A Phase 1b/2 Study of Selinexor, Carfilzomib, and Dexamethasone (SKd) in Relapsed / Refractory Multiple Myeloma (RRMM)

Abstract 3423

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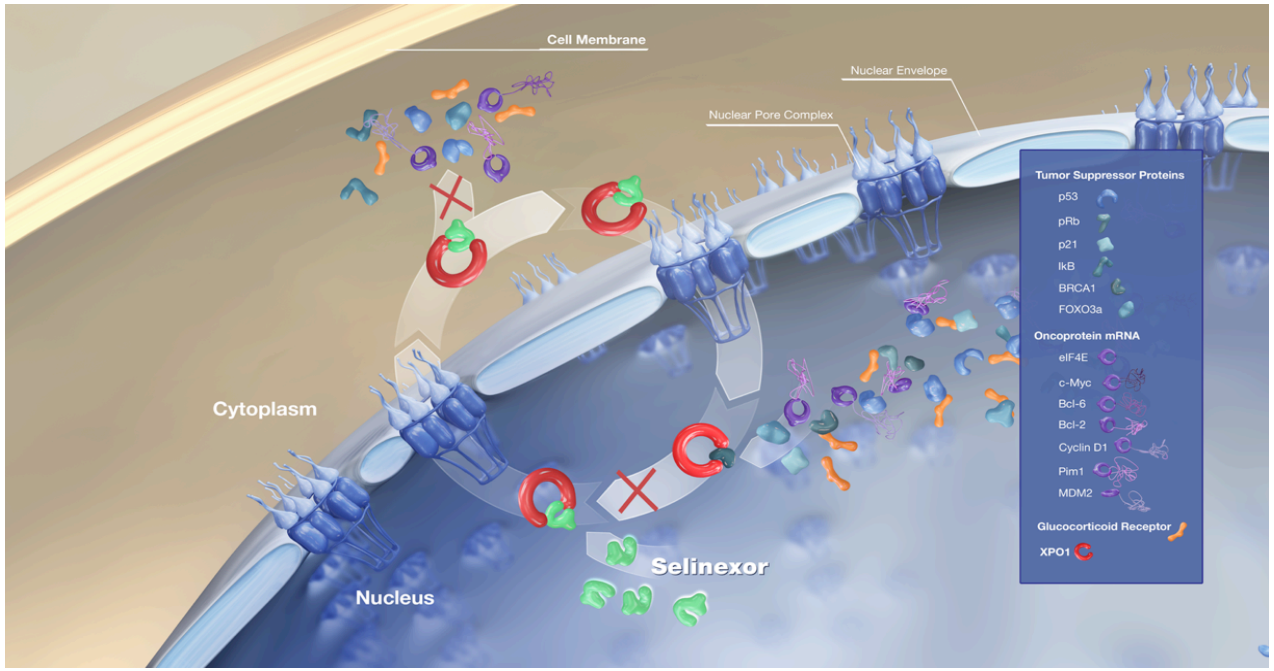
Selinexor Mechanism of Action



Exportin 1 (XPO1) is the major nuclear exporter for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, MDM2, cyclins)

XPO1 is overexpressed in MM:

- High XPO1 levels enable cancer cells to escape TSP mediated cell cycle arrest and induction of apoptosis
- XPO1 levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective XPO1 inhibitor; preclinical data demonstrate that selinexor:

- Reactivates multiple TSPs relevant to MM, inhibits NF-κB signaling, reduces c-Myc levels and reactivates GR signaling
- Demonstrates synergistic activity with proteasome inhibitors by forcing nuclear localization of high levels of TSPs
- In a clinical study, selinexor was shown to be safely combined with carfilzomib with an ORR of 63% (*Jakubowiak ASH 2016*)

STOMP Study Design

Selinexor and Backbone **T**reatments **O**f Multiple **M**yeloma **P**atients (**STOMP**) is an 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

Dose Limiting Toxicity (DLT) Was Determined in Dose Escalation Cycle 1 Only

- >1 missed dose (out of 4 doses – once-weekly selinexor dose schedules), or >2 missed doses (out of 6 doses – twice-weekly dose schedules) of selinexor during a cycle due to study-drug related toxicity
- Discontinuation of a patient before completing Cycle 1, due to study-drug related toxicity
- G3 nausea, vomiting, dehydration, diarrhea, or fatigue lasting >3 days despite optimal supportive medications
- G4 neutropenia lasting >7 days or G≥3 thrombocytopenia with clinically significant bleeding, petechiae, purpura

STOMP Study Design (SKd)

- **Patient Population SKd:** Patients with relapsed/refractory MM not refractory to carfilzomib; may have had prior PI treatment
- **SKd Dose Escalation Scheme:** A standard 3 + 3 design is used for all dose escalations and include 2 cohorts to evaluate once-weekly carfilzomib at 56 mg/m^2 or 70 mg/m^2 IV in combination with 80 – 100 mg once-weekly oral selinexor and low-dose dexamethasone

Drug	SVd ARM	SPd ARM	SRd ARM	SDd ARM	SKd Arm	SRd – Newly Diagnosed Patients
Selinexor, PO	60 – 80 mg BIW 80 – 100 mg QW	60 – 80 mg BIW 60 – 100 mg QW	60 – 80 mg BIW 80 – 100 mg QW	60 mg BIW 100 mg QW	80 – 100 mg QW	60 – 80 mg, QW
Bortezomib, SC	1.3 mg/m^2 – QW/BIW	--	--	--	--	--
Pomalidomide, PO	--	2 – 4 mg, QD	--	--	--	--
Lenalidomide, PO	--	--	25 mg, QD	--	--	25 mg, QD
Daratumumab, IV	--	--	--	16 mg/kg, QW	--	--
Carfilzomib, IV	--	--	--	--	56 – 70 mg/m^2 QW	--
Dexamethasone, PO	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW	20 mg BIW or 40 mg QW

Data presented will focus on the SKd arm. Dexamethasone (Dex) will be dosed on selinexor dosing days.

SVd, selinexor + bortezomib + dexamethasone; SPd, selinexor + pomalidomide + dexamethasone; SDd, selinexor + daratumumab + dexamethasone; SKd, selinexor + carfilzomib + dexamethasone; SRd, selinexor + lenalidomide + dexamethasone; BIW, Twice-Weekly; QD, Once-Daily; QW, Once-Weekly.

SKd Patient Characteristics

SKd Patient Characteristics	N
Enrolled as May 1, 2019 - 80 mg selinexor QW + 56 mg/m^2 carfilzomib - 80 mg selinexor QW + 70 mg/m^2 carfilzomib - 100 mg selinexor QW + 56 mg/m^2 carfilzomib	**9** 3 3 3
Median Age, Years (range)	71 (50 – 76)
Males : Females	3 (33%) : 6 (67%)
Median Years from Diagnosis to SKd Treatment, Years (range)	4 (3 – 11)
Median Prior Regimens (range)	**4 (2–8)**
-Bortezomib (Treated : Refractory)	9 (100%): 7 (78%)
-Carfilzomib Therapy (Treated : Refractory)	0% : 0%
-Lenalidomide (Treated : Refractory)	9 (100%) : 6 (67%)
-Pomalidomide (Treated : Refractory)	5 (56%) : 5 (56%)
-Daratumumab (Treated : Refractory)	5 (56%) : 5 (56%)
-Stem Cell Transplant	5 (56%)

SKd Treatment-Related Adverse Events ≥2 Patients

AE Term	80 mg Sel QW + 56 mg/m^2 Carfil IV				80 mg Sel QW + 70 mg/m^2 Carfil IV				100 mg Sel QW + 56 mg/m^2 Carfil IV				TOTAL (N=9)
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=3)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=3)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=3)**	
Thrombocytopenia	2 (66.7)	--	1 (33.3)	**3 (100.0)**	--	1 (33.3)	2 (66.7)	**3 (100.0)**	--	1 (33.3)	2 (66.7)	**3 (100.0)**	**9 (100.0)**
Anemia	2 (66.7)	--	--	**2 (66.7)**	1 (33.3)	2 (66.7)	--	**3 (100.0)**	1 (33.3)	--	--	**1 (33.3)**	**6 (66.7)**
Leukopenia	--	2 (66.7)	--	**2 (66.7)**	2 (66.7)	1 (33.3)	--	**3 (100.0)**	--	--	--	**--**	**5 (55.6)**
Neutropenia	1 (33.3)	1 (33.3)	--	**2 (66.7)**	1 (33.3)	1 (33.3)	--	**2 (66.7)**	--	--	--	**--**	**4 (44.4)**
Gastrointestinal													
Nausea	3 (100.0)	--	--	**3 (100.0)**	3 (100.0)	--	--	**3 (100.0)**	--	--	--	**--**	**6 (66.7)**
Anorexia	1 (33.3)	--	--	**1 (33.3)**	1 (33.3)	--	--	**1 (33.3)**	1 (33.3)	--	--	**1 (33.3)**	**3 (33.3)**
Vomiting	2 (66.7)	--	--	**2 (66.7)**	--	1 (33.3)	--	**1 (33.3)**	--	--	--	**--**	**3 (33.3)**
Constitutional													
Fatigue	1 (33.3)	--	--	**1 (33.3)**	2 (66.7)	--	--	**2 (66.7)**	--	1 (33.3)	--	**1 (33.3)**	**4 (44.4)**
Other													
Hyperglycemia	1 (33.3)	--	--	**1 (33.3)**	1 (33.3)	--	--	**1 (33.3)**	--	1 (33.3)	1 (33.3)	**2 (66.7)**	**4 (44.4)**
Hypoalbuminemia	1 (33.3)	--	--	**1 (33.3)**	1 (33.3)	--	--	**1 (33.3)**	--	--	--	**--**	**2 (22.2)**
Insomnia	--	--	--	**--**	1 (33.3)	--	--	**1 (33.3)**	1 (33.3)	--	--	**1 (33.3)**	**2 (22.2)**
Pneumonia	--	--	--	**--**	--	1 (33.3)	--	**1 (33.3)**	--	1 (33.3)	--	**1 (33.3)**	**2 (22.2)**

Adverse Events: The most common treatment-related adverse events were nausea, anemia, anorexia, and fatigue (mainly Grade 1/2). Thrombocytopenia and leukopenia were also common (mainly Grade 3/4). No related Grade 5 events were reported.

Treatment-Related Adverse Events as of May 1, 2019

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

SKd DLTs

Selinexor Dose	Carfilzomib Dose	Patients Enrolled	Patients with DLT	Dose Limiting Toxicity
***80 mg QW**	**56 mg/m^2 IV**	**3**	**--**	**No DLT and Enrollment is Ongoing**
80 mg QW	70 mg/m^2 IV	3	2	Grade 4 Thrombocytopenia and Grade 3 Pneumonia Grade 4 Thrombocytopenia
100 mg QW	56 mg/m^2 IV	3	2	Selinexor Dose Reduction due to Grade 3 Thrombocytopenia Selinexor Dose Reduction due to Grade 3 Vomiting

- ***Enrollment is ongoing in the once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2 cohort**

DLT, dose limiting toxicity; IV, Intravenous; QW, Once-Weekly.

SKd Efficacy

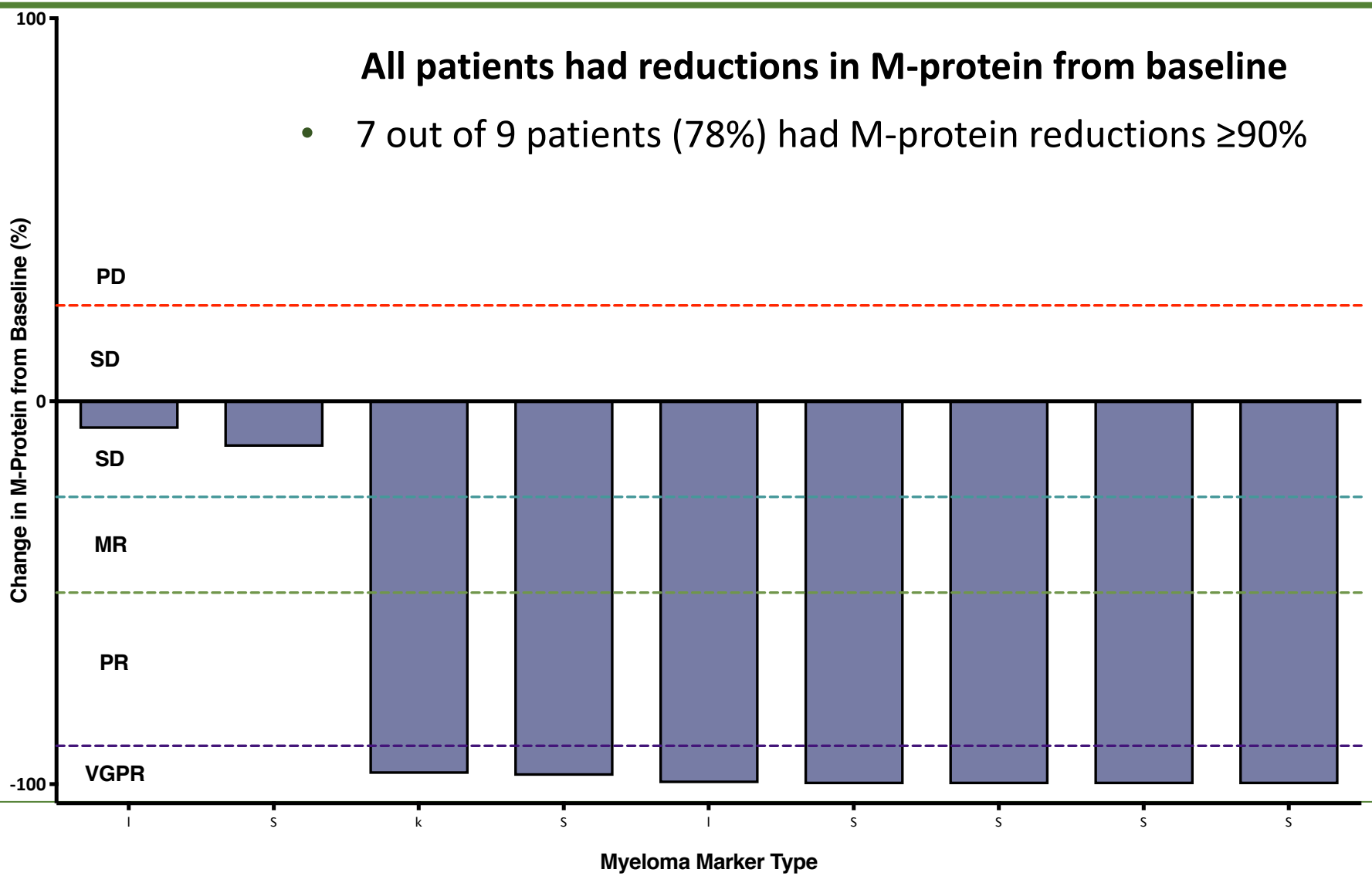
Best Responses† in Evaluable SKd Patients as of May 1, 2019									
Category	**N**	**ORR (%)**	**CBR (%)**	**CR (%)**	**VGPR (%)**	**PR (%)**	**MR (%)**	**SD (%)**	**PD (%)**
All Patients	**9**	**7 (78%)**	**7 (78%)**	**2 (22%)**	**5 (56%)**	--	--	2 (22%)	--

†Responses were adjudicated 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 May 1, 2019 based on interim unaudited data.

SKd Efficacy – M-Protein Effect

All patients had reductions in M-protein from baseline

- 7 out of 9 patients (78%) had M-protein reductions ≥90%



S = Serum M-protein
k = FLC-κ
l = FLC-λ

Summary and Conclusions

Selinexor, once-weekly, plus carfilzomib and low-dose dexamethasone (SKd) is being evaluated in an ongoing phase 1 study in patients with heavily pretreated MM

- **The most common AEs are: nausea, anemia, anorexia, fatigue, and Grade 3/4 thrombocytopenia and leukopenia, which are expected and can be managed with appropriate supportive care and/or dose modifications**
- **Confirmation of the RP2D of SKd is ongoing with once-weekly selinexor 80 mg + carfilzomib 56 mg/m^2**

Although the data are preliminary and based on a small number of patients, the convenient once-weekly combination of SKd rapidly (within 1 cycle) induces deep responses in patients with heavily pretreated MM, including those with disease refractory to bortezomib, lenalidomide, pomalidomide, and/or daratumumab