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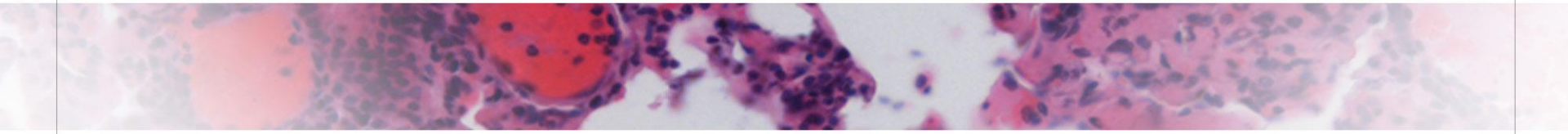

Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM)

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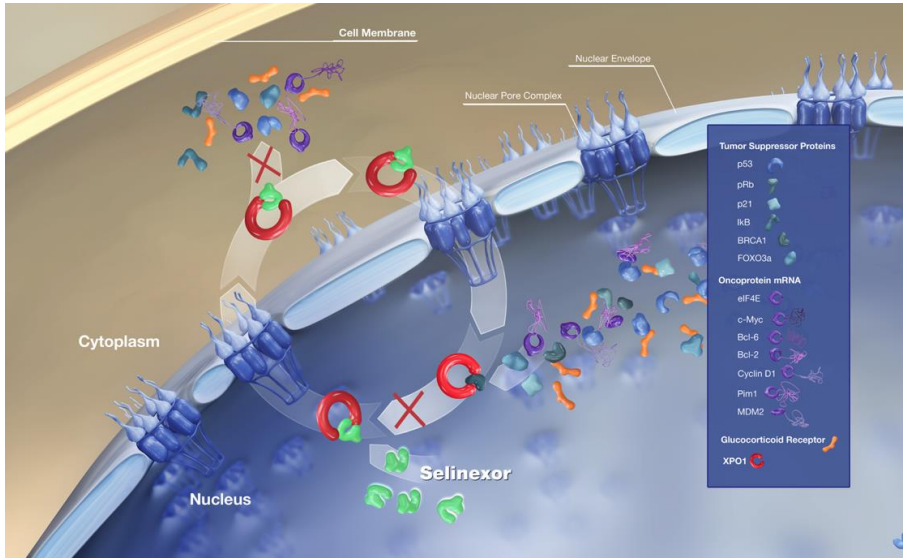
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export Reactivates Tumor Suppressor Proteins and Synergistic with Imids



Exportin 1 (XPO1) is a critical nuclear export protein:

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO3a) [1-3]
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, 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 supports that selinexor:

- Reactivates multiple TSPs by preventing nuclear export[1,2,6]
- Inhibits oncoprotein translation[1,2,6]
- Reactivates GR signaling in presence of dexamethasone[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, [8]Carlson et al., ESH, 2014

Background / Rationale: Selinexor and Pomalidomide in RRMM

- **Selinexor + dexamethasone in** MM refractory to at least one proteasome inhibitor, one immunomodulatory agents, and daratumumab (triple-class refractory) resulting in **26.2% ORR and 3.7 months of PFS**[1]
- MM-0034 trial **pomalidomide + dexamethasone** in patients with ≥ 2 prior MM therapy and refractory to lenalidomide and bortezomib after ≥ 2 consecutive cycles of each (alone or in combination), resulting in **31% ORR and 4 months of PFS**[2]
- Per STORM trial results, selinexor (+ dexamethasone) received accelerated approval from the FDA for patients with RRMM[3]
- Selinexor demonstrates synergistic activity in combination with lenalidomide *in vivo*[4]

[1]Chari et al., NEJM 2019, 381:8; [2]San-Miguel et al. Lancet Oncol 2013,14:1055;[3]XPOVIOTM (selinexor). Prescribing information. Reference ID:4457635—US FDA; [4]Carlson et al., ESH 2014;

PFS=progression-free survival, MM=multiple myeloma, ORR=overall response rate, RRMM=relapsed/refractory multiple myeloma

STOMP: Selinexor + Pd

Selinexor and Backbone Treatments Of Multiple Myeloma Patients

Objectives:

- 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:

- ANC ≥ 1,000/mm3 Hb ≥ 8.0 g/dL, platelet count ≥ 75,000/mm3
- Progressing or refractory to a previous regimen
- Previously undergone ≥2 cycles of lenalidomide and a proteasome inhibitor (in combination or separately)
- Pomalidomide-exposure is allowed only in escalation phase
- Smoldering MM, non-secretory MM, active plasma cell leukemia are excluded

SPd Dose Limiting Toxicities (DLT) and RP2D

Selinexor	Pomalidomide QD	Number of Patients Evaluable for DLT	Number of Patients With DLT	DLT
Once Weekly Selinexor (QW)				
100 mg PO	4 mg PO	3	0	
80 mg PO	4 mg PO	6	2	G3 febrile neutropenia; G4 ANC*
80 mg PO	3 mg PO	6	2	Pom dose reduction for G2 ANC/ G3 PLT; G3 febrile neutropenia
80 mg PO	2 mg PO	6	1	G3 febrile neutropenia
60 mg PO	4 mg PO	6	1	Selinexor dose hold for G3 anemia/ G4 thrombocytopenia

RP2D was Selinexor 60 mg days 1, 8, 15, 22 + Pomalidomide 4 mg days 1-21 q28 days

*Grade 5 related event of pneumonia at 80 mg selinexor QW + 4 mg pomalidomide QD (Cycle 5)

SPd Arm – Patient Characteristics (as of Nov 14, 2020)

	Total (N = 65)	RP2D (N = 20)
Median age, years (range)	64 (37 – 85)	65.5 (37 – 85)
Males (%): Females (%)	33 (51): 32 (49)	7 (35): 13 (65)
Median yrs from diagnosis to SPd treatment, years (range)	4.4 (0.9 – 22.8)	3.4 (1.1 – 9.2)
ISS Stage I (%): II (%): III (%): missing (%)	19 (29.2): 19 (29.2): 7 (10.8): 20 (30.8)	7 (35.0): 3 (15.0): 2 (10.0): 8 (40.0)
Median prior regimens (range)	**3 (1–10)**	**2.5 (1–10)**
Lenalidomide exposed (%): refractory (%)	65 (100.0): 57 (87.7)	20 (100.0): 15 (75.0)
Pomalidomide exposed (%): refractory (%)	19 (29.2): 19 (29.2)	3 (15.0): 1 (5.0)
Bortezomib exposed (%): refractory (%)	60 (92.3): 32 (49.2)	17 (85.0) : 7 (35.0)
Carfilzomib exposed (%): refractory (%)	27 (41.5): 22 (33.8)	11 (55.0): 7 (35.0)
Daratumumab exposed (%): refractory (%)	16 (24.6): 16 (24.6)	5 (25.0) : 4 (20.0)
Stem cell transplant (%)	47 (72.3)	8 (40.0)

Selinexor QW + Pom/Dex Treatment-Related Adverse Events

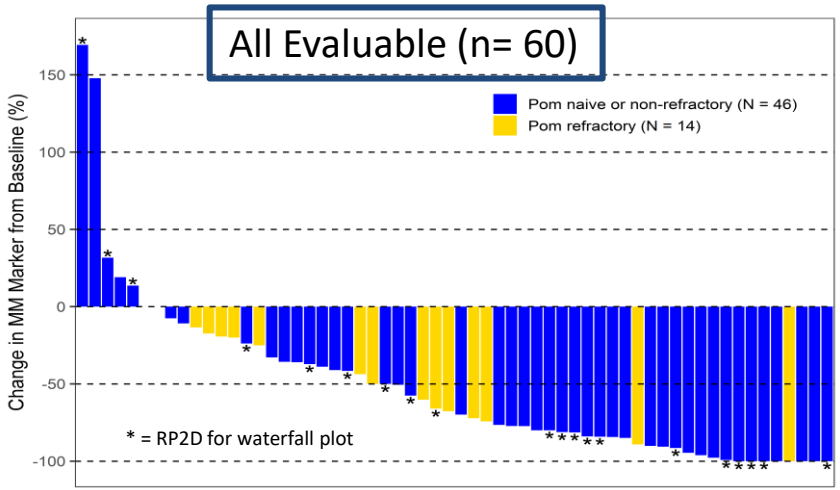
AEs (≥20% Patients) n=63 (as of Oct 1, 2020)		
Hematologic	Any Grade	Grade 3/4
Neutropenia	38 (60.3)	34 (54.0)
Anaemia	34 (54.0)	21 (33.3)
Thrombocytopenia	34 (54.0)	20 (31.7)
Leukopenia	15 (23.8)	8 (12.7)
Gastrointestinal		
Nausea	38 (60.3)	1 (1.6)
Decreased appetite	28 (44.4)	1 (1.6)
Diarrhea	18 (28.6)	0
Dysgeusia	13 (20.6)	0
Vomiting	13 (20.6)	1 (1.6)
Constitutional		
Fatigue	32 (50.8)	6 (9.5)
Weight decreased	24 (38.1)	0

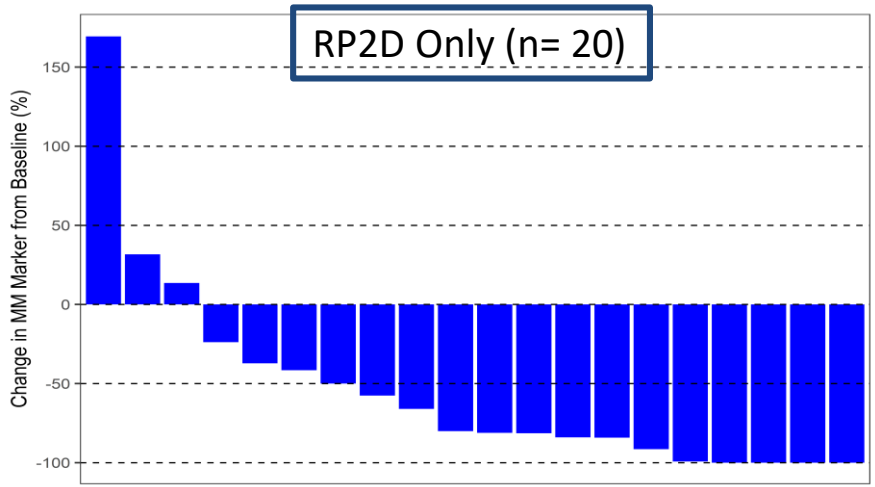
SPd Efficacy (as of November 14, 2020)

Best Responses in Evaluable SPd Patients

	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Pom naïve or non-refractory	46	25 (54.3)	33 (71.7)	1 (2.2)	†9 (19.6)	‡15 (32.6)	*8 (17.4)	10 (21.7)	3 (6.5)
Pom Refractory	14	5 (35.7)	9 (64.3)	--	1 (7.1)	4 (28.6)	4 (28.6)	5 (35.7)	-
RP2D: Selinexor 60 mg QW + Pom 4 mg	20	12 (60.0)	15 (75.0)	0	†6 (30.0)	‡6 (30.0)	*3 (15.0)	3 (15.0)	2 (10.0)

Responses were determined according to the International Myeloma Working Group (IMWG) criteria. † 2 VGPRs were unconfirmed. ‡ 1 PR was unconfirmed. *1 MR was unconfirmed. Responses as of November 14, 2020 based on interim unaudited data.

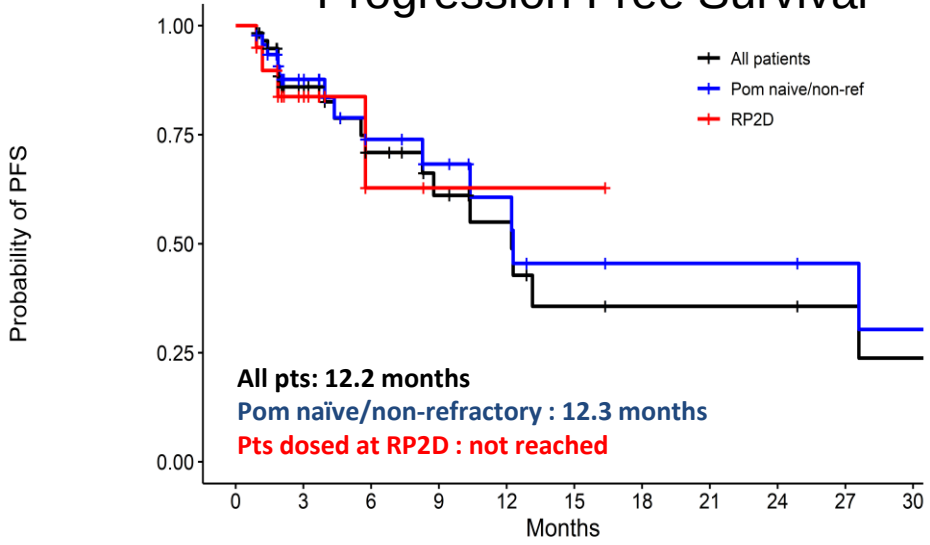




SPd highly active with prolonged PFS and DOR:

PFS in Pom-naïve/non-refractory MM was 12.3 months

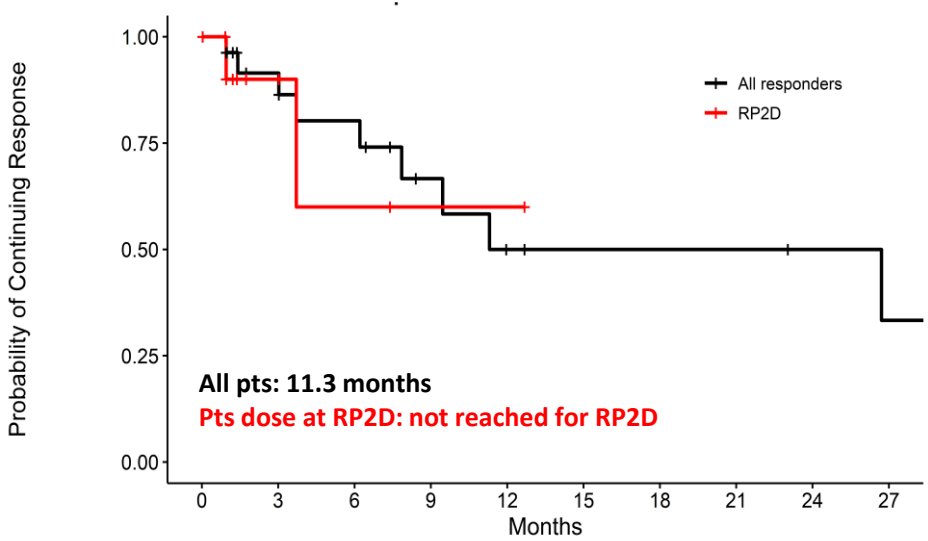
Progression Free Survival



Number at risk

All patients	60	31	17	12	9	5	4	4	4	3	2
Pom naive/non-ref	46	25	14	11	8	5	4	4	4	3	2
RP2D	20	9	2	1	1	1	0	0	0	0	0

Duration of Response



Number at risk

All responders	30	18	13	8	5	4	4	4	3	2
RP2D	12	4	2	1	1	0	0	0	0	0

Summary and Conclusions

Selinexor, once-weekly, can be safely combined with pomalidomide and low-dose dexamethasone (SPd) in patients with heavily pretreated MM

- **RP2D is selinexor 60 mg QW (pomalidomide 4 mg QD + dexamethasone 40 mg QW)**
- The most common TRAEs were: nausea, neutropenia, anemia, thrombocytopenia, fatigue
  - Expected and can be managed with appropriate supportive care and/or dose modifications

The all oral SPd combination is very active and responses are durable

- **ORR 60%** (≥ VGPR 30%) at the RP2D (compared to expected ORR ≤30% for pomalidomide + dex)[1]
- **CBR was 70% across all patient at RP2D**
- **PFS was 12.2 months for all patients and not reached for RP2D**

Data support planned phase 3 study of all oral combination of SPd vs Pd in patients with a prior PI, Imid and CD-38 mAb (XPORT-MM-031)

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