: 7 cohort A; 11 cohort B)	40/60 mg b.i.w. (cohort A); 80/100 mg q.w. (cohort B)	No DLT observed with b.i.w. SEL; however, the study proceeded with q.w. SEL only (cohort B): ORR 22% (2 VGPR, 1 PR) Longest DOR at data cut-off: 14 months	Nausea (N = 2), vomiting (N = 2), anorexia (N = 1). Fatigue (N = 2), hyperglycemia (N = 2), hypophosphatemia (N = 1), Thrombocytopenia (N = 11), anemia (N = 3), neutropenia (N = 5)
S-IPd https://doi.org/10.1182/blood-2023-184949	MYDRUG (NCT03732703) sub-protocol Y3	Completed (17 patients)	60 mg	ORR 52.9% mPFS 10.2 months mOS NR	No DLT. Eight patients (47.1%) experienced a serious AE with 2 patients (11.8%) undergoing treatment discontinuation. Two patients (11.8%) required dose reductions. Non-hematological AEs were G1/2
SRd https://doi.org/10.1182/blood-2020-140141	Phase I/II STOMP trial (arm 3) NCT02343042	Enrollment complete	Escalating dose (from 80 mg q.w. or from 60 mg b.i.w.)	ORR 60% mPFS NR mOS NR	Thrombocytopenia (63%), neutropenia (63%), nausea (4%), fatigue (17%), decreased appetite (8%), and weight loss (8%)
SPd 10.3389/fonc.2024.1352281	Phase I/II STOMP trial (arm 1) NCT02343042	Enrollment complete	40 mg 60 mg	ORR 50% ≥VGPR 28.6% mPFS 18.4 months 24-month OS 51.1% ORR 65% ≥VGPR 30% mPFS 9.5 months 24-month OS 51.1%	SPd-40 versus SPd-60 (all grades): Neutropenia (64.3% versus 75.0%), anemia (46.4% versus 65.0%), thrombocytopenia (42.9% versus 45.0%), fatigue (46.4% versus 75.0%), nausea (32.1% versus 70.0%) diarrhea (28.6% versus 35.0%)
SDd doi: 10.1002/jha2.122	Phase I/II STOMP trial (arm 5) NCT02343042	Enrollment complete	100 mg q.w. or 60 mg b.i.w.	In anti-CD38-naïve patients: ORR 73% ≥VGPR 37% mPFS 12.5 months mDOR 11.4 months 24-month OS 51.1% (No response in anti-CD38-exposed/refractory)	Thrombocytopenia (70.6%), nausea (70.6%), fatigue (61.8%), anemia (61.8%), neutropenia (50.0%)
S-DVd https://doi.org/10.3324/haematol.2023.284089	Phase II GEM-SELIBORDARA study	—	—	ORR 52.2% (part 1), 82% (part 2) ≥VGPR 21.7% (part 1), 53.4% (part 2) mPFS 7 months (part 1), 24 months (part2) 24-month OS 71.7% (part2)	Thrombocytopenia (34%), nausea (6%)
Newly diagnosed multiple myeloma					
Regimen	Clinical trial	Status of trial	SEL dosing	Clinical outcomes	Safety (G $\geq$ 3 AEs)
SRd https://doi.org/10.1182/blood-2020-140141	Phase I/II STOMP trial (arm 7) NCT02343042	Enrollment complete	60 mg q.w.	ORR 100% (1 CR, 4 VGPR, and 2 PR). mPFS NR (median FU 10.2 months)	Thrombocytopenia (38%), neutropenia (75%), fatigue (50%), decreased appetite (13%)
S-VRd	—	—	—	ORR 100% ≥VGPR 8/10 mOS NR mPFS NR	—

AEs, adverse events; b.i.w., bi-weekly; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; FU, follow-up; G, grade; m, median; MM, multiple myeloma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; q.w., once weekly; SDd, selinexor, daratumumab, dexamethasone; SEL, selinexor; SId, selinexor, ixazomib, dexamethasone; SKd, selinexor, carfilzomib, dexamethasone; SRd, selinexor, lenalidomide, dexamethasone; S-DVd, selinexor, daratumumab, bortezomib, dexamethasone; S-IPd, selinexor, ixazomib, pomalidomide, dexamethasone; S-VRd, selinexor, bortezomib, lenalidomide, dexamethasone; TRAEs, treatment-related adverse events; VGPR, very good partial response.

SELINEXOR-BASED COMBINATION THERAPIES

Besides approved SVd and Sd combinations, several other selinexor-based regimens are being explored in clinical trials or have shown preliminary evidence of efficacy in RRMM (Table 4).

PI-based

Among possible combinations, preclinical results on selinexor—carfilzomib—dexamethasone (SKd) were initially validated in a pivotal phase I trial on RRMM, showing good tolerability and promising efficacy.⁶⁰ Then, SKd was further

evaluated in the phase I/II STOMP trial (arm 6), an ongoing multiarm study (NCT02343042) evaluating different selinexor-based regimens in RRMM.⁶¹ Upon a dose-finding approach, weekly 80 mg selinexor proved tolerable and was selected as the recommended phase II dose (RP2D). Overall, 32 patients were enrolled in the SKd arm and 18 in the RP2D cohort (median age 69.5 years, four median prior LOTs, 53% carrying high-risk abnormalities, 68.8% TCR). The mPFS and DOR were 15 and 22.7 months, respectively; mOS was not reached. Similar results were observed in subgroup analysis of TCR and high-risk patients.⁶¹ Main G3/4 AEs were hematological (thrombocytopenia 47%, anemia 19%). ORR was 78%, with 44% $\geq$ VGPR. Notably, in a *post hoc* analysis, SKd combination resulted in high ORR (65.2%) and long survival (mPFS 15.0 months) in 23 patients previously treated with anti-CD38 mAbs, comparing favorably with other selinexor-based triplets.⁵² Preliminary safety and efficacy data among patients with RI and dialysis were also reported,⁶² while a study on heavily pretreated RRMM patients (25/30 carfilzomib-exposed/refractory, 6/30, to prior CAR-T therapy) showed 70% ORR, 5.3 months mPFS, and 23.3 months mOS with SKd, similarly in naive or carfilzomib-exposed patients, with no new safety issues,⁶³ making the SKd triplet attractive as a bridge to immunotherapies, despite modest long-term efficacy.

Furthermore, selinexor was evaluated in association with the oral PI ixazomib (SIId). The most relevant trial is a single-center experience from Memorial Sloan Kettering testing SIId in heavily pretreated RRMM patients, overall resulting in a 22% ORR and frequent dose reduction/treatment delays due to toxicities (mainly thrombocytopenia and GI toxicities), eventually leading to disease progression.⁶⁴ Meanwhile, the ongoing STOMP trial (arm 8) is evaluating SIId with 80-100 mg weekly selinexor dosage,⁶¹ whereas SIId plus pomalidomide (S-IPd) was tested in 17 functional high-risk patients with a median of two prior LOTs in the MYDRUG sub-protocol Y3, with 52.9% ORR and less frequent G3/4 thrombocytopenia, suggesting significant efficacy and a manageable toxicity profile when used in prior lines.⁶⁵

IMiD-based

As for IMiDs, selinexor—lenalidomide is under evaluation in different trials, both in the first-line and relapsed/refractory settings. Specifically, selinexor—lenalidomide—dexamethasone (SRd) was evaluated in 24 RRMM patients (median age 67 years, 1.5 median prior LOTs) in the STOMP trial (arm 3).^{66,67} The ORR was 60% in all assessable ($n = 20$) patients, with better responses observed among lenalidomide-naive than previously lenalidomide-exposed patients (92% versus 13% ORR). The mPFS and OS have not been reached yet. Common G3/4 TRAEs were hematological (63% thrombocytopenia, 63% neutropenia), while G3/4 nausea, fatigue, anorexia, and weight loss were <20%. Based on the activity of SRd in lenalidomide-naive patients, eight NDMM patients were enrolled (arm 7) at the RP2D, with 100% ORR and similar safety profile, thus

warranting further investigation on SRd, in both settings. In addition, SRd plus bortezomib (S-VRd) was evaluated in 10 NDMM patients (median age 62 years, two staged as Revised International Staging System 3 and three with high-risk cytogenetics) with EMD, resulting in 100% ORR, ($\geq$ VGPR in 8/10), while mPFS and mOS were not achieved. Regarding safety, 10% of patients reported G3/4 treatment-emergent thrombocytopenia, while other non-hematological AEs were G1 or 2.⁶⁸

The combination selinexor—pomalidomide—dexamethasone (SPd) was explored in arm 1 of the STOMP trial in 48 RRMM patients.^{69,70} Overall, results showed that the all-oral SPd combination was effective and generally tolerable in these patients. Indeed, with 40 mg selinexor, ORR was 50% (28.6% $\geq$ VGPR), mPFS was 18.4 months, and 24-month OS was 64.2%, while 60 mg selinexor resulted in 65% ORR (30.0% $\geq$ VGPR), 9.5 months mPFS, and 24-month OS of 51.1%. G3/4 AEs were mainly hematological.⁷⁰ Also, SPd has been evaluated in pomalidomide-naive RRMM patients who had received one to four prior anti-MM regimens including an IMiD, a PI, and an anti-CD38 mAb in the phase III EMN29 trial (NCT05028348), comparing efficacy, safety, and the impact on health-related QoL of SPd versus elotuzumab—Pd.

Anti-CD38-based

Selinexor—daratumumab—dexamethasone (SDd) was explored in 34 RRMM patients in the STOMP trial (arm 5). Collectively, anti-CD38 treatment-naive patients showed 73% ORR (37% $\geq$ VGPR) and 12.5 months mPFS, with 11.4 months DOR, while previously anti-CD38-exposed or -refractory (6%) patients showed no response. Common G3/4 hematological AEs were thrombocytopenia (47.1%) and anemia (32.4%), followed by neutropenia (26.5%). Also, more than one-third of patients experienced non-hematological AEs, mainly consisting of G1-2 nausea (70.6%), successfully managed with prophylactic/supportive care.⁶⁹ Recently, real-world data confirmed the efficacy of second-line SDd in lenalidomide-refractory patients.⁷¹

The addition of bortezomib to SDd (S-DVd) was evaluated in 57 RRMM patients in the open-label phase II SELIBORDARA trial,⁷² showing encouraging efficacy results and an overall manageable safety profile, with thrombocytopenia being the most common G3/4 hematological AE (34%), while G3/4 nausea was reported in 6%.

Finally, a recent study in 23 MM patients evaluated efficacy and safety of an SDd plus thalidomide (S-DTd) at first relapse.⁷³ ORR was 72%, while data on PFS are still immature. Interestingly, G3/4 GI AEs were lower compared with the BOSTON trial, confirming the efficacy of thalidomide in mitigating negative GI effects of selinexor.

Alkylator and venetoclax-based

It is noteworthy that, selinexor combination with chemotherapies and venetoclax offers an innovative solution for refractory and high-risk MM, and ongoing research focuses on refining patient selection and toxicity management to

improve patient outcomes.⁷⁴ Specifically, alkylating agents such as cyclophosphamide and melphalan are key in conditioning for autologous stem cell transplantation, and their combination with selinexor enhances apoptosis by increasing DNA damage and impairing repair via p53-dependent mechanisms. Notably, a recent study evaluated a novel conditioning regimen with selinexor and high-dose melphalan in 25 MM patients in partial remission, suggesting promising synergy.⁷⁵ Indeed, after 12 months, 52% of patients showed deeper responses, with 1-year PFS and OS rates of 87% and 96%, respectively, with no major adverse reactions. Further trials are needed to confirm these findings and improve outcomes. Also, preclinical studies showed that selinexor enhances the sensitivity of multidrug-resistant MM cells to doxorubicin, sparing non-myeloma cells, though results from trials were less encouraging.⁷⁶

Venetoclax, a BCL-2 inhibitor, is effective in MM patients harboring the t(11;14) translocation. However, resistance due to the up-regulation of the upregulation of the anti-apoptotic proteins myeloid cell leukemia-1 and B-cell lymphoma-extra large limits its broader use. By reducing the expression of these proteins, selinexor may enhance its activity, as evidenced by preclinical studies. In line with this, early clinical trials have shown promising results, even in patients progressed on venetoclax-based regimens, while offering a more tolerable treatment by optimizing selinexor's dose-dependent side-effects.⁷⁷ Preclinical models also show synergistic effects, including reduced cyclin D1 levels and improved outcomes in xenograft models, supporting the combination's potential.⁷⁸ The SELVEDge study, an investigator-initiated trial, is evaluating this combination in RRMM t(11;14)-positive patients.⁷⁹ None the less, given the distinct toxicity profiles of both agents, combination regimens based on selinexor and venetoclax should balance efficacy and tolerability, especially in elderly or frail patients. Identifying patients who will benefit from selinexor–venetoclax or selinexor–chemotherapy combinations is key, with t(11;14), high BCL-2 expression, and PI resistance as driving biomarkers.

Selinexor and immunotherapies

Another promising strategy could be represented by the combination of selinexor with novel T-cell-engaging agents, to maintain CAR-T effector or BsAbs therapy function and improve clinical potency. Preclinical studies have demonstrated the potential of selinexor in increasing T-cell fitness and enhancing immune susceptibility of cancer cells, without compromising T-cell health.^{22,80,81} In addition, the use of selinexor before anti-BCMA-targeted therapy in heavily pretreated RRMM patients enrolled in four clinical trials (STORM, STOMP, BOSTON, XPORT-MM-028) was not associated with inferior OS compared with the anti-BCMA agents.⁸² Moreover, a clinical trial (NCT05201118) is ongoing to explore safety and efficacy of a two-step schedule using selinexor both as a bridging therapy and as maintenance after anti-BCMA CAR-T cell in RRMM

patients with EMD. Preliminary results for the first two enrolled patients demonstrated deep and durable response at data-cut-off, with both patients achieving stringent complete response and survival of over 13 and 10 months, respectively, while exhibiting good tolerance.⁸³ Meanwhile, data on the use of selinexor with BsAbs in MM are lacking yet. Finally, a phase Ib/II study (NCT02343042) evaluating selinexor in combination with backbone treatments, including the novel cereblon E3 ubiquitin ligase modulator mezigdomide, is actively recruiting RRMM and NDMM patients.

CONCLUSION

The treatment landscape of MM has led to a paradigm shift over the past two decades, with unprecedented deep and durable responses. None the less, many patients, especially those with high-risk cytogenetics, RI, or early drug resistance, continue to face poor outcomes.

Selinexor,⁸⁴ a selective inhibitor of XPO1, has shown encouraging results and improved therapeutic efficacy in RRMM in combination with other agents across a broad spectrum of patients, including those with TCR disease, renal dysfunction, high-risk cytogenetics, and prior anti-CD38 therapy.

Although recent treatment guidelines have expanded the use of anti-BCMA-based therapies such as CAR-T cells or ADC-containing regimens in early relapse post-lenalidomide exposure, selinexor continues to represent a valuable option, especially for difficult-to-treat patient subgroups, where alternative strategies remain limited, or in patients ineligible to receive T-cell-redirecting therapies. Ongoing clinical trials continue to explore optimal dosing strategies, novel combinatorial approaches, and sequencing. Meanwhile, data on selinexor-based combinations before or after CAR-T, or among BsAbs, are eagerly awaited to help clarify its role in different settings and address persistent unmet clinical needs.

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