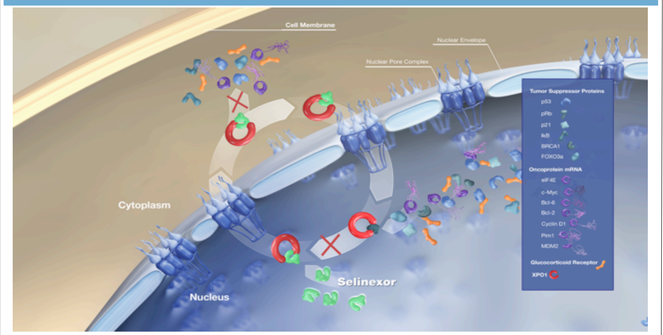
Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Newly Diagnosed Multiple Myeloma

Abstract #3165

Darrell J White[1], Suzanne Lentzsch[2], Cristina Gasparetto[3], Nizar Bahlis[4], Christine I Chen[5], Brea C. Lipe[6], Gary J. Schiller[7], Sascha A Tuchman[8], Heather J. Sutherland[9], Rami Kotb[10], Richard Leblanc[11], Michael Sebag[12], Christopher P Venner[13], Natalie Scott Callander[14], William I. Bensinger[15], Heidi Sheehan[16], Yi Chai[16], Kazuharu Kai[16], Jatin Shah[16], Sharon Shacham[16], Michael G. Kauffman[16], Muhamed Baljevic[17]

(1) Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada (2) Colombia University, New York (3) Duke Univ. Medical Center, Durham, NC (4) Southern Alberta Cancer Research Institute, Calgary, AB, Canada (5) Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; 6University of Rochester Medical College, Rochester, NY (7) David Geffen School of Medicine at UCLA, Los Angeles, CA (8) University of North Carolina, Chapel Hill, NC (9) Vancouver General Hospital, Vancouver, BC, Canada (10) Cancer Care Manitoba, Winnipeg, MB, Canada (11) Hopital Maisonneuve-Rosemont, Montreal, QC, Canada (12) Royal Victoria Hospital, Montreal, QC, Canada (13) Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada (14) Carbone Cancer Center, University of Wisconsin- Madison, Madison, WI (15) Myeloma and Transplant Program, Swedish Cancer Institute, Seattle, WA (16) Karyopharm Therapeutics, Newton, MA (17) University of Nebraska Medical Center, Omaha, NE

Selinexor Mechanism of Action



- **Exportin 1 (XPO1)** is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor, 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 a first-in-class 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)

Background and Rationale

- Selinexor (+dexamethasone) received accelerated approval from the FDA for patients with RRMM[1]
- Selinexor demonstrates synergistic activity in combination with lenalidomide *in vivo*
- In MM-009 study, lenalidomide 25 mg (Day1-21)+ dexamethasone 40 mg Days 1-4 achieve 61% ORR in MM patients who received ≥1 prior anti-MM therapy but not lenalidomide (or lenalidomide-naïve)[2]
- In STOMP study, SRd; Selinexor 60 mg twice weekly (BIW) or 80/60 mg once weekly (QW) + lenalidomide 25 mg (Day 1-21) + dexamethasone 40 QW achieved 60% ORR in relapse/refractory (RR) MM patients who received ≥1 prior anti-MM therapy. In lenalidomide-naïve MM patients, SRd achieved 92% ORR[3].

Hypothesis: Selinexor + Lenalidomide + Dexamethasone (SRd) is tolerable and derives promising responses in patients with newly diagnosed multiple myeloma (NDMM)

STOMP Study with SRd NDMM
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
  - Newly diagnosed multiple myeloma (NDMM)
  - Smoldering MM, non-secretory MM, active plasma cell leukemia are excluded

Investigation of SRd NDMM doses

SRd NDMM Dose Schedule

- Selinexor 40, 60, or 80 mg QW (Day 1, 8, 15, and 22)
- Dexamethasone 40 mg QW (Day 1, 8, 15, and 22)
- Lenalidomide 25 mg (Day 1-21)

28 days per cycle

Dose Levels	Selinexor	Dexamethasone	Lenalidomide
	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22	Days 1-21
2	80 mg	40 mg	25 mg
1	60 mg	40 mg	25 mg
-1	40 mg	40 mg	25 mg

SRd NDMM dose escalation scheme: a standard 3 + 3 design is used for dose escalations. Starting dose was dose level 1.

Patient Characteristics in SRd NDMM

Patient characteristics	N
Enrolled as of October 1, 2019 (enrollment ongoing)	
60 mg selinexor QW + 25 mg lenalidomide QD (Day 1–21) + dex 25 mg QW	8
Median age, years (range)	74 (51 – 86)*
Males : females	4 (50%) : 4 (50%)
ECOG Performance Status, 0 : 1 : 2	1 (13%) : 6 (75%) : 1 (13%)
Median time from diagnosis to SRd Treatment, years (range)	0.2 (0 – 6)
ISS Stage at initial diagnosis	
I	2 (25%)
II	4 (50%)
III	0
Unknown	2 (25%)
United States : Canada	4 (50%) : 4 (50%)
Race, white : other	7 (87.5) : 1 (12.5)

*median age of patients in SRd RRMM (N=24) was 67 (49 - 84) (White *et al.* presented at EHA 2019)

ISS=International Staging System, QD=once daily, QW=once weekly, RRMM=relapsed/refractory multiple myeloma; SRd=selinexor-lenalidomide-dexamethasone

SRd NDMM Dose-Limiting Toxicity (DLT)

- **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
  - Grade 3 nausea, vomiting, dehydration, diarrhea or fatigue lasting >3 days despite optimal supportive medications
  - Grade 4 neutropenia lasting >7 days or Grade ≥3 thrombocytopenia with clinically significant bleeding, petechiae or purpura

Selinexor Dose	Lenalidomide (Day 1-21)	Patients Enrolled	Patients DLT-evaluable	Patients with DLT	Dose Limiting Toxicity
80 mg QW	25 mg	0	0	0	NA
*60 mg QW	25 mg	8	5	0	NA
40 mg QW	25 mg	0	0	0	NA

*Enrollment is ongoing in the once-weekly selinexor 60 mg + lenalidomide 25 mg (Day 1-21) + dexamethasone 40 mg QW cohort. Three patients were not DLT evaluable; 1 did not finish cycle 1 due to social reasons and 2 missed doses during cycle 1 due to SAEs unrelated to study drugs.

SRd NDMM Treatment-Emergent Adverse Events in ≥25% Patients

AE term	Selinexor 60 mg QW + lenalidomide 25 mg QD + dexamethasone 40 mg QW Grade 1/2	Grade 3	Grade 4	Total (N=8)
Hematologic				
Neutropenia (%)	**1 (12.5)**	**5 (62.5)**	**1 (12.5)**	**7 (87.5)**
Anemia	1 (12.5)	4 (50.0)	--	**5 (62.5)**
Thrombocytopenia	1 (12.5)	2 (25.0)	--	**3 (37.5)**
Gastrointestinal				
Diarrhea	5 (62.5)	--	--	5 (62.5)
Nausea	**4 (50.0)**	**--**	**--**	**4 (50.0)**
Constipation	2 (25.0)	1 (12.5)	--	3 (37.5)
Abdominal pain	2 (25.0)	--	--	2 (25.0)
Asthenia	2 (25.0)	--	--	2 (25.0)
Constitutional				
Fatigue	**--**	**3 (37.5)**	**--**	**3 (37.5)**
Weight loss	**5 (62.5)**	**--**	**--**	**5 (62.5)**
Other				
Hypokalemia	3 (37.5)	--	--	3 (37.5)
Insomnia	2 (25.0)	1 (12.5)	--	3 (37.5)
Back pain	1 (12.5)	1 (12.5)	--	2 (25.0)
Dizziness	2 (25.0)	--	--	2 (25.0)
Hypomagnesemia	2 (25.0)	--	--	2 (25.0)
Hyponatremia	1 (12.5)	1 (12.5)	--	2 (25.0)
Hypotension	1 (12.5)	1 (12.5)	--	2 (25.0)
Lung infection	**1 (12.5)**	**1 (12.5)**	**--**	**2 (25.0)**
Muscle spasms	2 (25.0)	--	--	2 (25.0)
Syncope	1 (12.5)	1 (12.5)	--	2 (25.0)
Urinary tract infection	**1 (12.5)**	**1 (12.5)**	**--**	**2 (25.0)**

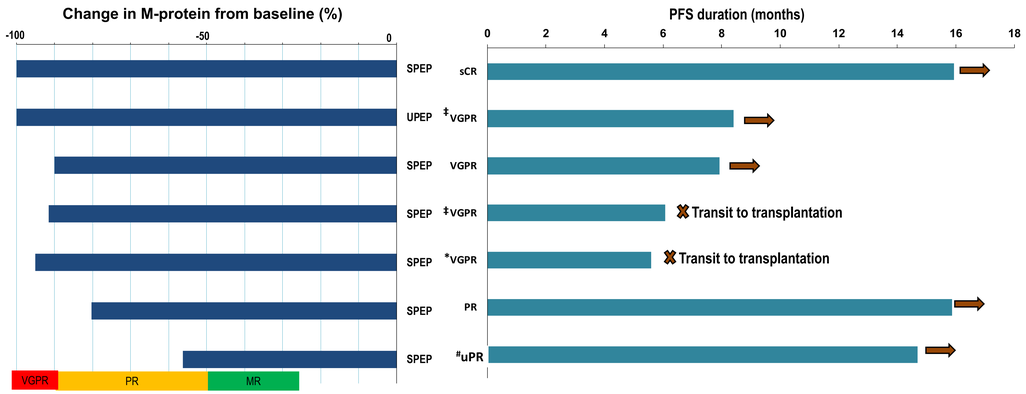
- No treatment-related Grade 5 events were reported

SRd NDMM Efficacy

Best responses in evaluable SRd NDMM patients as of October 1, 2019

Efficacy Endpoints	N*	ORR (%)	CBR (%)	CR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)
Efficacy Evaluable Patients	**7**	**6 (86)**	**7 (100)**	**1 (14%)**	**4‡ (57%)**	**1 (14)**	**1 (14%)**	**0**	**0**

Responses were adjudicated according to the *International Myeloma Working Group* criteria.*One patient was not evaluable for response due to withdrawn consent prior to disease follow-up. ORR=sCR+VGPR+PR, CBR=ORR+MR. Responses as of October 1, 2019 based on interim unaudited data. ‡one VGPR was confirmed on Oct 10, 2019 (after data cut); two VGPR are unconfirmed



Responses were adjudicated according to the *International Myeloma Working Group* criteria, One patient not evaluable for response due to withdrew consent prior to disease follow-up. Responses as of October 1, 2019 based on interim unaudited data. *One VGPR was confirmed on Oct 10, 2019. ‡There two VGPR were unconfirmed. # unconfirmed PR, this assessment was downregulated to MR for ORR estimation, MR=minimal response, PFS=progression-free survival, PR=partial response, sCR=stringent complete remission, SPEP=serum protein electrophoresis, SRd=selinexor-lenalidomide-dexamethasone, UPEP=urine protein electrophoresis, VGPR=very good partial response

Conclusions – Safety & Efficacy

- Selinexor is the first-in-class XPO1 inhibitor now approved for RRMM
- The RP2D is selinexor 60 mg QW, lenalidomide 25 mg QD, and dexamethasone 40 mg QW in patients with NDMM
- No new safety signals were observed; the AE profile was consistent with that seen for selinexor and lenalidomide
- The most common Grade ≥3 AEs were neutropenia, anemia, and fatigue
- Responses seen in 6/7 patients and are able to maintain on long term therapy
- All oral combination of selinexor-lenalidomide-dexamethasone appears to be active and well-tolerate
- Two patients, initially deemed as transplant-ineligible, transited to stem cell transplant
- Further investigation for NDMM patients, who are transplant-ineligible, is warranted

References

1. Food and Drug Administration. Selinexor Prescribing Information 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212306s000lbl.pdf [accessed 6 Nov 2019]. 2. Dimopoulos M, et al. N Engl J Med 2007;357:2123–32. 3. Dimopoulos MA, et al. Haematologica 2018;103(12):2088–96. 4. White D, et al. 17th International Myeloma Workshop September 12–15, 2019. Boston, MA, USA. Abstract OAB-083
2. Weber DM *et al.* N Engl J Med. 2007 Nov 22;357(21):2133-42. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.
3. White D *et al.* International Myeloma Workshpt (IMW) 2019, Boston MA OAB-083: Safety and Efficacy of the Combination of Selinexor, Lenalidomide and Dexamethasone (SRd) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM).

Acknowledgments

Patients, their families, and caregivers, investigators, co-investigators, and study teams at each participating center

This study was supported by Karyopharm Therapeutics.

QD=once-daily, QW=once-weekly, SRd=selinexor-lenalidomide-dexamethasone, NDMM=newly diagnosed multiple myeloma