Abstract #1854

Selinexor-Containing Regimens for the Treatment of Patients with Multiple Myeloma Refractory to Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

Ajai Chari[1], Dan T. Vogl[2], Sundar Jagannath[1], Jagoda K. Jasielec[3], Andrew DeCastro[4], TJ Unger[4], Jatin Shah[4], and Andrzej Jakubowiak[3]

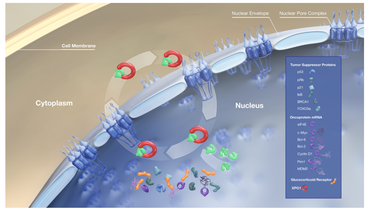
(1) Ichan School of Medicine at Mount Sinai, New York, NY; (2) Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; (3) University of Chicago Medicine, Chicago, IL; (4) Karyopharm Therapeutics Inc, Newton MA

Introduction

- Chimeric antigen receptor T-cell (CAR-T) therapy can induce responses in patients with heavily-pretreated multiple myeloma (MM), with median progression-free or event-free survival ranging between 7-12 months.[1]
- Unfortunately, CAR-T cell therapy is non-curative and all patients will relapse.
- Currently, there is minimal published data and no consensus on therapies after progression on CAR-T.

Selinexor – FDA approved for relapse/refractory multiple myeloma (July 2019)

- Selinexor is an oral, small-molecule inhibitor of the nuclear export protein exportin 1 (XPO1) that induces accumulation of tumor suppressor proteins in the nucleus, reductions in several oncoproteins, cell cycle arrest, and apoptosis of cancer cells.
- XPO1 is the most well characterized nuclear export protein and mediates export of tumor suppressor proteins (TSP) and many growth regulatory proteins.
- XPO1 is overexpressed in many cancers, including MM, and elevated levels are correlated with poor prognosis, increased bone lytic lesions, and resistance to therapy.



Selinexor in combination with dexamethasone (Sd) showed a 26.2% overall response rate (ORR) in the 122 patients with penta-exposed triple-class refractory multiple myeloma enrolled in STORM Part 2 (*Chari A et al., NEJM, 2019*)[2]

- Here, we report on observations of the activity of Sd alone or administered as a triplet in combination with bortezomib (SVd) or carfilzomib (SKd) in patients with MM whose disease has progressed after CAR-T therapy.

Methods

We identified 7 patients who had received lymphodepleting conditioning (fludarabine/cyclophosphamide, n=6; cyclophosphamide, n=1), followed by an effective dose of CAR-T cell therapy (>10^8 CAR-positive cell targeting B-cell maturation antigen for MM prior to being enrolled in a trial using a selinexor-containing regimen.

Selinexor Treatment of Refractory Myeloma

- STORM study (NCT02336815) – Selinexor (starting at 80 mg twice-weekly Days 1 and 3) plus dexamethasone (20 mg twice-weekly, Days 1 and 3); (n=1)
- Compassionate use program – Selinexor (100 mg once-weekly) plus bortezomib (1.3 mg/m^2 once-weekly for 4 of 5 weeks) and dexamethasone (40 mg once-weekly); (n=1)
- NCT02199665 trial – Selinexor (100 mg once-weekly) plus carfilzomib (20/56 mg/m^2 or 20/70 mg/m^2) and dexamethasone (40 mg once-weekly or 20 mg twice-weekly); (n=5)

Results

Table 1. Baseline Demographics

	Patient						
	1	2	3	4	5	6	7
Age	66	70	62	35	62	67	64
Sex	F	F	M	M	M	F	F
Ethnic Origin	White	White	White	White	White	White	White
ECOG Performance Status	1	0	1	1	1	1	1
ISS Staging at Diagnosis	III	II	I	II	I	II	Unknown
Time from Initial Diagnosis (Years)	6.3	15.9	9.8	8.9	10.0	4.8	8.0
Cytogenetics	t(14;16)	Gain (1q21), trisomy 3, 7, 9 plus IGH translocation	t(4; 14)	Hyperdiploidy with +1q and trisomy 9, 11, 15	t(4;14)	+1q, t(4;14), del 13	Complex hyperdiploid karyotype with del 1p
Extramedullary Plasmacytomas ≥ 1	No	Yes (2 sites)	No	Yes (2 sites)	Yes (2 sites)	Yes (3 sites)	Yes (1 site)
LDH at Baseline (U/L)	202	161	176	186	205	245	225
Prior Therapeutic Regimens (N)	10	15	7	5	11	6	12
Exposed/Refractory							
Bortezomib	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/No	Yes/Yes
Carfilzomib	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Lenalidomide	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No
Pomalidomide	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/Yes	Yes/No
Daratumumab	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/No	Yes/Yes	Yes/Yes
Elotuzumab	Yes/Yes	Yes/Yes	No/No	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Panobinostat	No/No	No/No	No/No	No/No	Yes/Yes	No/No	No/No
Anti-PD1/Anti-PDL1	Yes/Yes	No/No	Yes/Yes	No/No	No/No	No/No	No/No
Prior ASCT (#)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (2X)	Yes (1x)	Yes (3x)
CAR-T Best Response and Time to Progression (Months)	VGPR (4)	SD (4)	PR (7)	VGPR (5)	PR (3)	SD (2)	SD (1)
Selinexor Regimen	Sd	SKd	SKd	SKd	SKd	SKd	SVd
Increase in MM Marker from Screening to C1D1	23% (8 days)	91% (22 days)	48% (18 days)	51% (7 days)	17% (18 days)	0% (14 days)	21% (14 days)

ASCT, Allogeneic Stem Cell Transplant; CAR-T, Chimeric Antigen Receptor T-cell Therapy; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; LDH, Lactate Dehydrogenase; Sd, Selinexor and Dexamethasone; SKd, Selinexor, Carfilzomib, and Dexamethasone; SVd, Selinexor, Bortezomib, and Dexamethasone.

Refractory is defined as <25% decrease in M-protein while on therapy, or progression within 60 days of completing therapy.

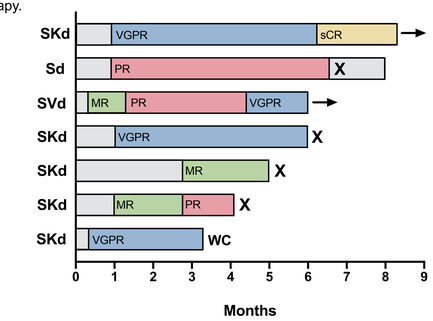
Time to progression is defined as the day the patient received CAR-T therapy until the day of documented disease progression.

Table 2. Efficacy of Selinexor-Containing Regimens Post CAR-T Therapy

Patient	Treatment Regimen	Best Response on Selinexor Regimen	Time to Response (≥ PR) (months)	Time on Study (months)	Duration of Response (≥ PR) (months)	Off Study Reason	Therapy After Selinexor Regimen
1	Sd	PR	0.9	8.0	5.6	Progressive Disease	TAK573
2	SKd	PR	2.7	4.1	1.4	Progressive Disease	Not Started
3	SKd	sCR	0.9	8.3+	7.4+	Ongoing	-
4	SKd	VGPR	1.0	6.0	5.0	Progressive Disease	CC220 + Carfilzomib
5	SKd	MR	-	5.0	-	Progressive Disease	DCEP
6	SKd	VGPR	0.3	3.7	3.4	WC	BET inhibitor
7	SVd	VGPR	1.4	6.0+	4.6+	Ongoing	-

DCEP, Dexamethasone, Cyclophosphamide, Etoposide, Cisplatin; MR, minimal response; PR, partial response; sCR, Stringent complete response; VGPR, very good partial response; WC, withdrawal of consent due to decreased quality of life; + indicates the patient is continuing therapy.

Figure 1. Swim Lane Plot of Time on Study
Grey indicates time on study without a known response per IMWG criteria. X, disease progression; arrow indicates patient continuing on therapy.



Conclusions

- **This is the first data set demonstrating anti-myeloma activity of a selinexor-based regimen in patients who have progressed after CAR-T therapy.**
- **The novel mechanism support selinexor-based combinations can be effective therapeutic options for the treatment of RRMM including MM that has progressed after CAR-T therapy and warrant further investigation.**
- **Selinexor-based combination regimens are treatment options that offer therapeutic benefit and should be considered in patients with relapsed myeloma including post-CAR-T cell therapy; this is increasingly important with the rising number of patients treated with such therapy and the earlier use of CAR-T cell therapy.**

References

[1]Cho S-F, Anderson KC, Tai Y-T. BCMA CAR T-cell therapy arrives for multiple myeloma: a reality. Ann Transl Med. 2018;6(Suppl 2):S93–S93.

[2]Chari, A. et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *N Engl J Med*. 2019 Aug 22;381(8):727-738.

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