Selinexor Supportive Care in Multiple Myeloma

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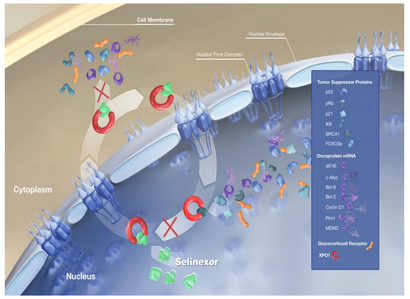
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)



[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

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]

Methods

- **We analyzed Karyopharm data on file for supportive care management from the BOSTON and STORM trials. The most common AEs will be reviewed and include thrombocytopenia, nausea, vomiting, weight loss, anorexia, and fatigue.**

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.**

The BOSTON Trial Design: XVd *vs.* Vd in Patients with MM

1:1 Randomization N=402

XVd N=195 *35-day cycles*
- **SEL:** 100 mg PO on days 1, 8, 15, 22, 29
- **BOR:** 1.3 mg/m^2 SC on days 1, 8, 15, 22
- **DEX:** 20 mg PO on days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30
- 5HT-3 prophylactic recommended

Vd N=207 *21-day cycles*
- **BOR:** 1.3 mg/m^2 SC on days 1, 4, 8, 11
- **DEX:** 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12
- Pts with prior Vd allowed on trial
- Patients with IRC confirmed PD on Vd could crossover to XVd

XVd

Primary Endpoint: PFS

Secondary Endpoints
- ORR
- ≥VGPR
- Grade ≥2 PN
- OS
- DoR
- TTNT
- Safety

The XVd regimen requires approximately **40% less bortezomib** than Vd which is **37% fewer clinic visits** over the first 6 months of treatment[5]

The STORM Trial Design: Xd in Patients with Relapsed/Refractory MM

MM documented refractory to ≥1 PI, ≥1 IMiD, Daratumumab, a glucocorticoid and last therapy (N=122)

Selinexor (80 mg) + dexamethasone (20 mg) Twice Weekly (Day 1 and 3)

Until PD or intolerability

Primary Endpoint: ORR **Secondary Endpoints: DOR, CBR, OS, PFS, Safety**

The Xd regimen safety data not shown, however data from the trial was used in determining supportive care regimens for MM patients [7]

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)

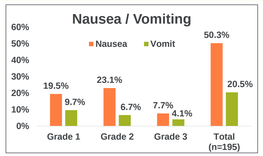
- Serum chemistry labs (Chem-7; sodium, BUN, creatinine), complete blood counts, and body weight
- Frequency may be reduced after 6-8 weeks

XVd – Selinexor Dose Modifications

100 mg (QW) Starting Dose → **80 mg (QW)** First Reduction → **60 mg (QW)** Second Reduction → **40 mg (QW)** Third Reduction

QW-Once weekly

XVd Treatment Emergent Adverse Events – Nausea / Vomiting

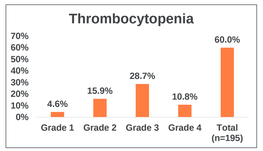


	Action
Grade 1 or 2*	• **Maintain** selinexor dose • **Implement** additional anti-nausea medications to supplement the required 5HT3 agonists using institutional guidelines and NCCN • **Add** olanzapine daily for 1-2 months
Grade 3	• **Add** NK1R antagonist and continue as outlined above • **Interrupt** 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
- **89%** of patients experiencing nausea ***with*** supportive care, resolved, median duration of 7 days
- **89%** of patients experiencing nausea ***without*** supportive care, resolved, median duration of 21 days
- **100%** of patients experiencing vomiting ***with*** supportive care, resolved, median duration of 2 days
- **100%** of patients experiencing vomiting ***without*** supportive care, resolved, median duration of 1 day

XVd Treatment Emergent Adverse Events – Thrombocytopenia



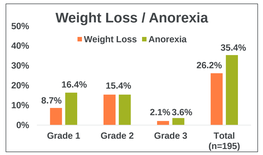
	Action
Grade 1 or 2 (Platelet count 50,000 - <75,000/mcL)	• **Maintain** selinexor dose • **Rule out** other causes
Grade 3 without bleeding (Platelet count 25,000 - 50,000/mcL)	• **Reduce** selinexor by 1 dose level • **Consider** modification of concomitant anti-platelet agent therapy • **Consider** TPO-RAs eg, romiplostim or eltrombopag
Grade 3 with concurrent bleeding (Platelet count 25,000 – 50,000/mcL) **or** **Grade 4 without bleeding** (Platelet count <25,000/mcL)	• **Transfuse** per clinical practice/institutional guidelines • **Delay** selinexor until platelets recover to Grade 2 • **Consider** modification of concomitant anti-platelet agent therapy • **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
- **90%** of patients* ***with*** a dose reduction in selinexor, resolved, median duration of 15 days
- **95%** of patients* ***with*** a dose interruption in selinexor, resolved, median duration of 13 days
- **83%** of patients* ***without*** a dose modification in selinexor resolved, median duration of 15 days

*Patients may or may not have had supportive care of platelet transfusions and/or platelet growth factors

XVd Treatment Emergent Adverse Events – Weight Loss / Anorexia

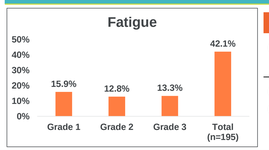


	Action
Grade 1 or 2	• **Maintain** selinexor dose • **Rule out** other causes • **Consider** a repeat nutritional consultation and nutritional supplements (eg, Ensure, Boost, etc.) • Institute supportive care medications per institutional guidelines and NCCN
Grade ≥ 2 Weight loss **or** **Grade ≥ 3 Anorexia**	• **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
- **85%** of patients experiencing anorexia ***with*** supportive care, resolved, median duration of 30 days
- **84%** of patients experiencing anorexia ***without*** supportive care, resolved, median duration of 20 days

XVd 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, 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
- **84%** of patient cases ***with*** supportive care, resolved, median duration of 8 days
- **62%** of patient cases ***without*** supportive care, resolved, median duration of 29 days