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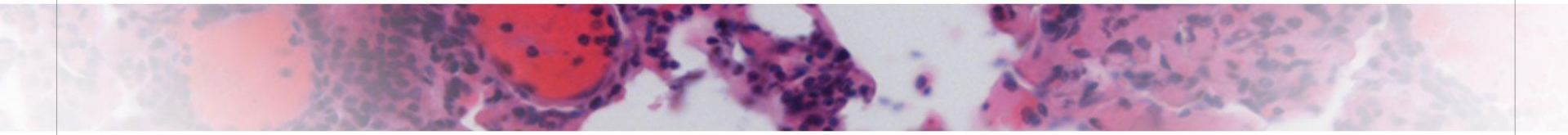

Selinexor in Combination with Carfilzomib and Dexamethasone, All Once Weekly (SKd), for Patients with Relapsed/Refractory Multiple Myeloma

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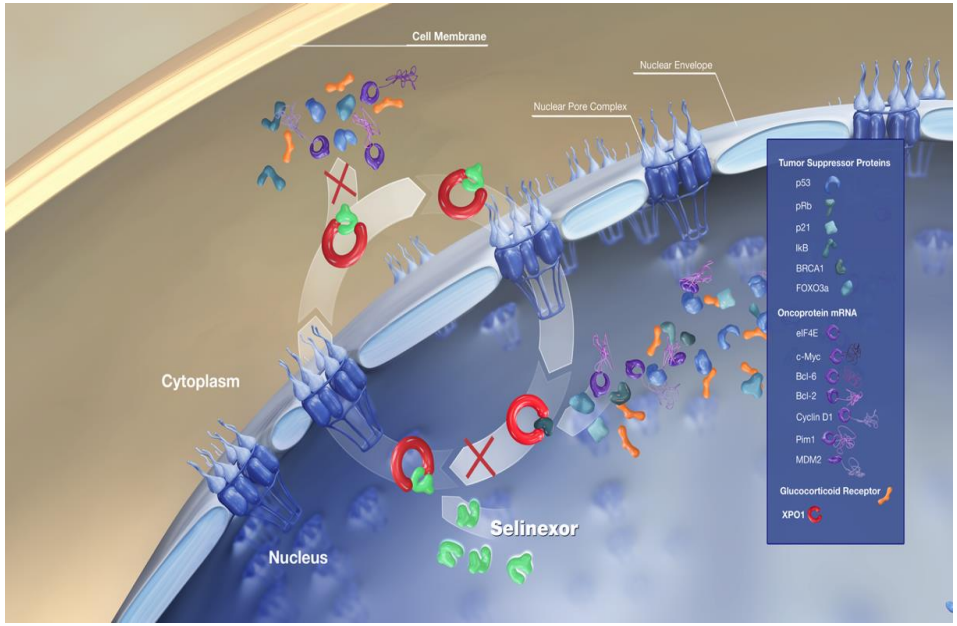
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export has Synergistic Activity in combination with Proteasome Inhibitors



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]**

[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

Selinexor and Carfilzomib Activity in Multiple Myeloma

- **Selinexor + dexamethasone in** patients with MM refractory to at least one proteasome inhibitor, one immunomodulatory agents, and daratumumab (triple-class refractory) resulting in **26.4% ORR and 4.4 months of PFS**[1]

- BOSTON validated the combination of Selinexor + Proteasome Inhibitor in phase 3 study:
  - **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 showed a synergistic antitumor effect with carfilzomib** ex-vivo in carfilzomib-refractory MM patient samples[4] and in preclinical xenograft MM model[5]

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

[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]Turner et al., Oncotarget, 2016 [5]Rosebeck S et al., Molecular Cancer Therapeutics 2016; [6]Jakubowiak AJ et al. British Journal of hematology 2019

ORR=overall response rate; PFS=Progression Free Survival; QW=once weekly; BIW=Twice a week; IMiD=immunomodulatory agent; PI=proteasome inhibitor,

Selinexor + Carfilzomib + Dexamethasone (SKd): Objectives / Inclusion Criteria and Patient Demographics

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:

- 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

Patient Characteristics (Enrolled as of October 1, 2020)	Total (N = 24)
Median Age, Years (range)	**70.5 (50 – 76)**
Males : Females	15 (62.5%) : 9 (37.5%)
ECOG Performance Status, 0 : 1 : 2	4 (16.7%) : 19 (79.2%): 1 (4.2%)
Median Years from Diagnosis to SKd Treatment, Years (range)	5.25 (2.7 – 11.3)
Median Prior Regimens (range)	**3 (1–8)**
-Bortezomib exposed	**24 (100.0%)**
-Carfilzomib exposed	**1 (4.2%)**
-Lenalidomide exposed	**23 (95.8%)**
-Pomalidomide exposed	**16 (66.7%)**
-Daratumumab exposed	**15 (62.5%)**
-Stem Cell Transplant	**19 (79.2%)**

DLTs and Treatment-Related Adverse Events ≥15% Patients

Selinexor Dose	Carfilzomib Dose	No. Pts Enrolled	No. Pts DLT-evaluable	No. Pts with DLT	Dose Limiting Toxicity
100 mg QW	56 mg/m^2 IV	3	*2	2	Dose Reduction for G3 PLT; Dose Reduction for G3 Emesis
80 mg QW	70 mg/m^2 IV	3	3	2	Grade 4 PLT and Grade 3 Pneumonia; Grade 4 PLT
80 mg QW	56 mg/m^2 IV	6	6	--	No DLT

Dose-Limiting Toxicity (DLT): Standard 3 + 3 design for dose escalations. Carfilzomib C1D1 dose 20 mg/m^2 per label. *One patient not DLT evaluable because platelet count <50x10^9/L C1D1.

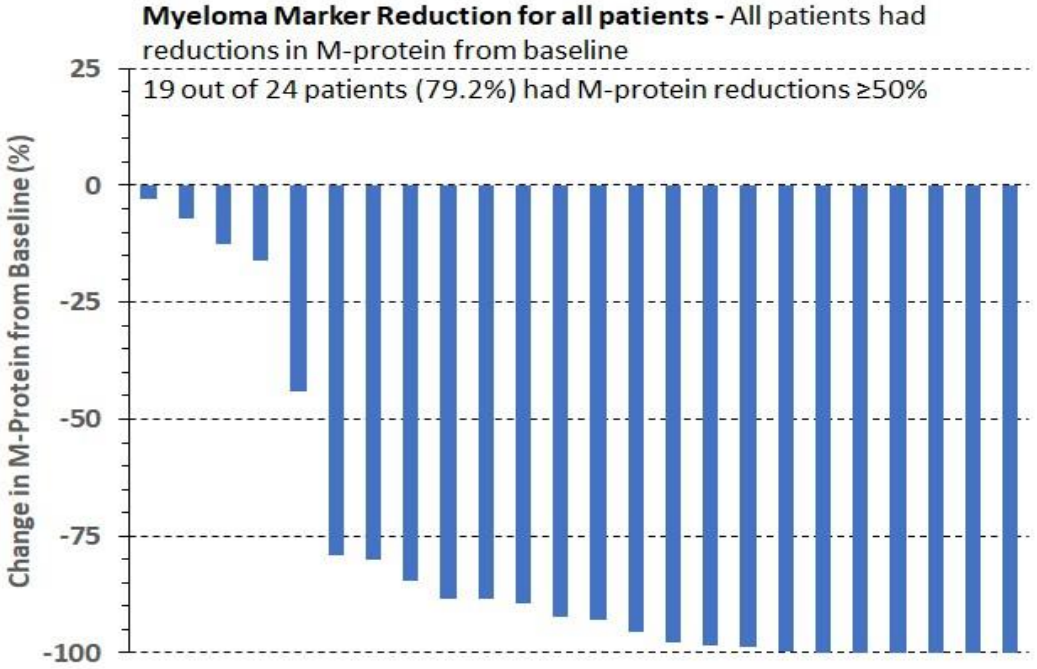
AEs ≥15% Patients (N=24)		
Hematologic	Any Grade	Grade 3/4
Thrombocytopenia	19 (79.2)	14 (58.3)
Anaemia	14 (58.3)	5 (20.8)
Leukopenia	8 (33.3)	3 (12.5)
Neutropenia	7 (29.2)	2 (8.3)
Gastrointestinal		
Nausea	17 (70.8)	1 (4.2)
Decreased appetite	12 (50.0)	1 (4.2)
Dysgeusia	9 (37.5)	0
Diarrhoea	5 (20.8)	0
Vomiting	5 (20.8)	1 (4.2)
Constipation	4 (16.7)	0

AEs ≥15% Patients (N=24) – Cont.		
Constitutional	Any Grade	Grade 3/4
Fatigue	14 (58.3)	2 (8.3)
Weight decreased	11 (45.8)	0
Insomnia	4 (16.7)	0
Other		
Hyperglycaemia	6 (25.0)	2 (8.3)
Hyponatraemia	4 (16.7)	1 (4.2)
Blurred vision	4 (16.7)	0

SKd Results in Deep Responses in heavily pretreated patients:

(100% Velcade Exposed; 95% prior Len; 67% prior Pom; 63% prior Dara)

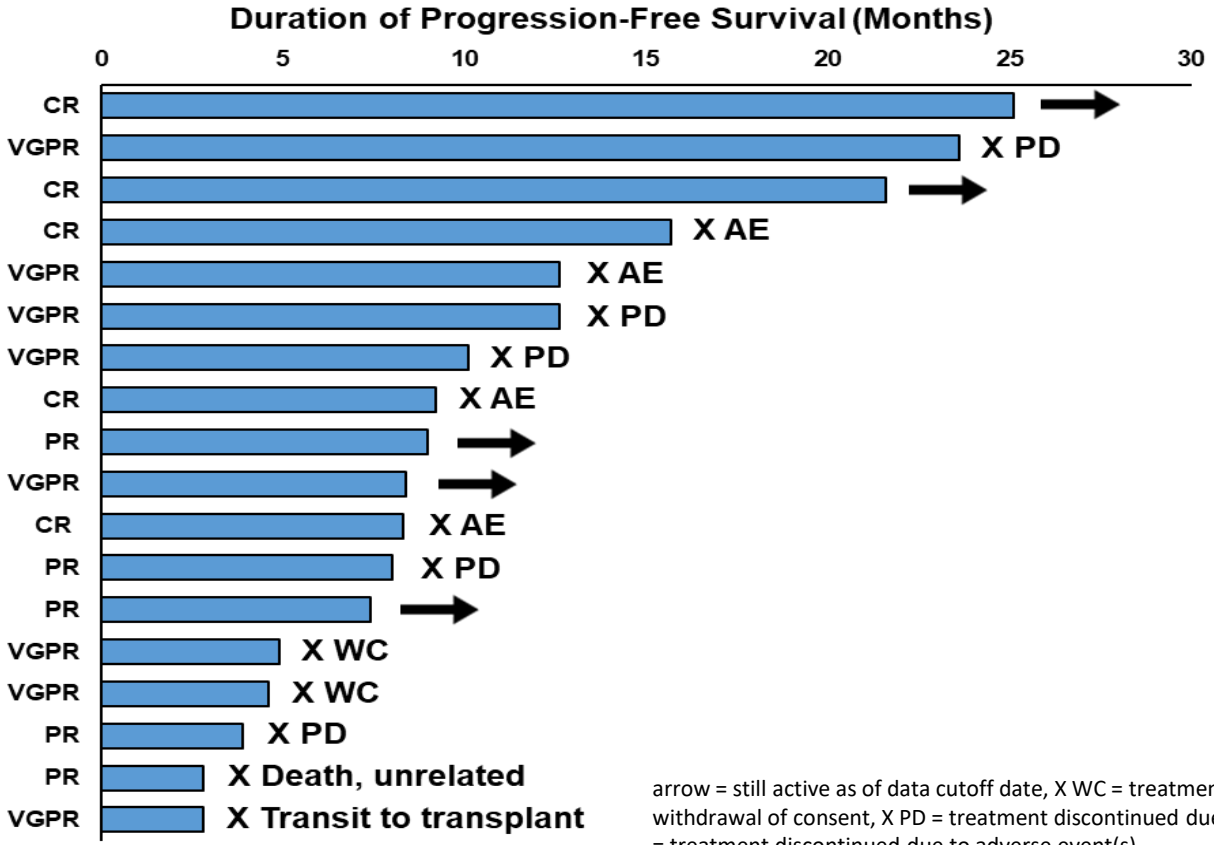
	Best Response (%) n=24
CR (%)	**5 (20.8%)**
VGPR (%)	**8 (33.3%)**
PR (%)	5 (20.8%)
MR (%)	1 (4.2%)
SD (%)	5 (20.8%)
ORR	**18 (75%)**
CBR	**19 (79.2%)**



(as of October 1, 2020)

Responses were determined according to the International Myeloma Working Group (IMWG) criteria. 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.

SKd Time on Therapy: Response are durable > 12 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 SKd with continuous weekly Selinexor is once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2 + dexamethasone 40 mg
- The combination is active and durable with an ORR of 75% with deep responses (≥ VGPR) in 54%, in patients who had a median of 3 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

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