Oral selinexor, Pomalidomide, and Dexamethasone (XPd) at Recommended Phase 2 Dose in Relapsed Refractory Multiple Myeloma (MM)

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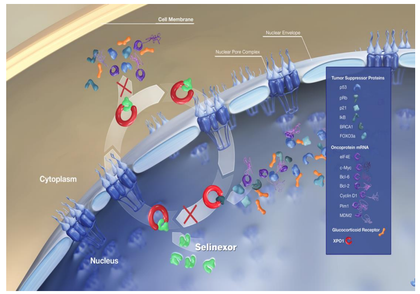
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export Reactivates Tumor Suppressor Proteins and is Synergistic with IMiDs



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 and suppresses NFkB activity[1,2,6]
- Inhibits oncoprotein translation[1,2,6]
- Reactivates glucocorticoid receptor (GR) signaling in presence of dexamethasone[7]

Selinexor demonstrated synergistic activity in combination with lenalidomide *in vivo*[8]

[1]Tai et al., Leukemia, 2014, [2]Fung & Chook, Semin Cancer Biol. 2014, [3]Parikh et al., J Hematol Oncol. 2014, [4]Gravina 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;

STOMP: Selinexor + Pomalidomide + Dexamethasone (XPd)
Selinexor and Backbone Treatments Of Multiple Myeloma Patients

Objectives:

- Primary endpoints:
  - Maximum Tolerated Dose (MTD)
  - Recommended Phase 2 Dose (RP2D)
  - **Overall Response Rate (ORR)**
- Secondary endpoints:
  - Safety and Tolerability per CTCAE
  - **Progression Free Survival (PFS)**
  - Overall Survival (OS)

Key eligibility criteria:

- ANC ≥ 1,000/mm^3, Hb ≥ 8.0 g/dL, Platelet count ≥ 75,000/mm^3
- Progressing or refractory to a previous regimen
- Previously undergone treatment with ≥2 cycles of lenalidomide and a proteasome inhibitor (in combination or separately)
- Prior pomalidomide-treatment is allowed, pomalidomide-refractory only allowed in the dose escalation phase
- Smouldering MM, non-secretory MM, active plasma cell leukemia are excluded

XPd Patient Characteristics (as of 31 March 2021)

	Total (N = 72)	RP2D (N = 20)
Median age, years (range)	64.0 (37 – 85)	65.5 (37 – 85)
Males (%): Females (%)	36 (50): 36 (50)	7 (35): 13 (65)
ISS Stage I (%): II (%): III (%): missing (%)	22 (30.6): 18 (25.0): 10 (13.9): 22 (30.6)	7 (35.0): 3 (15.0): 3 (15.0): 7 (35.0)
Median No. prior regimens (range)	**4.0 (1–12)**	**3.5 (1–12)**
Lenalidomide treated (%) : refractory (%)	72 (100.0) : 58 (80.6)	20 (100.0) : 16 (80.0)
Pomalidomide treated (%) : refractory (%)	21 (29.2) : 19 (26.4)	4 (20.0) : 3 (15.0)
Bortezomib treated (%) : refractory (%)	66 (91.7) : 36 (50.0)	17 (85.0) : 9 (45.0)
Carfilzomib treated (%) : refractory (%)	31 (43.1) : 27 (37.5)	12 (60.0) : 10 (50.0)
Anti-CD38 mAb treated (%) : refractory (%)	22 (30.6) : 20 (27.8)	6 (30.0) : 5 (25.0)
Stem cell transplant (%)	58 (80.6)	14 (70.0)

XPd Treatment-Related Adverse Events (≥20% Patients; as of 31 March 2021)

	Total N =72		RP2D N =20	
Hematologic	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	44 (61.1)	38 (52.8)	15 (75.0)	12 (60.0)
Anemia	38 (52.8)	21 (29.2)	13 (65.0)	5 (25.0)
Thrombocytopenia	35 (48.6)	20 (27.8)	9 (45.0)	5 (25.0)
Leukopenia	18 (25.0)	10 (13.9)	5 (25.0)	1 (5.0)
Gastrointestinal				
Nausea	44 (61.1)	1 (1.4)	14 (70.0)	0
Decreased appetite	30 (41.7)	1 (1.4)	6 (30.0)	0
Diarrhea	21 (29.2)	0	5 (25.0)	0
Vomiting	16 (22.2)	1 (1.4)	4 (20.0)	0
Constitutional				
Fatigue	39 (54.2)	7 (9.7)	13 (65.0)	1 (5.0)
Weight decrease	26 (36.1)	0	5 (25.0)	0

RP2D was Selinexor 60 mg on days 1, 8, 15, 22 + Pomalidomide 4 mg on days 1-21 + Dexamethasone 40 mg on days 1, 8, 15, 22; q28 days

XPd Efficacy (as of 22 April 2021)

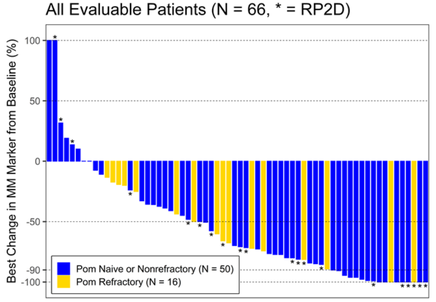
Best Responses in Evaluable XPd Patients

	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
RP2D: Selinexor 60 mg QW + Pom 4 mg	20	13 (65.0)	15 (75.0)	1 (5.0)	5 (25.0)	7 (35.0)	2 (10.0)	3 (15.0)	2 (10.0)
Pom Refractory among all pts dosed	16	7 (43.8)	11 (68.8)	0	2 (12.5)	5 (31.3)	4 (25.0)	5 (31.3)	0
Prior Anti-CD38 mAb	19	11 (57.9)	14 (73.7)	1 (5.3)	3 (15.8)	7 (36.8)	3 (15.8)	5 (26.3)	0

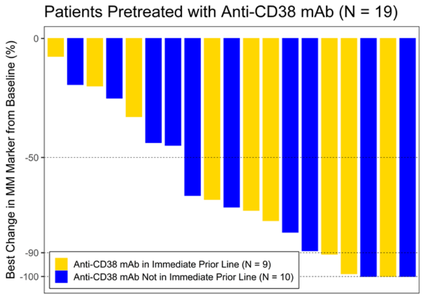
Responses were determined according to the International Myeloma Working Group (IMWG) criteria. Responses as of April 22, 2021 based on interim unaudited data.

XPd Efficacy (as of 22 April 2021) cont.

All Evaluable Patients (N = 66, * = RP2D)

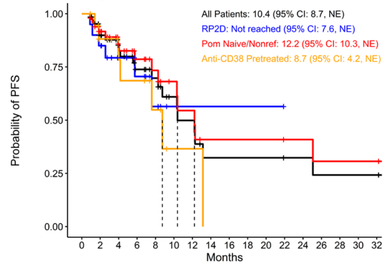


Patients Pretreated with Anti-CD38 mAb (N = 19)



XPd is Highly Active with Prolonged PFS and DOR: PFS in Pom-naïve or nonrefractory MM was 12.2 months

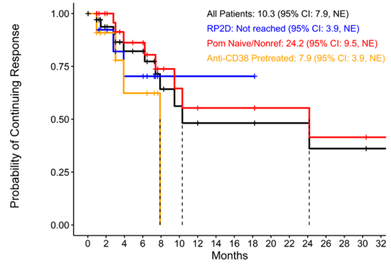
Progression-Free Survival



Number at risk

All Patients	66	46	32	23	17	11	9	5	5	5	5	4	4	3	3	3	3
RP2D	20	17	11	8	4	1	1	1	1	1	1	0	0	0	0	0	0
Pom Naive/Nonref	50	38	26	19	14	10	8	5	5	5	5	4	4	3	3	3	3
Anti-CD38 Pretreated	19	12	8	7	4	1	1	0	0	0	0	0	0	0	0	0	0

Duration of Response



Number at risk

All responders	35	27	19	18	9	7	5	5	5	5	4	4	4	3	3	3	2
RP2D	13	10	6	6	1	1	1	1	1	1	0	0	0	0	0	0	0
Pom Naive/Nonref	28	24	17	16	9	7	5	5	5	5	4	4	4	3	3	3	2
Anti-CD38 Pretreated	11	7	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0

Summary and Conclusions

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

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

The all-oral XPd combination is highly active and achieves durable responses

- **ORR was 65% (≥ VGPR 30%) at the RP2D (compared to expected ORR ≤30% for Pd alone)[1]**
- **CBR was 75% at the RP2D**
- **Median PFS was 12.2 months for pomalidomide naïve or non refractory RRMM patients and not reached for RP2D**
- **In patients previously treated with anti-CD38 mAb, ORR was 57.9% and median PFS 8.7 months**

These data support the planned phase 3 study of all-oral XPd vs Elo-Pd in RRMM patients with prior therapy of PI, IMiD and anti-CD38 mAb (XPORT-MM-031)

[1]San-Miguel et al. Lancet Oncol 2013,14:1055;

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