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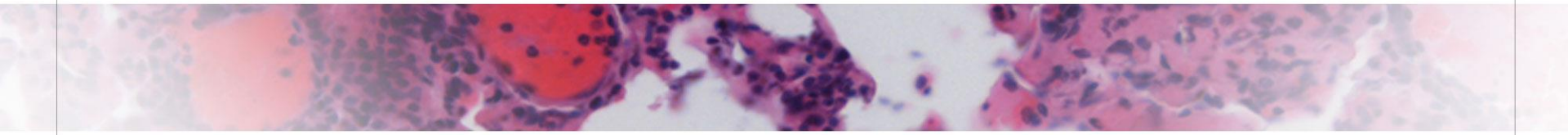

Selinexor, Lenalidomide and Dexamethasone (SRd) for Patients with Relapsed/Refractory and Newly Diagnosed Multiple Myeloma

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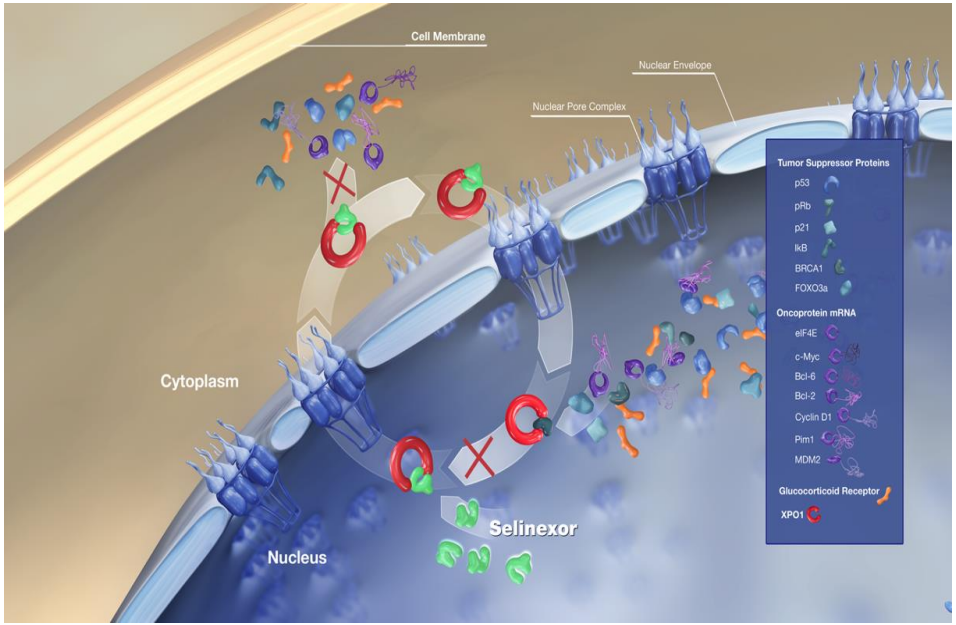
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export and Reactivates Tumor Suppressor Proteins



Exportin 1 (XPO1) is a critical nuclear exporter for tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO3a) [1-3] and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, MDM2, cyclin D1) [1,2,4]

XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis[1,2,5]
- **XPO1 levels correlate with poor prognosis** and drug resistance [1,2]

Selinexor is an oral selective **XPO1 inhibitor**; preclinical data demonstrates that selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-kB and c-Myc activity, and reactivates GR signaling in presence of dexamethasone[1,2,6,7]

[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]Schmidt et al., Leukemia, 2013, [6]Parikh et al., J Hematol Oncol. 2014, [7]Argueta et al., Oncotarget, 2018

Background / Rationale: Selinexor and Lenalidomide Activity in RRMM

- In the **STORM trial selinexor + dexamethasone** were given to patients with MM refractory to at least one proteasome inhibitor, one immunomodulatory agents, and daratumumab (triple-class refractory) resulting in **25.3% ORR and 3.7 months of PFS**[1]
- Per STORM trial results, selinexor (+ dexamethasone) received accelerated approval from the FDA for patients with RRMM[2]
- The **selinexor, bortezomib and dexamethasone (SVd) all QW regimen** showed **superior PFS (13.93 months vs. 9.46 months) and ORR (76.4% vs. 62.3%) with reduced peripheral neuropathy** compared with standard BIW bortezomib + dexamethasone[3]
- Selinexor demonstrated synergistic activity in combination with lenalidomide *in vivo*[4]
- In the MM-009 trial lenalidomide + dexamethasone were given to lenalidomide-naïve patients with ≥ 1 prior MM therapy, resulting in 61% ORR and 11.1 months of PFS[5]

PFS=progression-free survival, IMiD=immunomodulatory agent, MM=multiple myeloma, ORR=overall response rate, PI=proteasome inhibitor, QD=once daily, QW=once weekly, RRMM=relapsed/refractory multiple myeloma

[1]Chari et al., NEJM 2019, 381:8; [2]XPOVIOTM (selinexor). Prescribing information. Reference ID:4457635—US FDA; [3]Grosicki, et al. Lancet 2020 [4]Carlson et al., ESH 2014; [5]Weber et al., New England Journal of Medicine, 2007.

STOMP Study with Selinexor + Lenalidomide + Dexamethasone (SRd) Selinexor and Backbone Treatments Of Multiple Myeloma

Object:

- Primary endpoint: maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and overall response rate (ORR)
- Secondary endpoint: Safety per CTCAE and progression free survival (PFS)

Key Inclusion/Exclusion criteria:

- Age ≥ 18 y.o.
- WBC ≥ 1,500/mm^3 Hb ≥ 8.0 g/dL, platelet count ≥ 75,000/mm^3
- RRMM patients who received ≥ 1 prior therapeutic regimen, prior lenalidomide is allowed however, patients with MM refractory to lenalidomide are excluded
- NDMM patients with no prior therapy other than corticosteroids

Patient Characteristics (Enrolled as of October 1, 2020)	NDMM (N = 8)	RRMM (N = 24)
Median Age, Years (range)	74 (51 – 86)	67 (49 – 84)
Males : Females	4 : 4	13 : 11
ECOG Performance Status, 0 : 1 : 2	1 : 6 : 1	5 : 15: 4
Median Years from Diagnosis to SRd Treatment, (range)	0.2 (0.0 – 5.7)	4.5 (0.4 – 22.2)
Median Regimens (range)	0	2 (1–8)
-Bortezomib exposed	0	24 (100.0)
-Carfilzomib exposed	0	4 (16.7)
-Lenalidomide exposed	0	9 (37.5)
-Pomalidomide exposed	0	5 (20.8)
-Daratumumab exposed	0	4 (16.7)
-Stem Cell Transplant	0	12 (50.0)

Treatment-Related Adverse Events ≥15% Patients

	NDMM (N=8)		RRMM (N=24)	
Hematologic	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Thrombocytopenia	5 (62.5)	3 (37.5)	17 (70.8)	15 (62.5)
Neutropenia	6 (75.0)	6 (75.0)	15 (62.5)	15 (62.5)
Anaemia	5 (62.5)	4 (50.0)	7 (29.2)	4 (16.7)
Gastrointestinal				
Nausea	4 (50.0)	0	14 (58.3)	1 (4.2)
Decreased appetite	1 (12.5)	1 (12.5)	12 (50.0)	2 (8.3)
Diarrhoea	5 (62.5)	0	8 (33.3)	0
Vomiting	1 (12.5)	0	7 (29.2)	0
Constipation	2 (25.0)	0	5 (20.8)	0
Dehydration	1 (12.5)	0	4 (16.7)	1 (4.2)
Constitutional				
Fatigue	5 (62.5)	4 (50.0)	13 (54.2)	4 (16.7)
Weight decreased	5 (62.5)	0	10 (41.7)	2 (8.3)
Asthenia	1 (12.5)	0	4 (16.7)	1 (4.2)
Insomnia	3 (37.5)	1 (12.5)	2 (8.3)	0
CNS				
Dizziness	1 (12.5)	0	5 (20.8)	0

RP2D in NDMM and RRMM:

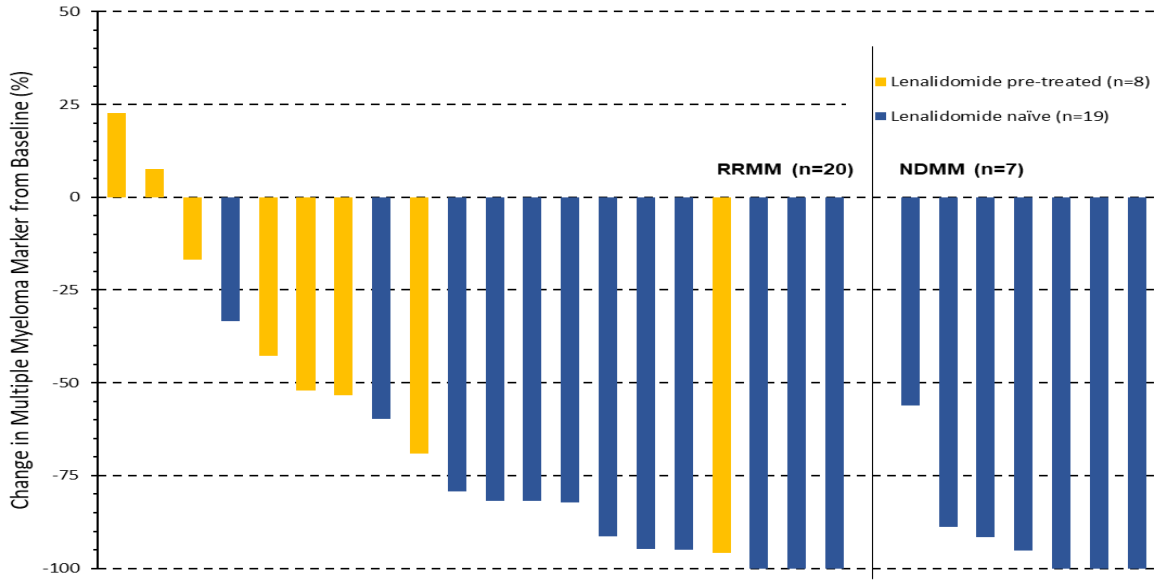
- Selinexor 60 mg on Days 1, 8, 15, 22
- Lenalidomide 25 mg po days 1-21
- Dexamethasone 40 mg on Days 1, 8, 15, 22

2/6 patients had a DLT at Selinexor 80 mg cohort: (G4 PLT, n=2)

(as of October 1, 2020)

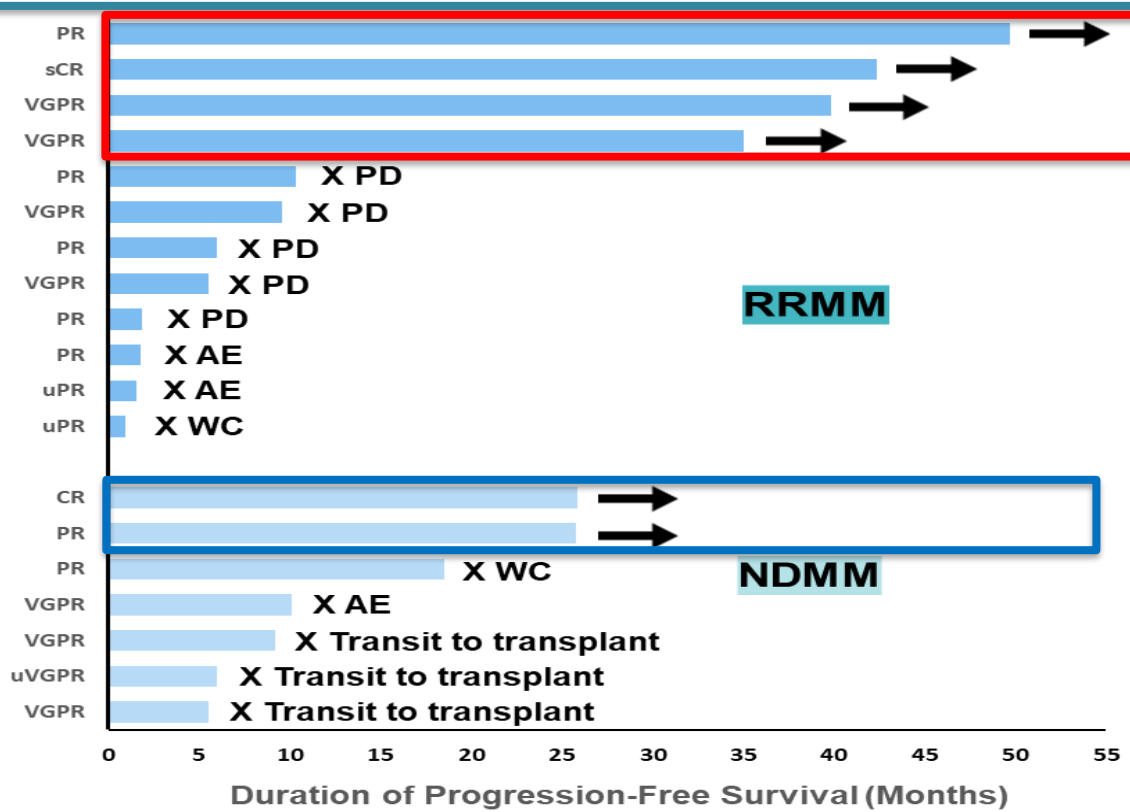
Selinexor – Lenalidomide – dex Efficacy: ORR

Best Responses in Evaluable SRd Patients									
Category	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Len-Naïve Evaluable RRMM Patients	12	11 (91.7)	11 (91.7)	1 (8.3)	4 (33.3)	6 (50.0)†	0	1 (8.3)	0
Len-Exposed/Refractory MM	8	1 (12.5)	3 (37.5)	-	-	1 (12.5)	2 (25.0)	4 (50.0)	1 (12.5)
Efficacy Evaluable NDMM Patients	7*	7 (100)	7 (100)	1 (14.3)	4 (57.1)‡	2 (28.6)	-	-	-



Responses were determined according to the International Myeloma Working Group (IMWG) criteria. †2 PRs were unconfirmed. ‡1 VGPR was unconfirmed. *1 patient was efficacy not evaluable due to withdrawal of consent during cycle 1. ORR=Overall Response Rate (CR+VGPR+PR), CBR=Clinical Benefit Rate (ORR+MR), CR=Complete Response, VGPR=Very Good Partial Response, PR=Partial Response, MR=Minimal Response, SD=Stable Disease, PD=Progressive Disease. Responses as of October 1, 2020 based on interim unaudited data.

Selinexor –Lenalidomide- dex Efficacy: Time on Therapy: Durable Response with Time on Therapy > 2 years



Patients ongoing with RRMM with PFS > 35 months

Patients ongoing with NDMM with PFS > 24 months

arrow = still active as of data cutoff date, X WC = treatment discontinued due to withdrawal of consent, X PD = treatment discontinued due to progressive disease, X AE = treatment discontinued due to adverse event(s)

Summary and Conclusions

- **The RP2D of SRd is once-weekly selinexor 60 mg + Lenalidomide 25 mg daily (days 1-21) + once-weekly dexamethasone 40 mg**
- **The combination is highly active with ORR – 100% in NDMM patients and 92% in Len-naïve RRMM**
- **The responses are durable with patients on > 2-3 years**
- **The most common TRAEs are thrombocytopenia, neutropenia, nausea, and fatigue which are expected and can be managed with supportive care and/or dose modifications**
- **All oral combination of selinexor / lenalidomide / dexamethasone appears to be highly active, well tolerated and warrants further investigation**

Acknowledgements

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