INTERNATIONAL MYELOMA FOUNDATION

Selinexor: Best Practices for Optimizing Treatment

Discussion with IMF Nurse Leadership Board

November 16, 2021
Virtual Round Table

IMF NURSE LEADERSHIP BOARD

INTERNATIONAL MYELOMA FOUNDATION

Table of Contents

IMF NURSE LEADERSHIP BOARD

Overview

On November 16, 2021, several members of the International Myeloma Foundation (IMF) Nurse Leadership Board (NLB) convened for a virtual round table. The key objective of the round table was to discuss best practices around optimizing treatment duration with selinexor therapy for patients with multiple myeloma (MM). Additional objectives included the identification of resources and communication strategies to facilitate optimal management and supportive care for patients with MM on selinexor therapy in community practice.

The specific objectives of the discussion included the following:

Key Objective:
Discuss best practices around optimizing treatment duration

Additional Objectives:

1. Summarize the main decision points driving the current use of selinexor
2. Review latest trial data and their clinical significance
3. Discuss the current state of selinexor usage in academic and community practice settings
4. Identify strategies and best practices for managing selinexor-based combinations to support patients

Summary of Key Points

1. Selinexor is a first-in-class oral selective inhibitor of nuclear export approved for patients with MM who have received at least one prior therapy
2. Selinexor in combination with a proteasome inhibitor (PI) may be an option for patients who have failed anti-CD38 monoclonal antibody (MAb) therapy; or, for patients who are unable to tolerate an immunomodulatory drug (IMiD), once-weekly selinexor in combination with once-weekly bortezomib and dexamethasone (XVd) may be considered in second- or third-line therapy
3. In addition to once weekly XVd, other National Comprehensive Cancer Network (NCCN)-recommended combination selinexor regimens include, selinexor in combination with daratumumab and dexamethasone (XDd), selinexor with carfilzomib and dexamethasone (XKd), and an all-oral selinexor with pomalidomide and dexamethasone (XPd) triplet
4. Once-weekly dosing schedule of selinexor in XVd demonstrated improved tolerability compared to the twice-weekly dosing schedule of Xd
5. A proactive approach is essential to support patients on selinexor therapy, with a focus on managing selinexor-associated cytopenia, nausea, anorexia, gastrointestinal (GI) toxicity, and fatigue

Introduction

MM is an incurable malignancy of plasma cells that primarily affects older adults aged 65 to 74 years, with a median age of diagnosis of 69 years.[1,2] MM accounts for 1.8% of all new cancer cases, with 34,920 new MM diagnoses and 12,410 deaths projected in 2021 in the United States.[1] The proliferation and accumulation of abnormal plasma cells can result in bone damage and failure of marrow, along with organ damage and increased susceptibility to infections.[3,4] Although MM is considered rare, it is the second most common hematologic malignancy.[1] It is more prevalent in men than in women and among those of African descent.[1]

The therapeutic landscape of MM has undergone remarkable expansion in the last 2 decades, with regulatory approval of many novel therapies and a concomitant and steady improvement in disease-free and overall survival (OS) of patients with MM.[5-7] The introduction of agents with novel mechanisms, including MAbs, IMiDs, next-generation PIs, and combinations thereof, has enabled these remarkable improvements in patient outcomes, with more promising therapies currently under investigation.[7-9] Despite significant advances in MM management, relapse and disease progression are nearly inevitable, and most patients have multiple relapses as their disease becomes refractory to PIs, IMiDs, and/or MAbs.[6,10] Furthermore, each additional line of therapy (LOT) and development of disease refractory to multiple drug classes is associated with progressively shorter durations of remission or response, and ultimately, shorter survival.[6,8,10,11] RRMM management continues to be challenging, not only due to the limited number of clinically effective options for patients who progress on 3 primary classes (PIs, IMiDs, and anti-CD38 MAbs), but also due to the complexity in therapeutic decision-making posed by rapid expansion of options at earlier LOTs following first relapse.[12,13]

As more patients receive PIs, IMiDs, and MAbs in earlier lines, the evolving MM landscape presents an opportunity to introduce different mechanisms of action (MOAs) to treat the disease. This becomes especially true for those who progress on anti-CD38 MAbs, representing a new subset of patients with an unmet need.[11] Selinexor is a first-in-class oral selective inhibitor of nuclear export that binds covalently to Cys528 in the cargo-binding pocket of the major nuclear export protein, exportin 1 (XPO-1).[14,15] XPO-1 is a nuclear export protein with a global pleiotropic function in the nuclear export of proteins and different RNA species; in addition to exporting tumor suppressors (TSPs) such as p53 and retinoblastoma protein, XPO-1 exports transcription factors, cell cycle regulators, cell growth regulators, and oncogenic messenger RNAs (mRNAs) bound to eukaryotic translation initiation factor 4E (eIF4E).[16,17] Moreover, XPO-1 is overexpressed in MM cells, and XPO-1 overexpression in MM is associated with increased bone disease and poor

prognosis.[14,18,19] XPO-1 inhibition leads to nuclear retention of TSPs, restoring their function and activity; additional effects of XPO-1 inhibition include nuclear retention and functional activation of glucocorticoid receptor by selinexor-dexamethasone treatment and suppression of oncoprotein production via entrapment of oncogenic mRNA-eIF4E complexes in the nucleus.[20,21] Selinexor-mediated nuclear retention of TSPs in clonal plasma cells is a key mechanism that drives the selective apoptosis of myeloma cells, although selinexor-mediated effects on myeloma cells are likely to be more complex, involving additional/TSP-independent mechanisms.[12,14,16] Moreover, selinexor exhibits synergistic activity with other agents used in myeloma therapy, including PIs, IMiDs, and MAbs, in ex vivo drug sensitivity assays and in vivo, thereby establishing the rationale for selinexor combination regimens for treatment of MM.[22-24] Indeed, XVd was the first selinexor combination therapy approved for the treatment of patients with RRMM who received at least 1 prior LOT (at first relapse).[25] The approval, in December 2020, was based on data from the phase 3 BOSTON trial in which efficacy analyses favored XVd with a median progression-free survival (PFS) of 13.9 months vs 9.5 months for twice-weekly dosing of bortezomib with dexamethasone (Vd) alone.[25,26] Other selinexor combination regimens are currently being evaluated in MM, including in the phase 1/2, open-label, multi-arm STOMP study.[27-29]

In the roundtable forum, the IMF NLB discussions focused on optimal strategies for educating and engaging not only patients, but also nurses, oncologists, and other clinicians, especially those in community practice, involved in managing/comanaging patients with MM on selinexor therapy. The NLB also discussed approaches for coordinating and managing supportive care for patients throughout the continuum of their selinexor therapeutic journey, including strategies for optimizing the use of selinexor in community practice using best practices for providing supportive care and managing toxicities. The NLB also provided insights on selinexor's current and potential future position in the MM treatment paradigm.

Clinical Data for Selinexor and Position of Selinexor in the MM Treatment Paradigm

BOSTON Study

The phase 3, global, open-label, randomized controlled BOSTON trial compared the efficacy and safety of XVd with Vd in patients with MM who had received 1 to 3 prior therapies.[26] As mentioned before, the data showed a significant PFS benefit with XVd over Vd (median PFS 13.9 months vs 9.5 months), translating to a 30% reduced risk of progression or death. Notably, this therapeutic benefit was achieved with 40% less bortezomib and 25% less dexamethasone during the first 24 weeks of treatment. Patients randomized to the XVd arm received selinexor as a fixed oral 100-

mg once-weekly dose on days 1, 8, 15, 22, and 29 of each 5-week cycle and bortezomib subcutaneously at 1.3 mg/m^2 once weekly on days 1, 8, 15, and 22 of each 5-week cycle (compared with the twice-weekly approved dosing schedule of 1.3 mg/m^2 subcutaneously on days 1, 4, 8, and 11 used in the Vd arm). The selinexor dosing of 100 mg once weekly used in the BOSTON study was based on the recommended phase 2 dose (RP2D) identified for the XVd arm in the STOMP study (discussed in detail below).[27] This once-weekly dosing schedule of selinexor demonstrated improved tolerability[26] compared with the 80-mg twice-weekly dosing schedule used in the STORM study of selinexor with dexamethasone (Xd; referred to hereafter as selinexor monotherapy).[14] Of note, nearly two-thirds of patients in the XVd arm had a selinexor dose reduction. The median dosage was 80 mg (range, 30-137 mg) once weekly.[30]

The most common (≥10% of patients in either arm) grade 3/4 treatment-emergent adverse events (TEAEs) (XVd vs Vd, respectively) included thrombocytopenia (40% vs 17%), anemia (16% vs 10%), pneumonia (12% vs 10%), and fatigue (13% vs 1%). The rates of overall (32.3% vs 47.1%) and grade ≥2 (21.0% vs 34.3%) peripheral neuropathy were significantly lower in the XVd arm compared with the Vd arm, respectively; grade 3/4 peripheral neuropathy rates also trended lower with XVd, respectively (4.6 % vs 8.8%).[26] The modified dosing schedule used in the BOSTON XVd arm resulted in the use of approximately 40% less bortezomib than that used in the Vd arm and also 37% fewer clinic visits over the first 6 months of treatment. Based on the efficacy observed with selinexor in combination with just weekly dosing of bortezomib in the BOSTON study, XVd gained regulatory approval for patients with RRMM who received at least 1 prior LOT.[25]

STOMP Study

STOMP is an ongoing study that is assessing the maximum tolerated dose, efficacy, safety, and recommended phase 2 dose of once-/twice-weekly selinexor in combination with various MM therapies across multiple triplet and quadruplet regimens, primarily in patients with RRMM.[31] To date, data for the XKd, XPd, and XVd arms have indicated that the once-weekly dosing schedule for selinexor demonstrates clinical efficacy in combination with other therapies.[27-29,32-34] Consistent with the BOSTON data, XVd yielded high response rates in RRMM in STOMP, with a median PFS of 9.0, 17.8, and 6.1 months for all, PI-nonrefractory, and PI-refractory populations, respectively.[27] The all-oral XPd combination had higher clinical activity than the expected response with Pd (overall response rate [ORR] 65% with XPd vs expected ORR ≤30% with Pd). Moreover, the responses were durable, with an overall median PFS of 10.4 months and PFS of 12.2 months in the subgroup of patients whose disease was naïve or nonrefractory to pomalidomide.[29] The RP2D was selinexor 60 mg once weekly, pomalidomide 4 mg

daily, and dexamethasone 40 mg once weekly. Clinical activity of the XKd triplet was also evident, with an ORR of 78.1% in all patients who had previously received a median of 4 LOTs, consistent with that in other carfilzomib-based regimens, including daratumumab-carfilzomib combinations for MM.[33] The XKd triplet yielded an overall median PFS of 15.0 months (95% CI, 12.0 to not estimable [NE]; at a median follow-up of 8.0 months), with a median duration of response of 22.7 months (95% CI, 11.8-NE; median follow-up 5.6 months); median OS was not reached (95% CI, NE to NE; median follow-up 15.1 months).[33] Notably, XKd demonstrated ORR of 66.7% in patients who had triple-class refractory disease; XPd yielded an ORR of 64% overall and 100% at the RP2D (60-mg once-weekly selinexor) in patients with prior exposure to daratumumab/anti-CD38 MAb therapy.[33,34]

Perspective of the IMF NLB on Selinexor Clinical Studies

Overall, the NLB noted that selinexor is primarily being used in combination regimens in their practice, and that practice has also shifted away from selinexor monotherapy at a twice-weekly dosing schedule to a once-weekly dosing schedule in combination therapies. Based on currently available data and their in-practice experiences, the NLB concluded that selinexor combination therapies offer the advantage of improved tolerability without compromising clinical activity, and in the case of XPd, the convenience of an all-oral combination. All-oral regimens may offer additional advantages in community practice, where infusion appointments/clinics may be limited or not readily accessible. The once-weekly dosing schedule in combinations may allow for use of selinexor at lower doses (down to 40 mg once weekly) in some frail patients, enabling sustained treatment, favorable response, and improved tolerability. Overall, the NLB felt that given the current efficacy data available for the various selinexor combinations, the data in support of anti-CD38 MAb therapies at first relapse are richer and stronger than those for selinexor combinations after 1 LOT/first relapse. However, Nurse Leaders noted clinical scenarios where selinexor combinations may be of interest at this point in care: Selinexor in combination with a PI may be an option for patients who have failed anti-CD38 MAb therapy, or, for patients who are unable to tolerate an IMiD, XVd may be considered in second- or third-line therapy.

Selinexor Dosing Considerations

Overall, the NLB reported a shift in practice toward the once-weekly dosing schedule for selinexor and combination regimens. Concerning dosing considerations, a Nurse Leader noted that treatment may be initiated at higher doses for optimizing efficacy, with the option to dose reduce based on tolerability. Other Nurse Leaders noted that they initiate treatment at the middle of the dose range schedule, at 60 or 80 mg once weekly, and titrate up or down based on how well the patient tolerates the

dose. Overall, the impression was that the MOA, rather than the specific dose, may be a determinant of whether the patient responds to this new class of agent. The NLB indicates that having the flexibility to apply different dosing schedules can help optimize treatment duration, facilitating the goal of obtaining favorable clinical benefits while sustaining tolerability.

Position of Selinexor in the MM Treatment Paradigm

The NCCN Clinical Practice Guidelines for MM include XVd (other recommended regimen) and XPd (useful in certain circumstances; after 2 prior therapies including bortezomib and an IMiD), as well as XDd and XKd; useful in certain circumstances) for patients with early relapse (1-3 prior therapies).[4] The guidelines also include Xd for patients with late relapse (>3 prior therapies), after ≥4 prior therapies, and in patients whose disease is refractory to ≥2 PIs, ≥2 IMiDs, and an anti-CD38 MAb.[4]

The NLB noted that selinexor is currently used in large part in combination therapies. A Nurse Leader noted that for patients who have failed MAb therapy, selinexor in combination with a PI may be an option. Nurses/advanced practice providers who are more intimately acquainted with the patient's treatment history and other factors may refer patients for selinexor combination therapies, as appropriate. A Nurse Leader noted that selinexor is also used as bridging therapy for patients who are awaiting chimeric antigen receptor T-cell infusion.

Engaging Community Practitioners to Facilitate the Goal of Optimizing Selinexor Therapy

Currently, selinexor regimens are mostly referred from or initiated at academic institutions. There appear to be some instances where selinexor is prescribed by community providers. However, the practice trend is one in which an increased number of selinexor regimens are first recommended by academic centers for patients who are later referred to community practices, following the initial consultation. Unfortunately, community practices may have limited resources to provide adequate and regularly scheduled supportive care. In addition, the earlier challenges with toxicity management with the twice-weekly dosing schedule may contribute to limiting widespread selinexor use, especially in community settings.

The NLB noted the importance of educating and engaging clinicians in community practice on key aspects of the MOA, toxicity profile, dosing, efficacy, and management strategies for optimizing selinexor clinical benefit. The following were noted as key aspects of upfront discussions with clinicians in community practice:

MOA

It is important to discuss the unique MOA of selinexor (**Figure 1**) and its implications on clinical efficacy and toxicity so that

clinicians in turn can educate their patients. Selinexor is a drug with an MOA that has a global effect on various TSPs,[14,17] unlike therapies designed against myeloma-specific targets, such as with B-cell maturation antigen–targeted therapies.[35] Limited experience with selinexor in community practice may be one disadvantage associated with its novel MOA and first-in-class approval.

Risk-Benefit Profile

The NLB identified the toxicity profile of selinexor as another key component of discussions with community providers. They noted that there may be a perception that selinexor is exclusively a later-line agent; with that in mind, it is important to communicate that with newer combinations and once-weekly dosing, it may be possible to consider selinexor earlier in the treatment continuum. Reminding community nurses and providers that selinexor is an oral drug, but nevertheless has its own unique toxicity profile that requires careful management, is important as well. Educating community providers on the history of selinexor and the evolution of its dosing can also help address lingering concerns or discomfort about the potential side effects. A Nurse Leader commented that notifying the entire care team of potential AEs that could require monitoring and management could ensure supportive care preparation in advance and coordination and adjustments, as needed, throughout the treatment continuum.

Oral Route of Administration

Several features of selinexor therapy for MM may be particularly advantageous in community and rural practice settings. These include:

- The oral route of administration
- Potential for improved tolerability without compromised efficacy with the once-weekly dosing schedule
- Potential for improved tolerability and optimal therapeutic benefit with the lower dose of selinexor in combination regimens
- Availability of all-oral combination regimens, such as XPd

Nonclinical Concerns

Although there were no overarching nonclinical concerns—such as insurance coverage for selinexor therapies or access to supportive care medications—expressed by the NLB, they did note that there may be geographical variations in how the different dosing schedules and formulations are covered by insurance agencies. Inclusion of selinexor monotherapy (Xd) and combinations (XPd, XVd, XDd, and XKd) in the NCCN practice guidelines for MM[4] has facilitated insurance approval for these therapies. It is important to inform providers, especially those in community practice with resource limitations, of the KaryForward patient support program for assisting patients receiving selinexor in a range of areas, including insurance coverage, financial assistance, and care coordination resources and personnel.[36]

Enrollment in such patient support programs can facilitate access to key resources and personnel, such as care coordinators and nurse navigators, without which there may be significant underutilization of novel agents like selinexor in community practice. Enrollment in the program also provides access for patients to the selinexor starter kit, in addition to facilitating discussions around medications and toxicity/AE concerns with a nurse navigator, as well as transmitting patient-reported concerns to the provider.

Managing Toxicities Associated With Selinexor Therapies

With the emergence of data supporting selinexor dosing changes and combination regimens and increased use of this agent in clinical practice, strategies for preventing, mitigating, and managing selinexor-associated toxicities and AEs have also been identified.

Overview of Selinexor-associated Toxicities

To date, selinexor has been administered to more than 3000 patients with hematologic/solid malignancies as monotherapy or in combinations.[37] The most common AEs associated with selinexor therapy are GI (nausea, vomiting, and diarrhea), constitutional (fatigue, decreased appetite), hematologic (thrombocytopenia and neutropenia), and biochemical (hyponatremia) toxicities. Importantly, selinexor-associated AEs are largely dose- and schedule-dependent, reversible, and occur without evidence of major organ damage or cumulative toxicities after long-term treatment.[37]

Perspective of NLB on Selinexor-associated Toxicities and Management Strategies

Patients and clinicians may have different perspectives regarding selinexor-associated toxicities. For instance, GI toxicities are often the most worrisome for patients due to their impact on their quality of life (QoL). Weight loss may also be a distressing AE for patients and caregivers. Providers, on the other hand, need to consider the proportional weight loss in the context of the baseline weight and overall status of individual patients. A Nurse Leader also pointed out that while weight loss is an important surrogate for malnutrition, it is not the only surrogate, and this AE should be assessed in the context of the patient's overall profile and nutritional status. Addition of a nutritionist to the care team was identified as a strategy for proactive management of weight loss/nutrition concerns.

From a provider perspective, the NLB noted that thrombocytopenia is a concern that requires proactive management. Proactive preparation was identified as a critical component for managing all potential selinexor-associated toxicities. Such preparation includes providing a medication calendar to manage not only selinexor but also any prophylactic medications and additional therapies/supportive care (eg,

fluid infusions, planning for follow-ups long-term to monitor potential toxicities).

The NLB identified calendars as critical tools to ensure medication adherence and compliance, especially with oral medications like selinexor that do not have a daily dosing schedule. Moreover, addition of other medications, such as prophylactic antiemetics, and follow-up assessments to the calendars further facilitates patient management and compliance. Currently, there is no specific calendar tool or application used universally or uniformly across practices for patients with MM who are being treated with selinexor regimens. Availability of customizable, readily accessible calendar tools and their integration into practice may be potentially challenging to implement in everyday clinical practice due to time, technological, or other constraints. Access to a pharmacy team to manage medications can help address the challenges with implementing medication calendars. Medication checklists provided by pharmacists, for instance, are repositories for patient-specific information on the medications, doses, and schedules, as well as the timing and purpose of the medication.

Overall, the NLB noted that the scope of supportive care measures depends on the baseline status of the patient. For instance, if the patient has cytopenia prior to selinexor initiation, then a thrombopoietin (TPO) inhibitor would be an important consideration in anticipation of the need for managing thrombocytopenia.

Supportive Care for Patients on Selinexor Therapy

Principles of Supportive Care for Patients on Selinexor Therapy

Unlike most other oral agents currently employed in MM treatment, selinexor requires considerable supportive care.[12,37] As discussed previously, a proactive approach is essential to support patients on selinexor therapy, with a focus on managing selinexor-associated cytopenia, nausea, anorexia, GI toxicity, and fatigue.[12,37] Following the approval of the Xd regimen and based on the then-available prescribing information, cumulative experience of a panel of experts from the International Myeloma Working Group and the IMF NLB, and guidance from the manufacturer of selinexor, consensus recommendations were published for clinical management of patients with MM receiving selinexor therapy.[12]

Key principles of supportive care for patients on selinexor therapy include[12,37]:

- **Prevention of nausea with 2 prophylactics antiemetics –** supplementing with a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist (eg, ondansetron 2–3 times daily) with daily olanzapine and/or neurokinin-1 receptor antagonists
- **Strategies for maintaining hydration**—ensuring adequate water intake as well as salt-containing drinks to minimize hyponatremia risk and consideration of intravenous fluid administration
- **Nutrition support**—providing additional food snacks and/or higher-calorie supplements, as needed; nutrition

consult; and consideration of appetite stimulants (megestrol acetate)
- **Cytopenias management**—monitoring complete blood counts with differential weekly or twice weekly (if starting platelet count = 50,000/µL); providing platelet transfusion support or holding selinexor if platelet count <25,000/µL; considering additional platelet-stimulating agents such as romiplostim; granulocyte colony-stimulating factors for patients with neutropenia, as indicated
- **Hyponatremia management**—monitoring hydration status and serum sodium levels; employing salt tablets or salty snacks, as needed

Complete blood counts, standard blood chemistries, body weight, nutritional status, and volume status should be monitored at baseline and during treatment, as indicated, with more frequent monitoring during the first 3 months of selinexor therapy.[30] Supportive care measures, including maintenance of adequate fluid and caloric intake throughout treatment, consideration of intravenous fluids, prophylactic anti-emetics, administration of 5-HT3 receptor antagonists and other antinausea agents before and during treatment with selinexor, are also highlighted in the updated prescribing information for selinexor.[30]

Evolution of Supportive Care With New Approvals and Further Clinical Experience

Overall, the NLB noted that the supportive care measures recommended by the expert panel continue to be critical and relevant in the current clinical context of selinexor therapy, with a shift in practice toward the weekly dosing schedule of selinexor and selinexor-containing triplet regimens. They noted that proactive management, especially during the first month or so, is critical to the success of and compliance with selinexor therapy. With the improved tolerability profile of the weekly dosing schedule, the NLB recommended using a vigilant but less aggressive approach than with the twice-weekly schedule in the Xd regimen.

The NLB noted that while community practices may use selinexor only exactly as indicated in the prescribing information or clinical trials, by holding the drug for patients with low platelet counts, academic centers may have more experience and resources for providing platelet support and optimizing the duration of selinexor therapy. Obtaining prior authorization for use of TPO inhibitors before initiating selinexor therapy may be a helpful strategy. The NLB also noted that platelet counts of 50,000/µL per se do not preclude the use of selinexor therapy, provided the underlying cause for the thrombocytopenia is apparent and can be addressed using supportive care. A Nurse Leader commented that hyponatremia that is associated with selinexor appears to be asymptomatic, unlike typical acute hyponatremia associated with the risk of loss of consciousness or death.

In their clinical practice, the NLB schedules supportive care appointments at a higher frequency (initially weekly) during the first few weeks of treatment and adjusts the frequency of these follow-ups and the

intensity of interventions once the patient is acclimated to selinexor therapy.

Key Resources and Documents to Share With the Care Team and Community Practitioners

The NLB identified key resources and documents to share with care teams and community providers to facilitate management of patients receiving selinexor therapy (summarized in **Table 1**).

Patient Engagement and Communication Strategies

Key Components of Discussions of Selinexor Therapies With Patients

Just as with providers, upfront discussions with patients should also include the novel MOA, oral route of administration, toxicity profile, efficacy, dosing, and supportive care measures. It is recommended to include these components as part of the first conversation with patients when selinexor is presented as an option. Discussions with patients need to be individualized in terms of dosing, their compliance with oral medications, capacity to manage their medications outside of the clinic, and their ability to report toxicity concerns. Assessing the patient's understanding of and interest in their therapeutic options and their specific needs can also help adapt patient discussions. As with providers, patients and caregivers should also be informed about patient support programs.

Differentiating Discussions With Patients and Providers

Patient-focused discussions may need to be streamlined compared with provider-focused discussions, while addressing some of the same major aspects of selinexor therapy. For instance, using key words such as "tumor suppressors" can help convey the basic cellular MOA of selinexor to patients. To set expectations with patients on dosing, patients should be educated on how dosing can be tailored to the patient's needs/profile (eg, frailty), therapeutic goals (therapeutic efficacy vs tolerability/QoL concerns, rate of disease progression, bridging therapy vs treatment), and therapeutic history (LOTs, prior exposures).

Closing Statements

The initial experience with the twice-weekly dosing schedule of selinexor monotherapy for treatment of patients with late relapse may have left an unfavorable impression, acting as a barrier to selinexor's use, especially in community practice settings. When discussing selinexor with the care team and providers/nurses in community practice, it is critical to highlight the current once-weekly dosing schedule. The care team and clinicians should also be educated on the availability of and evolving data for selinexor combination regimens with improved tolerability and clinical benefit. The potential convenience and advantages of all-oral combinations may be of particular interest to community providers. Additional aspects to discuss with the care

team and providers include some of the unique/uncommon aspects of selinexor therapy in MM: the novel first-in-class MOA; the toxicity profile, including GI-focused adverse reactions; and proactive approaches for preventing, mitigating, and managing toxicities. Similarly, discussions with patients should include key aspects of selinexor's MOA, dosing considerations, efficacy, and toxicity profile. Improving awareness of patients, caregivers, and providers for patient support resources can be valuable, especially in regions/practice settings where access to nurse navigators/care coordinators may be limited. Moreover, potential process improvements that help streamline when and how information on patient support programs and enrollment options are shared with patients, such as at the time of selinexor prescription, may further facilitate patient support and management.

Selinexor has a unique MOA and in combination therapies, offers a way to complement other agents currently available for treatment of MM, thereby providing additional options for patients with myeloma and their families.

Acknowledgments: The IMF would like to thank the roundtable attendees, authors, and Eubio, LLC for providing medical writing support for this meeting, which was sponsored by Karyopharm.

Attendees

Beth Faiman, PhD, RN, MSN, APRN-BC, AOCN (Co-Chair; Cleveland Clinic Taussig Cancer Institute)
Kevin Brigle, PhD, NP (Co-Chair; Virginia Commonwealth University Massey Cancer Center)
Donna Catamero (Mount Sinai Health System)
Patricia Mangan, RN, MSN, APRN-BC (Abramson Cancer Center, University of Pennsylvania)
Kimberly Noonan, MS, RN, ANP, AOCN (Dana-Farber Cancer Institute)
Tiffany Richards, PhD, ANP-BC (MD Anderson Cancer Center)
Mary Steinbach, DNP, APRN (Huntsman Cancer Hospital Institute)
Daniel Verina, DNP, RN, ACNP-BC (Mount Sinai Medical Center)

References

1. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: Myeloma. 2021. Accessed January 11, 2022. https://seer.cancer.gov/statfacts/html/mulmy.html

2. Rodriguez-Otero P, Paiva B, San-Miguel JF. Roadmap to cure multiple myeloma. *Cancer Treat Rev*. 2021;100:102284. doi:10.1016/j.ctrv.2021.102284

3. American Cancer Society. What is multiple myeloma? February 28, 2018. Accessed January 11, 2022. https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html

4. Kumar SK, Callander NS, Adekola K, et al. National Comprehensive Cancer Network clinical practice guidelines in oncology (NCCN guidelines). Multiple myeloma. Version 4.2022. Published online December 14, 2021. Accessed March 4, 2022. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

5. Gulla A, Anderson KC. Multiple myeloma: the (r)evolution of current therapy and a glance into future. *Haematologica*. 2020;105(10):2358-2367. doi:10.3324/haematol.2020.247015

6. Mikhael J. Treatment options for triple-class refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2020;20(1):1-7. doi:10.1016/j.clml.2019.09.621

7. Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia*. 2017;31(9):1915-1921. doi:10.1038/leu.2016.380

8. Braunlin M, Belani R, Buchanan J, Wheeling T, Kim C. Trends in the multiple myeloma treatment landscape and survival: a U.S. analysis using 2011-2019 oncology clinic electronic health record data. *Leuk Lymphoma*. Published online October 7, 2020. doi:10.1080/10428194.2020.1827253

9. Caers J. The road to a cure: emerging treatments for multiple myeloma. *Cancers (Basel)*. 2020;12(12):3593. doi:10.3390/cancers12123593

10. Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia*. 2018;32(2):252-262. doi:10.1038/leu.2017.329

11. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275. doi:10.1038/s41375-019-0435-7

12. Mikhael J, Noonan KR, Faiman B, et al. Consensus recommendations for the clinical management of patients with multiple myeloma treated with selinexor. *Clin Lymphoma Myeloma Leuk*. 2020;20(6):351-357. doi:10.1016/j.clml.2019.12.026

13. Nathwani N, Bertamini L, Banerjee R, Gay F, Shah N, Krishnan A. When and how to treat relapsed multiple myeloma. *Am Soc Clin Oncol Educ Book*. 2021;41:358-375. doi:10.1200/EDBK_320129

14. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med*. 2019;381(8):727-738. doi:10.1056/NEJMoa1903455

15. Sun Q, Carrasco YP, Hu Y, et al. Nuclear export inhibition through covalent conjugation and hydrolysis of leptomycin B by CRM1. *Proc Natl Acad Sci U S A.* 2013;110(4):1303-1308. doi:10.1073/pnas.1217203110

16. Azizian NG, Li Y. XPO1-dependent nuclear export as a target for cancer therapy. *J Hematol Oncol*. 2020;13(1):61. doi:10.1186/s13045-020-00903-4

17. Gravina GL, Senapedis W, McCauley D, Baloglu E, Shacham S, Festuccia C. Nucleo-cytoplasmic transport as a therapeutic target of cancer. *J Hematol Oncol*. 2014;7:85. doi:10.1186/s13045-014-0085-1

18. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia*. 2014;28(1):155-165. doi:10.1038/leu.2013.115

19. Schmidt J, Braggio E, Kortuem KM, 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(12):2357-2365. doi:10.1038/leu.2013.172

20. Mo CC, Jagannath S, Chari A, et al. Selinexor for the treatment of patients with previously treated multiple myeloma. *Expert Rev Hematol*. 2021;14(8):697-706. doi:10.1080/17474086.2021.1923473

21. Chen CI, Gutierrez M, Siegel DS, et al. Selinexor demonstrates marked synergy with dexamethasone (Sel-Dex) in preclinical models and in patients with heavily pretreated refractory multiple myeloma (MM). *Blood*. 2014;124(21):4773.

22. Shain KH, Renatino-Canevarolo R, Meads MB, et al. Characterization of synergistic selinexor combinations of dexamethasone, pomalidomide, elotuzumab and daratumumab in primary MM samples ex vivo. *Blood*. 2020;136(suppl 1):29-30. doi:10.1182/blood-2020-140485

23. Sudalagunta PR, Meads MB, Canevarolo RR, et al. Abstract 1061: characterization of synergistic selinexor combinations with dexamethasone, pomalidomide, elotuzumab, and daratumumab in primary MM cells. *Cancer Res*. 2021;81(13 suppl):1061. doi:10.1158/1538-7445.AM2021-1061

24. Kashyap T, Argueta C, Aboukameel A, et al. Selinexor, a selective inhibitor of nuclear export (SINE) compound, acts through NF-κB deactivation and combines with proteasome inhibitors to synergistically induce tumor cell death. *Oncotarget*. 2016;7(48):78883-78895. doi:10.18632/oncotarget.12428

25. FDA approves selinexor for refractory or relapsed multiple myeloma. Press release. US Food and Drug Administration. Published online June 11, 2021. Accessed November 23, 2021.

26. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet*. 2020;396(10262):1563-1573. doi:10.1016/S0140-6736(20)32292-3

27. Bahlis NJ, Sutherland H, White D, et al. Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. *Blood*. 2018;132(24):2546-2554. doi:10.1182/blood-2018-06-858852

28. Gasparetto C, Lipe B, Tuchman S, et al. Selinexor containing regimens in patients with multiple myeloma (MM) previously treated with anti-CD38 monoclonal antibodies (αCD38 mAbs). *J Clin Oncol*. 2021;39(15 suppl):e20020. doi:10.1200/JCO.2021.39.15_suppl.e20020

29. White D, Chen C, Baljevic M, et al. Oral selinexor, pomalidomide, and dexamethasone (XPd) at recommended phase 2 dose in relapsed refractory multiple myeloma (MM). *J Clin Oncol*. 2021;39(15 suppl):8018. doi:10.1200/JCO.2021.39.15_suppl.8018

30. XPOVIO (selinexor) tablets. Package insert. Karyopharm Therapeutics Inc.; 2021.

31. Selinexor and backbone treatments of multiple myeloma patients (STOMP). ClinicalTrials.gov identifier: NCT02343042. Updated December 2, 2021. Accessed March 11, 2022. https://clinicaltrials.gov/ct2/show/NCT02343042

32. Gasparetto C, Lipe B, Tuchman S, et al. Once weekly selinexor, carfilzomib, and dexamethasone (SKd) in patients with relapsed/refractory multiple myeloma (MM). *J Clin Oncol*. 2020;38(15 suppl):8530. doi:10.1200/JCO.2020.38.15_suppl.8530

33. Gasparetto C, Schiller GJ, Tuchman SA, et al. Once weekly selinexor, carfilzomib and dexamethasone in carfilzomib non-refractory multiple myeloma patients. *Br J Cancer*. Published online November 20, 2021. doi:10.1038/s41416-021-01608-2

34. White D, Chen CI, Baljevic M, et al. Once weekly oral selinexor, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma. Presented at: American Society of Hematology Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Accessed March 13, 2021. https://ash.confex.com/ash/2021/webprogram/Paper148759.html

35. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. *J Hematol Oncol*. 2020;13(1):125. doi:10.1186/s13045-020-00962-7

36. Karyopharm Therapeutics, Inc. KaryForward Patient Support by Karyopharm. May 2021. Accessed January 11, 2022. https://www.karyforward.com/

37. Gavriatopoulou M, Chari A, Chen C, et al. Integrated safety profile of selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. *Leukemia*. 2020;34(9):2430-2440. doi:10.1038/s41375-020-0756-6

Figure 1. Selinexor Mechanism of Action.

The import and export of proteins and other macromolecules from the nucleus to the cytoplasm and vice versa is a highly regulated process involving nuclear import and export protein receptors.[16] XPO-1 is the major nuclear export protein and exports a plethora of cargo molecules, including TSPs, transcription factors, cell cycle regulators, and eIF4E-bound oncogenic mRNAs.[16,17] XPO-1 is overexpressed in MM.[14] Selinexor-mediated inhibition of XPO-1 restores nuclear localization and function of TSPs, nuclear retention of IκB, which inhibits hyperactive NF-κB in myeloma cells.[14] Selinexor-mediated trapping of eIF4E-bound oncogenic mRNAs in the nucleus results in decreased expression of oncoproteins, including c-myc, BCL2, cyclin D, MDM2, and survivin, which are often overexpressed in MM.[14,16,17] Overall, inhibition of XPO-1 by selinexor restores TSPs and other cargo, thereby activating their normal function and promoting cell cycle arrest and apoptosis in malignant myeloma cells.[14]

BRCA1, BReast CAncer gene 1; eIF4e, eukaryotic initiation factor 4E; IκB, inhibitor of NF-κB; MM, multiple myeloma; mRNA, messenger RNA; NF-κB, nuclear factor kappa B; Par-4, protease-activated receptor 4; PP2A, protein phosphatase-2A; pRB, phosphorylated retinoblastoma protein; SINE, selective inhibitor of nuclear export; TSP, tumor suppressor protein; XPO-1, exportin 1.

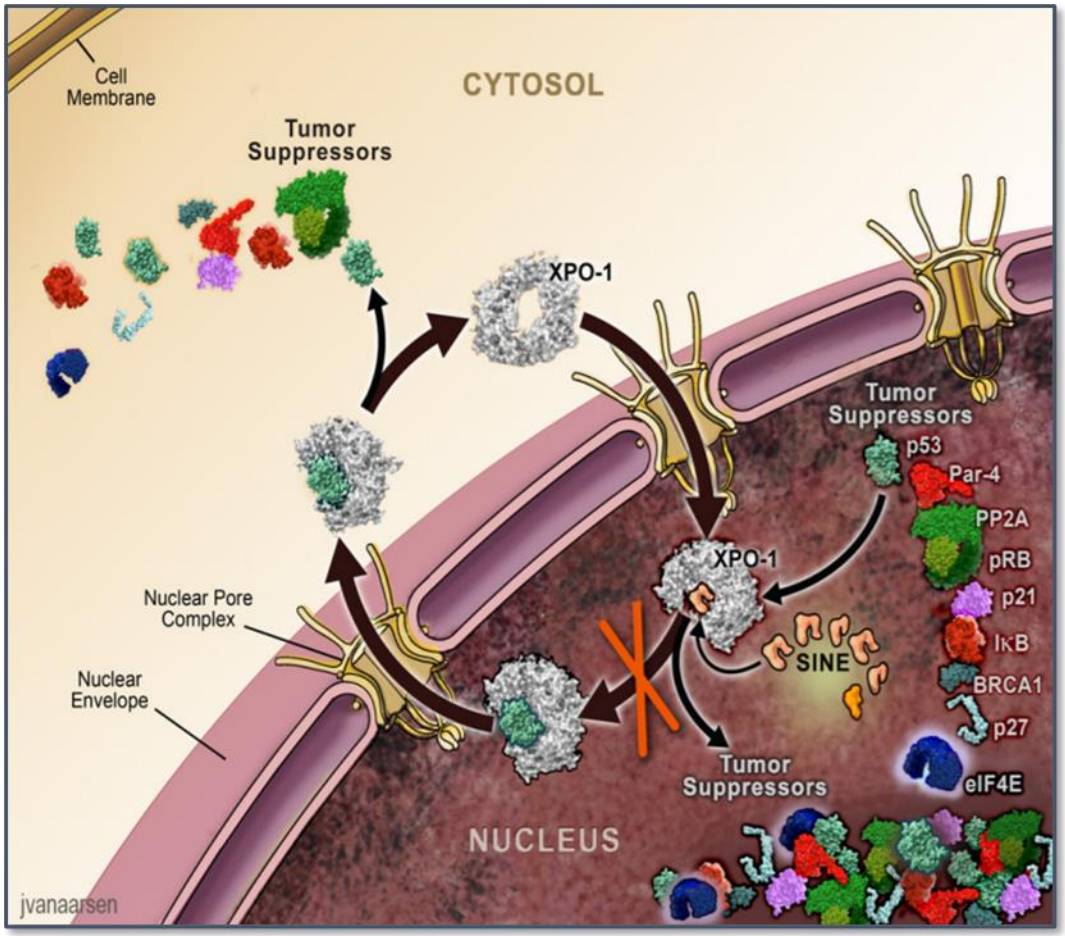
Cell Membrane
CYTOSOL
Tumor Suppressors
XPO-1
Tumor Suppressors
p53
Par-4
PP2A
pRB
p21
IκB
BRCA1
p27
eIF4E
XPO-1
SINE
Nuclear Pore Complex
Nuclear Envelope
Tumor Suppressors
NUCLEUS
jvanaarsen

Table 1. Proposed Tools and Resources to Facilitate Optimization of Selinexor Treatment Duration and Clinical Benefit

Tools and Resources for Patients and Caregivers
All patient-focused discussions and communications need to be individualized in terms of dosing, compliance with oral medications, capacity of patient to manage their medications outside of the clinic, and reporting toxicity concerns
Upfront discussions with patients should include: • Description of the unique MOA of selinexor and the implications for clinical efficacy and toxicity profile in MM • Use of key words such as "tumor suppressors" to convey the novel MOA to patients • Oral route of administration and the availability of all-oral combination regimens • Toxicity profile (including potential GI AEs) and proactive strategies for managing AEs • Requirement for potential prophylactic medications to prevent/mitigate/manage toxicities • Expectations of potential dosing changes based on tolerability
Information on the patient support programs that can help address patient-specific concerns or issues such as insurance coverage, financial assistance, discussion of medications and/or adverse effects, and care coordination
Suggested Tools and Resources for Providers
Upfront discussions with providers in community practice should include: • The unique MOA of selinexor and the implications for clinical efficacy and toxicity profile in MM • The history of selinexor and the evolution of the dosing schedule to lower doses in combination regimens at once-weekly instead of twice-weekly dosing and its impact on improving tolerability • Oral route of administration and advantages and diasdvantages of oral agents • Toxicity profile and proactive strategies for managing potential AEs
These resources should be shared with community providers: • **The consensus recommendations for managing patients with MM treated with selinexor were published in 2020[12]** • **The "Tip Sheet" accompanying the publication that includes recommendations for prophylactic medications such as 5-hydroxytryptamine 3 receptor antagonists for managing nausea and TPO receptor agonists for managing thrombocytopenia**
Calendar tools to plan not only for medications but also follow-up assessments and fluid intake appointments to facilitate proactive individualized patient management
Additional specialists to coordinate various apsects of care prior to, during, and after seleinxor therapy: • Nutritionists for managing the impact of GI AEs and weight loss

• Pharmacists to implement medication calendars and facilitate medication management
Information on the KaryForward patient support program for assisting patients receiving selinexor on a range of issues, including insurance coverage, financial assistance, and care coordination resources and personnel

AE, adverse event; GI, gastrointestinal; MM, multiple myeloma; MOA, mechanism of action; TPO, thrombopoietin.