Selinexor, Pomalidomide, and Dexamethasone (SPd) in Patients with Relapsed or Refractory Multiple Myeloma

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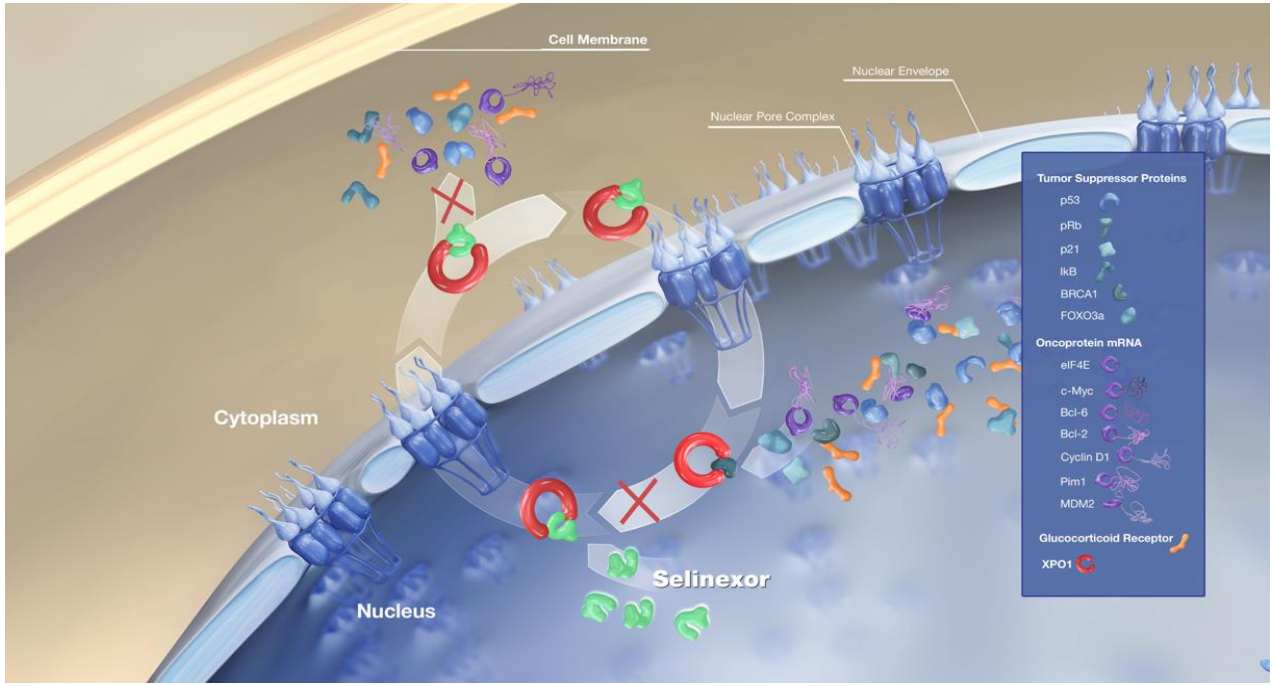
Selinexor Mechanism of Action



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 multiple myeloma (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 and reduces c-Myc levels
- Reactivates GR signaling in combination with dexamethasone (dex)
- Demonstrates synergistic activity in combination with pomalidomide (Pom) and lenalidomide (Len) *in vitro* and *in vivo*

Background / Rationale:
Selinexor and Pomalidomide Activity in RRMM

- Selinexor (+ dexamethasone) received accelerated approval from the FDA for patients with RRMM
- Selinexor demonstrates synergistic activity in combination with pomalidomide *in vivo*[1]
- **All oral combination strategies to improve outcomes are needed**

STORM:
Selinexor + Dexamethasone
Patients with MM refractory to at least one proteasome inhibitor, one immunomodulatory agents, and daratumumab (triple-class refractory)

ORR: 26%
PFS: 3.7 months

MM-003:
Pomalidomide + dexamethasone[2]
Patients ≥ 2 prior MM therapy and refractory to LEN and BORT after ≥ 2 consecutive cycles of each (alone or in combination)

ORR: 21%
PFS: 3.6 months

PFS=progression-free survival, IMiD=immunomodulatory agent, MM=multiple myeloma, ORR=overall response rate, PI=proteasome inhibitor, QD=once daily, QW=once weekly, RRMM=relapsed/refractory multiple myeloma

[1]*Carlson et al., ESH 2014*
[2]*San-Miguel et al. Journal of Clinical Oncology* 31, no. 15_suppl 8510-8510. *2013*
[3]*White et al., IMW 2019*

STOMP Study with Selinexor + Pd

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
- 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 ≥2 cycles of lenalidomide and a proteasome inhibitor (in combination or separately)
- Pomalidomide-exposure is allowed only in escalation phase
- Smoldering MM, non-secretory MM, active plasma cell leukemia are excluded

SPd dose escalation in selinexor once (QW) and twice weekly (BIW) schedule

Selinexor once weekly (QW) + Pd
(28 days each cycle)

Dose Levels	Selinexor	Dexamethasone	Pomalidomide
	Days 1, 8, 15 and 22	Days 1, 8, 15, and 22	Days 1-21
2	100 mg PO	40 mg PO	4 mg PO
1	80 mg PO	40 mg PO	4 mg PO
-1	80 mg PO	40 mg PO	3 mg PO
-2a	60 mg PO	40 mg PO	3 mg PO
-2b	60 mg PO	40 mg PO	4 mg PO
-2c	80 mg PO	40 mg PO	2 mg PO

Selinexor twice weekly (BIW) + Pd
(28 days each cycle)

Dose Levels	Selinexor	Dexamethasone	Pomalidomide
	Days 1, 3, 8, 10, 15, and 17	Days 1, 3, 8, 10, 15, 17, 22, and 24	Days 1-21
2	80 mg PO	20 mg PO	4 mg PO
1	60 mg PO	20 mg PO	4 mg PO
-1	60 mg PO	20 mg PO	3 mg PO
-2	40 mg PO	20 mg PO	3 mg PO

SPd dose escalation scheme: a standard 3 + 3 design was used for dose escalations for both QW and BIW schedules. Dose level 1 was the starting dose for both QW and BIW schedule.

SPd Arm – Patient Characteristics (as of Oct 1, 2019)

SPd patient characteristics	Total (N = 51)
Median age, years (range)	**64 (43 – 85)**
Males (%) : Females (%)	27 (53) : 24 (47)
Median years from diagnosis to SPd treatment, years (range)	**4.8 (1 – 23)**
Median prior regimens (range)	**4 (1–13)**
ISS Stage I : II : III : unknown	15 (29) : 15 (29) : 8 (16) : 13 (25)
Lenalidomide exposed (%) : refractory (%)	51 (100) : 49 (96)
Pomalidomide exposed (%) : refractory (%)	17 (33) : 17 (33)
Bortezomib exposed (%) : refractory (%)	48 (94) : 20 (39)
Carfilzomib exposed (%) : refractory (%)	20 (39) : 14 (27)
Stem cell transplant (%)	39 (76)

SPd Dose Limiting Toxicities (DLT)

Selinexor (mg)	Pomalidomide QD (mg)	Patients DLT evaluable	Patients with DLT	DLT
BIW				
80	4	4	0	
60	4	6	1	G3 fatigue
60	3	6	1	G3 febrile neutropenia
QW				
100	4	3	0	
80	4	6	2	G3 febrile neutropenia; G4 neutropenia
80	3	6	2	Pomalidomide dose reduction for G2 neutropenia/G3 thrombocytopenia; G3 febrile neutropenia
80	2	6	1	G3 febrile neutropenia
60	4	6	1	Selinexor dose holds for G3 anemia/G4 thrombocytopenia

BIW, twice-weekly; DLT, dose limiting toxicity; QD, once-daily; QW, once-weekly.

SPd Efficacy:
ORR of 56% in Pom Naïve / Len Refractory MM ORR

Best responses* in evaluable patients treated with SPd as of October 1, 2019									
Patient population	**N†**	**ORR (%)**	**CBR (%)**	**CR (%)**	**VGPR‡ (%)**	**PR‡ (%)**	**MR‡ (%)**	**SD (%)**	**‡PD (%)**
All	46	**23 (50)**	**34 (74)**	--	7 (15)	16 (35)	11 (24)	11 (24)	1 (2)
Pomalidomide-naïve	32	**18 (56)**	**25 (78)**	--	6 (19)	12 (38)	7 (22)	6 (19)	1 (3)
Pomalidomide-exposed	14	**5 (36)**	**9 (64)**	--	1 (7)	4 (29)	4 (29)	5 (36)	--

*Responses were adjudicated according to the International Myeloma Working Group criteria. †Five patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, one withdrawal of consent before disease follow up, one death related to PD, one PD before C2D1. ‡One unconfirmed VGPR, two unconfirmed MR, one unconfirmed PD.
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, 2019 based on interim unaudited data.

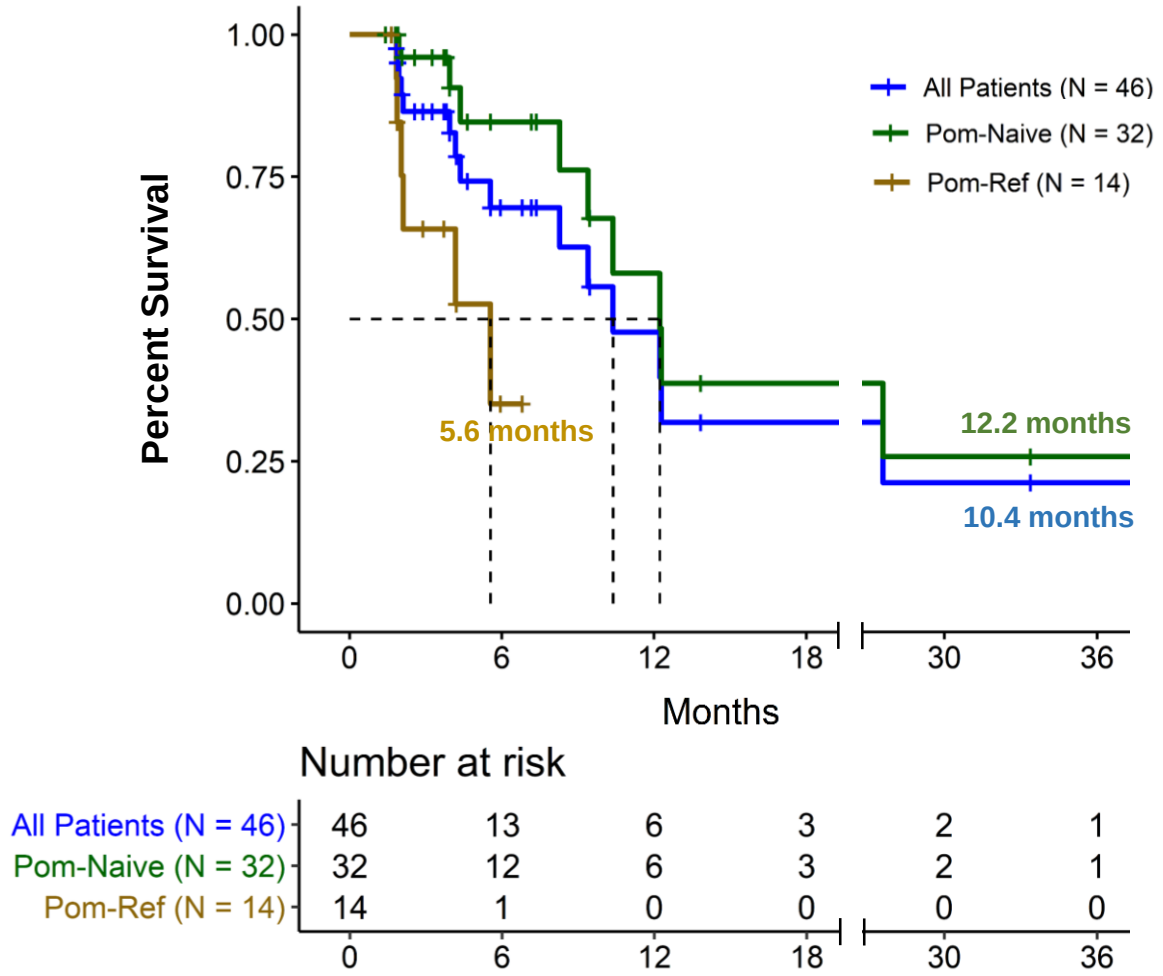
Selinexor QW + Pom/dex Treatment-Related Adverse Events
(≥20% Patients)

AE	60/80/100 selinexor QW + 2/3/4 mg pomalidomide QD			
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=33)**
Neutropenia (%)	3 (9%)	7 (21%)	12 (36%)	22 (67%)
Thrombocytopenia	8 (24%)	7 (21%)	2 (6%)	17 (52%)
Anemia	6 (18%)	9 (27%)	--	15 (45%)
Leukopenia	7 (21%)	3 (9%)	2 (6%)	12 (36%)
Gastrointestinal				
Nausea	17 (52%)	--	--	17 (52%)
Anorexia	12 (36%)	--	--	12 (36%)
Vomiting	9 (27%)	--	--	9 (27%)
Diarrhea	8 (24%)	--	--	8 (24%)
Constitutional				
Fatigue	14 (42%)	3 (9%)	--	17 (52%)
Weight loss	13 (39%)	--	--	13 (39%)
Dizziness	6 (18%)	--	--	6 (18%)
Other				
Hyponatremia	3 (9%)	3 (9%)	1 (3%)	7 (21%)

3 G5 events: Intracranial hemorrhage in cycle 2; Febrile Neutropenia in cycle 1; Pneumonia in cycle 5

Treatment-Related Adverse Events as of October 1, 2019

SPd Progression Free Survival of 12.2 months in Pom Naïve Len refractory MM



Median PFS among evaluable patients was **10.4** months. Median PFS in Pom-naïve and Len-refractory or relapsed MM was **12.2** months (versus ~4 months expected for the standard Pd regimen).

SPd-Related AEs are comparable between Selinexor 60 mg/Pom 4 mg and Selinexor 80 mg/Pom 2 mg

AE term	80 mg selinexor QW + 2 mg pomalidomide QD				60 mg selinexor QW + 4 mg pomalidomide QD			
Hematologic	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=10)**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Total (N=6)**
Neutropenia	--	2 (20.0)	3 (30.0)	5 (50.0)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)
Thrombocytopenia	--	2 (20.0)	1 (10.0)	3 (30.0)	1 (16.7)	2 (33.3)	--	3 (50.0)
Anemia	--	3 (30.0)	--	3 (30.0)	1 (16.7)	2 (33.3)	--	3 (50.0)
Gastrointestinal								
Nausea	9 (90.0)	--	--	9 (90.0)	3 (50.0)	--	--	3 (50.0)
Anorexia	3 (30.0)	--	--	3 (30.0)	1 (16.7)	--	--	1 (16.7)
Diarrhea	2 (20.0)	--	--	2 (20.0)	2 (33.3)	--	--	2 (33.3)
Vomiting	3 (30.0)	--	--	3 (30.0)	1 (16.7)	--	--	1 (16.7)
Constitutional								
Fatigue	5 (50.0)	1 (10.0)	--	6 (60.0)	4 (66.7)	--	--	4 (66.7)
Weight loss	6 (60.0)	--	--	6 (60.0)	1 (16.7)	--	--	1 (16.7)
Other								
Insomnia	2 (20.0)	--	--	2 (20.0)	2 (33.3)	--	--	2 (33.3)

Better Responses with Selinexor 60 mg QW + Pomalidomide 4 mg + Dex

Best responses in evaluable patients treated with SPd as of October 1, 2019								
Dose Levels	Group	N	**ORR (%)**	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)
Selinexor 80 mg QW + Pom 2 mg QD + Dex 40 mg QW	All	10	**4 (40)**	7 (70)	--	2 (20)	2 (20)	3 (30)
	Pom-naïve	5	**3 (60)**	4 (80)	--	2 (40)	1 (20)	1 (20)
Selinexor 60 mg QW + Pom 4 mg QD + Dex 40 mg QW	All	6	**5 (83)**	6 (100)	--	1 (17)	4 (67)	1 (17)
	Pom-naïve	5	**4 (80)**	5 (100)	--	1 (20)	3 (60)	1 (20)

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. Responses as of October 1, 2019 based on interim unaudited data.

Summary and Conclusions

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

- **RP2D is selinexor 60 mg QW (pomalidomide 4 mg QD + dexamethasone 40 mg QW)**
- The most common AEs were**: nausea, anorexia, fatigue, neutropenia, anemia, thrombocytopenia**
  - **E**xpected and can be managed with appropriate supportive care and/or dose modifications

The all oral SPd combination is very active and produces responses which are durable

- **ORR 56%** in lenalidomide refractory, pomalidomide-naïve patients (compared to expected ORR ≤30% for pomalidomide + dexamethasone)[1] and 19% of patients achieved VGPR
- **CBR was 74% across all patients, and 78% in pomalidomide-naïve patients**

Phase 3 study with this novel combination of SPd; XPORT-MM-032 is in a planning phase

[1] Pomalyst Package Insert; Initial US Approval 2013; Celgene Corporation

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- Vancouver General Hospital, Vancouver, BC, Canada
- Swedish Cancer Institute, Seattle, WA
- Royal Victoria Hospital, Montreal, QC, Canada
- Hopital Maisonneuve-Rosemont, Montreal, QC, Canada
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