Once Weekly Selinexor, Carfilzomib, and Dexamethasone (XKd) in Heavily Pretreated Multiple Myeloma (MM)

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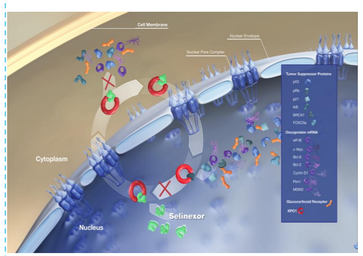
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export shows synergistic anti-tumor activity with Proteasome Inhibitors



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]
- Exhibits synergistic activity with proteasome inhibitors by forcing nuclear localization of high levels of TSPs[8]

Background / Rationale: Selinexor and Carfilzomib in RRMM

- Once weekly selinexor with bortezomib and dexamethasone showed superior PFS, ORR and TTNT compared to Bortezomib-Dexamethasone and received full FDA approval for patients with MM with at least one prior therapy[9]
- Selinexor showed a synergistic antitumor effect with carfilzomib ex-vivo in carfilzomib-refractory MM patient samples[10] and in a preclinical xenograft MM model[11].

Hypothesis: Once weekly (QW) carfilzomib and QW selinexor + Dexamethasone is tolerable and derives promising responses in RRMM patients

ORR=Overall Response Rate, PFS=Progression Free Survival, TTNT=Time to Next Treatment

STOMP: Selinexor + Carfilzomib + Dexamethasone (XKd)
Selinexor and Backbone Treatments Of Multiple Myeloma Patients

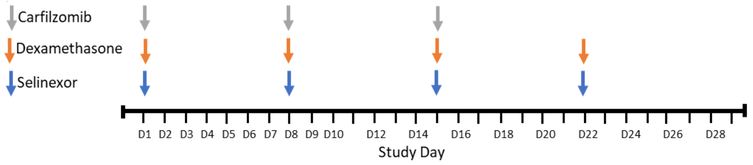
Objectives:

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

Key Inclusion/Exclusion criteria:

- Age ≥ 18 years old at the time of informed consent
- ECOG 0-2
- WBC ≥ 1,500/mm^3 Hb ≥ 8.0 g/dL, platelet count ≥ 75,000/mm^3
- Progressing or refractory to a previous regimen
- Prior proteasome inhibitors are allowed, however, patients with MM refractory to carfilzomib are excluded

XKd Treatment Schedule



[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]Kashyap et al., Oncotarget. 2016 [9]Grosicki et al., Lancet. 2020, 396:1563; [10]Turner et al., Oncotarget, 2016 [11]Rosebeck S et al., Molecular Cancer Therapeutics 2016;

XKd Dose Limiting Toxicities (DLT) and RP2D

Selinexor Dose	Carfilzomib Dose	Patients Enrolled	Patients DLT-evaluable	Patients with DLT	Dose Limiting Toxicity
100 mg QW	56 mg/m^2 IV	3	*2	2	Selinexor dose reduction grade 3 thrombocytopenia (no bleeding); Selinexor dose reduction due to grade 3 vomiting
80 mg QW	70 mg/m^2 IV	3	3	2	Grade 3 pneumonia and Grade 4 thrombocytopenia (no bleeding); Grade 4 thrombocytopenia (no bleeding)
80 mg QW	**56 mg/m^2 IV**	**6**	**6**	**--**	**No DLT**

RP2D was Selinexor 80 mg + Carfilzomib 56 mg/m^2 + dexamethasone 40 mg

XKd Patient Characteristics (as of 31 March 2021)

	RP2D (N = 18)	Total (N = 32)
Median age, years (range)	68.5 (51 – 76)	69.5 (35 – 76)
Males (%): Females (%)	12 (66.7) : 6 (33.3)	20 (62.5) : 12 (37.5)
Median years from diagnosis to XKd treatment, years (range)	5.3 (2.7 – 11.3)	5.3 (0.4 – 11.3)
ECOG Performance Status, 0 (%) : 1 (%): 2 (%)	3 (16.7%) : 15 (83.3%) : 0 (0)	8 (25.0) : 22 (68.8) : 2 (6.3)
Median No. prior regimens (range)	**4 (1 – 8)**	**4 (1 – 8)**
Bortezomib treated (%) : refractory (%)	18 (100.0) : 8 (44.4)	32 (100.0) : 14 (43.8)
Carfilzomib treated (%) : refractory (%)	1 (5.6) : 1 (5.6)	3 (9.4) : 1 (3.1)
Lenalidomide treated (%) : refractory (%)	17 (94.4) : 11 (61.1)	31 (96.9) : 17 (53.1)
Pomalidomide treated (%) : refractory (%)	12 (66.7) : 8 (44.4)	23 (71.9) : 17 (53.1)
Anti-CD38 mAb treated (%) : refractory (%)	11 (61.1) : 10 (55.6)	22 (68.8) : 20 (62.5)
Stem cell transplant (%)	14 (77.8)	23 (71.9)

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

	RP2D (N = 18)		Total (N = 32)	
Hematologic	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Thrombocytopenia	14 (77.8)	9 (50.0)	21 (65.6)	15 (46.9)
Anaemia	11 (61.1)	2 (11.1)	16 (50.0)	5 (15.6)
Leukopenia	5 (27.8)	2 (11.1)	10 (31.3)	3 (9.4)
Neutropenia	6 (33.3)	1 (5.6)	9 (28.1)	2 (6.3)
Gastrointestinal				
Nausea	14 (77.8)	2 (11.1)	23 (71.9)	2 (6.3)
Decreased appetite	9 (50.0)	1 (5.6)	15 (46.9)	1 (3.1)
Dysgeusia	7 (38.9)	0	10 (31.3)	0
Diarrhoea	3 (16.7)	0	8 (25.0)	0
Constitutional				
Fatigue	10 (55.6)	1 (5.6)	17 (53.1)	3 (9.4)
Weight decrease	8 (44.4)	0	12 (37.5)	0

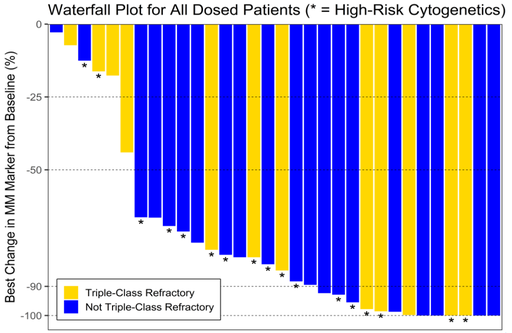
XKd Efficacy (as of 22 April 2021)

Best Responses in Evaluable XKd Patients

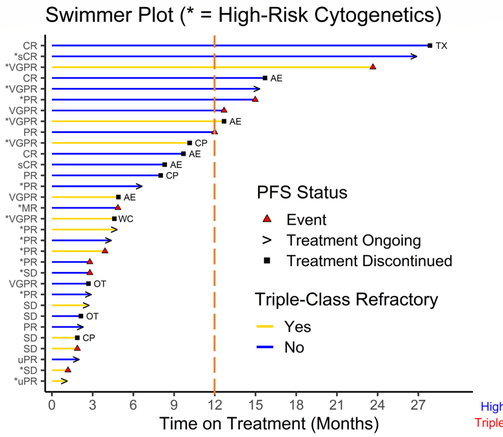
	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)
Overall	32	25 (78.1)	26 (81.3)	5 (15.6)	8 (25.0)	12 (37.5)	1 (3.1)	6 (18.8)
Prior lines of therapy								
1 – 2	8	7 (87.5)	7 (87.5)	3 (37.5)	3 (37.5)	1 (12.5)	0	1 (12.5)
≥ 3	23	17 (73.9)	18 (78.3)	2 (8.7)	5 (21.7)	10 (43.5)	1 (4.3)	5 (21.7)
High-risk cytogenetics†								
No	15	11 (73.3)	11 (73.3)	4 (26.7)	3 (20.0)	4 (26.7)	0	4 (26.7)
Yes	17	14 (82.4)	15 (88.2)	1 (5.9)	5 (29.4)	8 (47.1)	1 (5.9)	2 (11.8)

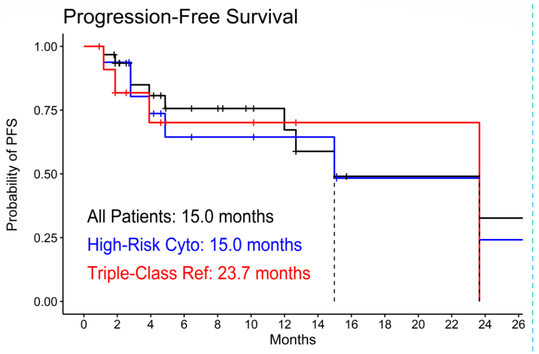
†Defined as any of del(17p), t(4;14), t(14;16), or gain 1q at initial diagnosis or screening.

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



XKd is Highly Active: PFS in all Patients was 15.0 months





Number at risk

All Patients	32	27	19	14	13	10	8	6	3	3	3	3	2	2
High-Risk Cyto.	17	15	11	7	6	6	5	4	2	2	2	2	1	1
Triple-Class Ref.	12	8	6	3	3	3	2	1	1	1	1	1	0	0

TX = Toxicity to study drug; AE = Adverse event; CP = Disease Progression (Clinical Progression); WC = Withdrawal by patient; OT = Other

Summary and Conclusions

- The RP2D of XKd with continuous weekly selinexor is once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2 + dexamethasone 40 mg
- The combination is highly active and durable with a PFS of 15 months and an ORR of 78.1% with deep responses (≥ VGPR) in 40.7%, in patients who had a median of 4 lines of prior therapy
- The most common TRAEs are thrombocytopenia, nausea, anemia, fatigue and anorexia which are expected and can be managed with supportive care and/or dose modifications
- Further exploration with selinexor dosing on days 1, 8 and 15 q 28 days is ongoing; currently recommended dosing is selinexor 80 mg (d 1, 8, 21) + carfilzomib 56 mg/m^2 (days 1, 8, 21) + dexamethasone 40 mg QW of 28-day cycles

Acknowledgments

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