Once Weekly Selinexor, Carfilzomib, and Dexamethasone (SKd) in Patients with Relapsed/Refractory Multiple Myeloma (MM).

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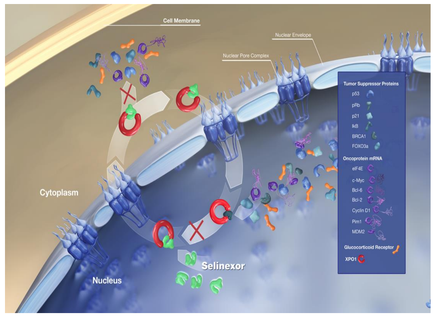
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)



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]

[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

Background: Selinexor and Carfilzomib Activity in Multiple Myeloma

- Selinexor 80 mg twice weekly (BIW) (+ Dexamethasone 20 mg BIW) received accelerated approval from the FDA for patients with RRMM[1]
- **Selinexor showed a synergistic antitumor effect with carfilzomib** ex-vivo in carfilzomib-refractory MM patient samples[2] and in preclinical xenograft MM model[3].
- Once weekly carfilzomib is preferred schedule of carfilzomib administration

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

IMiD=immunomodulatory agent, ORR=overall response rate, PI=proteasome inhibitor, QW=once weekly, SKd=selinexor-carfilzomib-dexamethasone

[1]Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212306s000lbl.pdf; [2]Turner et al., Oncotarget, 2016 [3]Rosebeck S et al., Molecular Cancer Therapeutics 2016; [4]Jakubowiak AJ et al. British Journal of hematology 2019; [5]Alsina M et al. International Myeloma Workshop (IMW) 2019.

STOMP Study with Selinexor + Carfilzomib + Dexamethasone (SKd) Selinexor and Backbone Treatments Of Multiple Myeloma Patients

Open-label, dose escalation (Phase 1) and expansion (Phase 2) study evaluating selinexor in combination with other anti-myeloma therapies in patients with newly diagnosed and relapsed/refractory multiple myeloma (MM)

Objectives:

- Primary endpoint: maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
- Secondary endpoint: overall response rate (ORR) and duration of response (DOR) for each arm independently

Key Inclusion/Exclusion criteria:

- Age ≥ 18 y.o. 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

SKd Dose Escalation – Treatments Schedule

Dose Levels	Selinexor	Dexamethasone	Carfilzomib
	Days 1, 8, 15 and 22	Days 1, 8, 15 and 22	Days 1, 8, and 15
1	100 mg PO	40 mg IV or PO	56 mg/m^2 IV
-1	80 mg PO	40 mg IV or PO	56 mg/m^2 IV
-1a*	80 mg PO	40 mg IV or PO	70 mg/m^2 IV

SKd dose escalation scheme: a standard 3 + 3 design was used for dose escalations. Starting dose was dose level 1. Carfilzomib's C1D1 dose is always 20 mg/m^2 per carfilzomib's label.

Patient Characteristics

Patient Characteristics (Enrolled as of May 1, 2020)	Total (N = 24)
Median Age, Years (range)	70.5 (50 – 76)
Males : Females	15 (62.5%) : 9 (37.5%)
Race, White: African American: Other	15 (62.5%) : 6 (25.0%) : 3 (12.5%)
ECOG Performance Status, 0 : 1 : 2	4 (16.7%) : 18 (75.0%): 2 (8.3%)
Median Years from Diagnosis to SKd Treatment, Years (range)	5.01 (2.7 – 11.3); n=23
Median Prior Regimens (range)	**3 (1–8); n=23**
-Bortezomib exposed	**24 (100.0%)**
-Carfilzomib exposed	1 (4.2%)
-Lenalidomide exposed	**23 (95.8%)**
-Pomalidomide exposed	**15 (62.5%)**
-Daratumumab exposed	**14 (58.3%)**
-Stem Cell Transplant	**19 (79.2%)**

Dose-Limiting Toxicity (DLT)

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 due to Grade 3 Thrombocytopenia; Selinexor Dose Reduction due to Grade 3 Vomiting
80 mg QW	70 mg/m^2 IV	3	3	2	Grade 4 Thrombocytopenia and Grade 3 Pneumonia; Grade 4 Thrombocytopenia
****80 mg QW**	**56 mg/m^2 IV**	**6**	**6**	**--**	**No DLT**

IV, Intravenous; QW, Once-Weekly.

*One patient was not DLT evaluable because platelet count was <50x10^9/L on C1D1.

**Enrollment is ongoing in the once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2 cohort. Two patients after the first 6 patients were not included in the DLT assessment.

Treatment-Related Adverse Events ≥3 Patients (as of May 1, 2020)

AE Term	Non MTD + MTD			TOTAL
	Grade ½ n (%)	Grade 3 n (%)	Grade 4 n (%)	(N=24) n (%)
Hematologic				
Thrombocytopenia	4 (16.6)	6 (25)	7 (29.1)	17 (70.8)
Anemia	8 (33.3)	5 (20.8)	--	13 (54.2)
Leukopenia	5 (20.8)	3 (12.5)	--	8 (33.3)
Neutropenia	4 (16.6)	2 (8.3)	--	6 (25.0)
Gastrointestinal				
Nausea	16 (66.6)	--	--	16 (66.6)
Anorexia	10 (41.6)	1 (4.1)	--	11 (45.8)
Vomiting	4 (16.6)	1 (4.1)	--	5 (20.8)
Diarrhea	5 (20.8)	--	--	5 (20.8)
Constipation	4 (16.6)	--	--	4 (16.6)
Constitutional				
Fatigue	11 (45.8)	2 (8.3)	--	13 (54.2)
Body weight loss	9 (37.5)	--	--	9 (37.5)
Malaise	3 (12.5)	--	--	3 (12.5)
Other				
Dysgeusia	9 (37.5)	--	--	9 (37.5)
Hyperglycemia	4 (16.6)	1 (4.1)	1 (4.1)	6 (25.0)
Hyponatremia	3 (12.5)	1 (4.1)	--	4 (16.7)
Insomnia	4 (16.6)	--	--	4 (16.6)
Blurred Vision	4 (16.6)	--	--	4 (16.6)
Hypocalcaemia	3 (12.5)	--	--	3 (12.5)
Hypokalaemia	3 (12.5)	--	--	3 (12.5)
Peripheral Sensory Neuropathy	3 (12.5)	--	--	3 (12.5)

AE, adverse event; Carfil, carfilzomib; IV, intravenous; QW, Once-Weekly; Sel, selinexor.

SKd Efficacy (as of May 1, 2020)

Best Responses† in Evaluable SKd Patients

Category	N	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
All Efficacy Evaluable Patients	24	**17 (70.8%)**	**18 (75%)**	4 (16.7%)	8* (33.3%)	5(20.8)	1 (4.2%)	6 (25%)	--

†Responses were determined according to the International Myeloma Working Group (IMWG) criteria. * 1 VGPR is unconfirmed. 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 May 1, 2020 based on interim unaudited data.

Figure 1: Duration of Progression Free Survival

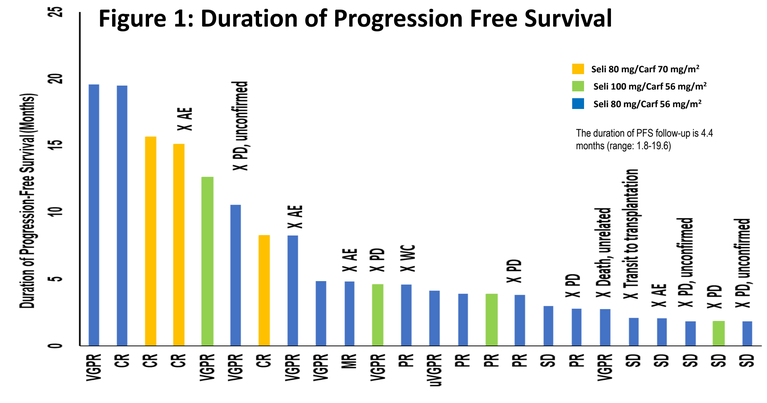
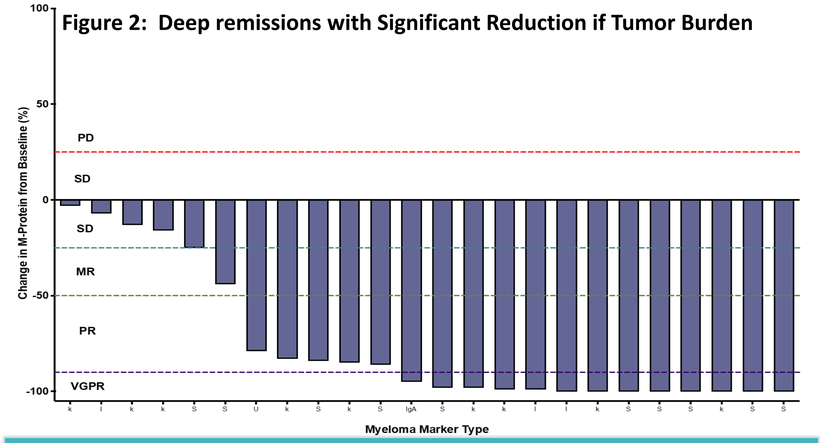


Figure 2: Deep remissions with Significant Reduction if Tumor Burden



Summary and Conclusions

- **The RP2D of SKd is once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2**
- **The combination is active with an ORR of 70.8% with deep responses (CR 16.7 %, VGPR 33.3%) in patients who had a median of 3 lines of prior therapy.**
- **The most common AEs are nausea, anemia, fatigue and Grade 3/4 thrombocytopenia, which are expected and can be managed with appropriate supportive care and/or dose modifications**
- **Selinexor, once-weekly, can be safely combined with once weekly carfilzomib and low-dose dexamethasone and is an active combination that warrants further investigation**

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