Selinexor, Daratumumab, and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (MM)

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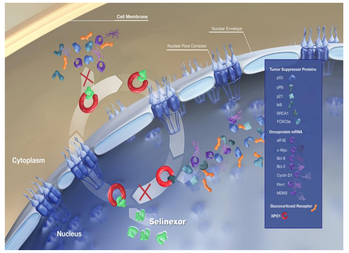
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)



Exportin 1 (XPO1) is a critical nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO3a) [1-3]
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, 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 supports that selinexor:

- Reactivates multiple TSPs by preventing nuclear export[1,2,6]
- Inhibits oncoprotein translation[1,2,6]
- Reactivates GR signaling in presence of dexamethasone[7]
- **Enhances daratumumab activity *ex-vivo* against myeloma cells**[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]Gasparetto et al., Blood. 2017

Background: Daratumumab and Selinexor Activity in Heavily-Treated MM

Daratumumab and Selinexor Single Agent Activity in Heavily-Treated MM

SIRIUS: Daratumumab [9]Refractory to PI and IMiD

ORR: 29.2% (Overall) **ORR: 21.2%** (Quad-Ref) **DOR: 7.4 months** (Overall) **PFS: 3.7 months** (Overall)

STORM: Selinexor + Dexamethasone[10]Refractory to Dara, PI, and IMiD

ORR: 26.2% **ORR: 25.3%** (Penta-Ref) **DOR: 4.4 months** (Overall) **PFS: 3.7 months** (Overall)

[9]Lonial S, et al. Lancet. 2016; [10]Chari A, et al. N Engl J Med. 2019.

STOMP SDd Arm Study Design

Objective:

- Maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) ORR, PFS, and duration of response (DOR)

Patient Populations:

- Patients who received ≥3 prior lines of therapy for MM, including a PI and an IMiD Or patients with MM refractory to both a PI and an IMiD

Patient Characteristics and DLTs

Enrolled as of January 2, 2020 **60 mg selinexor BIW + 16 mg/kg daratumumab QW** **100 mg selinexor QW + 16 mg/kg daratumumab QW (RP2D)**	**34** **3** **31**
Median Age, Years (range)	**68** (44 – 83)
Males : Females	**19** (56%) : **15** (44%)
Median Time from Diagnosis to SDd Treatment, Years (range)	5.6 (<1 – 14)
Median Prior Regimens (range) Proteasome Inhibitor (Treated: Refractory) Immunomodulatory Drug (Treated: Refractory) Quad exposed* Autologous Stem Cell Transplant Daratumumab Treated	**3 (2–10)** 34 (100%) : 29 (85%) 34 (100%) : 26 (76%) 8 (23.5%) 25 (73.5%) 2 (6%)

*patients pre-treated with bortezomib, carfilzomib, lenalidomide, and pomalidomide

Dose Level	Treatment Regimen	Patients Enrolled (# of Patients with DLT)	Dose-Limiting Toxicity (DLT)
0	Selinexor, oral 60 mg (Days 1, 3) Twice Weekly Daratumumab per label, Dexamethasone, oral 20 mg BIW Twice Weekly	3 (2)	Grade 2 fatigue and Grade 3 thrombocytopenia (both requiring reduction to 100 mg QW selinexor)
-1	Selinexor, oral 100 mg Once Weekly. Daratumumab and Dexamethasone per label	6 (0)	No DLTs were reported in the 100 mg QW cohort

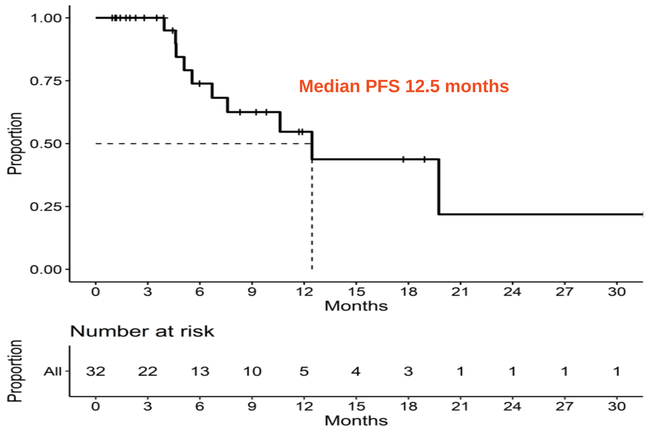
Treatment-Related Adverse Events in ≥10% Patients (RP2D Patients)

AE Term	Number of Patients (Percent of Patients)			
	Grade 1/2	Grade 3	Grade 4	Total (N=34)
Hematologic				
Thrombocytopenia	8 (23.5)	10 (29.4)	6 (17.6)	**24 (70.6)**
Anemia	10 (29.4)	11 (32.4)	--	**21 (61.8)**
Neutropenia	8 (23.5)	9 (26.5)	--	**17 (50.0)**
Leukopenia	5 (14.7)	11 (32.4)	--	**16 (47.1)**
Lymphopenia	1 (2.9)	5 (14.7)	1 (2.9)	**7 (20.6)**
Gastrointestinal				
Nausea	21 (61.8)	3 (8.8)	--	**24 (70.6)**
Dysgeusia	14 (41.2)	--	--	**14 (41.2)**
Anorexia	12 (35.3)	--	--	**12 (35.3)**
Diarrhea	11 (32.4)	1 (2.9)	--	**12 (35.3)**
Constipation	10 (29.4)	--	--	**10 (29.4)**
Vomiting	9 (26.5)	1 (2.9)	--	**10 (29.4)**
Constitutional				
Fatigue	15 (44.1)	6 (17.6)	--	**21 (61.8)**
Weight Loss	7 (20.6)	1 (2.9)	--	**8 (23.5)**
Dizziness	6 (17.6)	--	--	**6 (17.6)**
Other				
Hyponatremia	7 (20.6)	4 (11.8)	--	**11 (32.4)**
Insomnia	10 (29.4)	--	--	**10 (29.4)**
Blurred Vision	10 (29.4)	--	--	**10 (29.4)**
Hyperglycemia	5 (14.7)	1 (2.9)	--	**6 (17.6)**
Dyspnoea	5 (14.7)			**5 (14.7)**
Infusion Related Reaction	3 (8.8)	1 (2.9)	--	**4 (11.8)**

Safety data cutoff of January 2, 2020

- No treatment-related AE or SAE leading to death were reported
- Nine patients had at least one serious adverse event (SAE). SAEs were as follows: two rhinovirus infection (5.9% of patients), two thrombocytopenia (5.9%), two pneumonia (5.9%), one acute kidney injury (2.9%), one diarrhea (2.9%), one fatigue (2.9%), one hypokalemia (2.9%), one infusion related reaction (2.9%), one nausea (2.9%), one vomiting (2.9%).
- All non-hematological AEs were Grade 1 or 2 and reversible with or without supportive care
- Hematological AEs including thrombocytopenia were manageable by dose interruptions/reduction with or without supportive care

Figure 1: Progression Free Survival

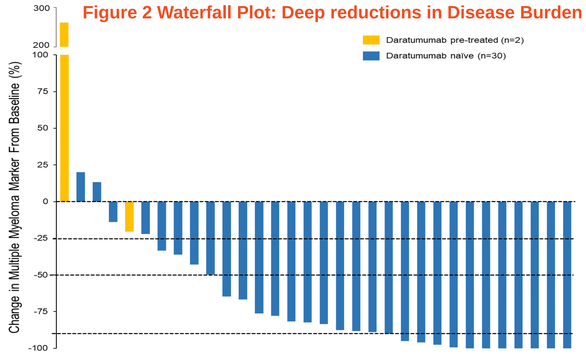


Selinexor-Daratumumab-Dex: Efficacy

Category	N*	ORR (%)	VGPR (%)	PR‡ (%)	CBR (%)	MR‡ (%)	SD (%)	PD (%)
All	32	**22 (69%)**	**11 (34%)**	**11 (34%)**	26 (81%)	4 (13%)	5 (16%)	1 (3%)
Daratumumab Naïve	**30**	**22 (73%)**	**11 (37%)**	**11 (37%)**	**26 (87%)**	4 (13%)	4 (13%)	--
RP2D	29	**20 (69%)**	**9 (31%)**	**11 (38%)**	24 (83%)	4 (14%)	4 (14%)	1 (3%)

Note. Responses were investigator reported according to the International Myeloma Working Group criteria. *Two patients withdrew consent prior to disease follow-up and were, therefore, not included in the analysis of response. †Out of 11 PRs, 1 PR was unconfirmed. ‡ Out of 4 MRs, 1 MR was unconfirmed.
Out of 7 quad-exposed (efficacy evaluable) patients, 4 patients (ORR of 57.1%) achieved ≥PR and 6 achieved ≥ MR (CBR of 85.7%).
Abbreviations: CBR, clinical benefit rate; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
Responses as of **January 2, 2020** based on interim unaudited data.

Figure 2 Waterfall Plot: Deep reductions in Disease Burden (n=32)



Key Results and Conclusion

Once Weekly Selinexor with Daratumumab/Dexamethasone is Highly Active, Produces Deep and Durable Responses in Patients with RRMM Who Were Heavily Pretreated

- RP2D was established as selinexor 100 mg once weekly (QW), daratumumab 16 mg/kg (per label), dexamethasone 40 mg QW
- **ORR and CBR were 73% and 87%** respectively in daratumumab-naïve patients
- Median progression-free survival was 12.5 months in all patients who had median of 3 prior therapies
- Common treatment-related AEs with SDd were thrombocytopenia, anemia, neutropenia, nausea, dysgeusia, anorexia, and fatigue

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