Selinexor Supportive Care in Diffuse Large B-Cell Lymphoma

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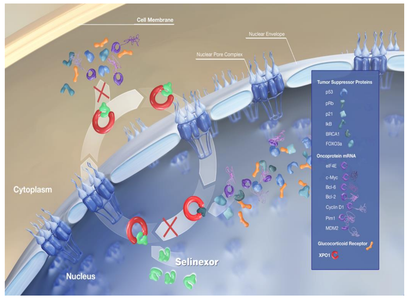
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)



Exportin 1 (XPO1) is a critical nuclear export protein for:
- Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO)[1-3]
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)[1,2,4]

XPO1 Overexpression Causes:
- Tumor suppressor proteins (e.g., p53, IkB and FOXO) and glucocorticoid receptor inactivation and enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation

Selinexor (X) is an oral selective XPO1 inhibitor that reactivates multiple TSPs and inhibits oncoprotein translation

Selinexor is now FDA approved for the following indications:
- In combination with bortezomib and dexamethasone (XVd) for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy (BOSTON Trial)[5]
- Monotherapy for the treatment of patients diffuse large B-cell lymphoma (DLBCL) who have received 2 prior lines of systemic therapy (SADAL Trial)[6]
- In combination with dexamethasone for the treatment of relapsed / refractory MM (Xd) (STORM Trial)[7]

[1]Tai et al., Leukemia, 2014, [2]Fung HY, Chook YM. Semin Cancer Biol. 2014, [3]Parikh et al., J Hematol Oncol. 2014, [4]Gravina GL, et al., BMC Cancer. 2015 [5]Grosicki S, et al. Lancet. 2020, [6]Kalakonda N, et al. Lancet Haematol. 2020, [7]Chari A, et al., New England Journal of Medicine 2019

Methods

We analyzed Karyopharm data on file for supportive care management from the SADAL trial, and we were able to combine recommendations to create evidence-based supportive care guidelines for DLBCL patients. The most common AEs will be reviewed and include thrombocytopenia, nausea, vomiting, weight loss, anorexia, and fatigue.

The SADAL Trial Design: Single Agent, Selinexor in Patients with DLBCL

Relapsed or refractory, de novo or transformed* DLBCL:

- **2-5 prior therapies, not currently eligible for hematopoietic stem cell transplantation**
- **≥PR on last prior therapy, 60 days from end of last therapy; otherwise ≥14 weeks from end of most recent systemic therapy**

N=134

Oral Selinexor 60† mg
Selinexor twice weekly (4-week cycle)

100 mg Selinexor BIW Arm was closed

Until PD or Intolerability

- **Primary Endpoint:** ORR **Secondary Endpoints:** DOR, DCR, safety[6]
- **Exploratory Endpoints:** PFS, OS, comparisons of PFS, ORR, DOR, DCR, QoL and OS in patients with GCB vs non-GCB DLBCL, further describe PK properties, PDn studies in peripheral blood and/or tumor biopsies[6]

*Transformed only from indolent NHL. †100 mg dose discontinued due to similar response. **S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma

Conclusions

- **The management of selinexor AEs is thoroughly detailed and involves close monitoring, prophylactic anti-emetics, dose interruptions and/or reductions, and other supportive care therapeutic interventions.**
- **Side effects associated with selinexor are generally manageable and/or reversible with appropriate supportive care and/or dose modifications.**

Starting a Patient on Selinexor Guidelines

- **Side effects related to selinexor are largely: dosage and schedule dependent and may be mitigated with prophylactic anti-emetics and standard monitoring with dose adjustments as needed**
- **Prophylactic prevention of nausea is more successful in controlling this adverse event and preventing escalation to more severe grades than starting antiemetics after symptoms begin**

Double Anti-Nausea Coverage

- **Ondansetron** 8mg PO – 30-60 mins prior to each dose and maintained for 36-48 hours after the dose **and**
  - **Olanzapine** 2.5 mg - 5.0 mg PO QHS **or**
  - **Rolapitant** 180 mg PO 2 hours before selinexor once every 2 weeks **or**
  - **Aprepitant** 125 mg PO QAM day 1 and 80 mg for 2 days each week*
- Alternatively, once weekly oral dose of **Akynzeo®** (netupitant 300 mg + palonosetron 0.5 mg)
- One or both anti-emetics may be tapered after 6-8 weeks **and** Maintain hydration and caloric intake

*If using aprepritant, the dose of dexamethasone may need to be reduced. PO, taken by mouth; QAM, every morning; QHS, at bedtime.

Standard Weekly Monitoring (First 6-8 Weeks)

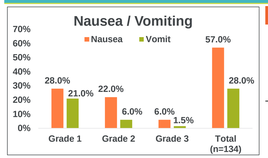
- Serum chemistry labs (Chem-7; sodium, BUN, creatinine), complete blood counts, and body weight
- Frequency may be reduced after 6-8 weeks

SADAL – Selinexor Dose Modifications

60 mg (BIW) Starting Dose → **40 mg (BIW)** First Reduction → **60 mg (QW)** Second Reduction → **40 mg (QW)** Third Reduction → **20 mg (QW)** Fourth Reduction

BIW-Twice weekly
QW-Once weekly

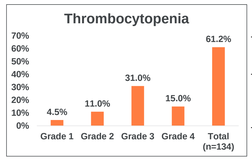
SADAL Treatment Emergent Adverse Events – Nausea / Vomiting



	Action
Grade 1 or 2	• **Maintain** selinexor dose • **Implement** additional anti-nausea medications to supplement the required 5HT3 agonists using institutional guidelines and NCCN • **Add** olanzapine daily for 1-2 months
Grade 3	• **Add** NK1R antagonist and continue as outlined above • **Interrupt** dosing with selinexor improved to ≤Grade 2 or baseline • **Restart** selinexor at 1 dose level lower

Nausea / Vomiting Guidelines: 5-HT3 antagonist, Olanzapine, NK1 receptor antagonist, Benzodiazepines, Cannabinoid agonists, Selinexor dose modifications
- **Prophylaxis:** Provide at least 2 prophylactic antiemetics prior to starting patient on selinexor
- **74%** of patients experiencing nausea ***with*** supportive care, resolved, median duration of 23 days
- **60%** of patients experiencing nausea ***without*** supportive care, resolved, median duration of 36 days
- **94%** of patients experiencing vomiting ***with*** supportive care, resolved, median duration of 3 days
- **90%** of patients experiencing vomiting ***without*** supportive care, resolved, median duration of 1 day

SADAL Treatment Emergent Adverse Events – Thrombocytopenia



	Action
Platelet count 50,000 – <75,000/mcL (any occurrence)	• **Interrupt** one dose of selinexor; **Restart** selinexor at the same dose level
Platelet count 25,000 – <50,000/mcL **without bleeding** (1st occurrence)	• **Interrupt** selinexor; **Monitor** until platelet count returns to at least 50,000/mcL • **Reduce** selinexor by 1 dose level; **Consider** TPO-RAs eg, romiplostim or eltrombopag
Platelet count 25,000 – <50,000/mcL **with bleeding** (any occurrence)	• **Interrupt** selinexor; **Monitor** until platelet count returns to at least 50,000/mcL • **Restart** selinexor at 1 dose level lower, after bleeding has resolved • **Administer** platelet transfusions per clinical guidelines; **Consider** TPO-RAs eg, romiplostim or eltrombopag
Platelet count <25,000/mcL (any occurrence)	• **Interrupt** selinexor; **Monitor** until platelet count returns to at least 50,000/mcL • **Restart** selinexor at 1 dose level lower; **Administer** platelet transfusions per clinical guidelines • **Consider** TPO-RAs eg, romiplostim or eltrombopag

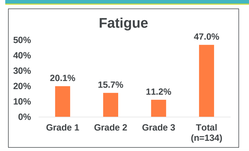
Thrombocytopenia Guidelines: Platelet transfusions / platelet growth factors, Selinexor dose modifications
- **Prophylaxis:** Monitor CBC differential at baseline and during treatment with selinexor
- **81%** of patient cases ***with*** supportive care, resolved, median duration of 16 days
- **43%** of patient cases ***without*** supportive care, resolved, median duration of 20 days

SADAL Treatment Emergent Adverse Events – Weight Loss / Anorexia

	Action
Grade 1 or 2	• **Maintain** selinexor dose • **Rule out** other causes • **Consider** a repeat nutritional consultation and nutritional supplements (eg, Ensure, Boost, etc.) • Institute supportive care medications per institutional guidelines and NCCN
Grade ≥ 2 Weight Loss or Grade ≥ 3 Anorexia	• **Consider** a repeat nutritional consultation and nutritional supplements (eg, Ensure, Boost, etc.) • **Institute** supportive care medications per institutional guidelines and NCCN • **Interrupt** dosing with selinexor improved to Grade 1 or baseline and weight stabilizes • **Reduce** selinexor by 1 dose level when resuming treatment

Weight Loss / Anorexia Guidelines: Olanzapine, Appetite stimulants, Dronabinol, Selinexor dose modifications
- **Prophylaxis:** Nutritional counseling prior at the start of selinexor treatment, track body weight and nutritional status at baseline and during treatment
- **50%** of patients experiencing anorexia ***with*** supportive care, resolved, median duration of 12 days
- **53%** of patients experiencing anorexia ***without*** supportive care, resolved, median duration of 29 days

SADAL Treatment Emergent Adverse Events – Fatigue



	Action
Grade 1	• **Maintain** selinexor dose • **Institute** supportive care per institutional guidelines and NCCN
Grade 2: Lasting > 7 days or Grade 3	• **Institute** supportive care per institutional guidelines and NCCN • **Interrupt** selinexor dose until resolved to Grade 1 or baseline • **Reduce** selinexor dose by 1 dose level

Fatigue Guidelines: Methylphenidate, Dexamethasone, Selinexor dose modifications
- **Prophylaxis**: Check for underlying causes of preexisting or predisposition to developing fatigue (eg, depression, dehydration, anemia, etc.) If anemic, consider transfusing for hemoglobin < 8 g/dL
- **82%** of patient cases ***with*** dose modification, resolved, median duration of 16 days
- **37%** of patient cases ***without*** dose modification, resolved, median duration of 25 days