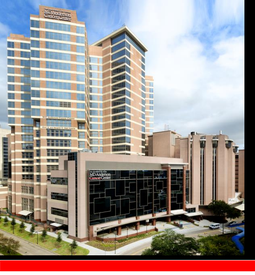

Phase IB Study to Evaluate the Safety of Selinexor (KPT-330) in Combination with Pembrolizumab in Patients with Advanced Malignancies- the Melanoma Experience (NCT02419495)

Isabella C. Glitza Oliva[1], Sapna Patel[1], Abdulrazzak Zarifa[2], Cheuk Hong Leung[3], Heather Lin[3], Lacey McQuinn[2], Jing Gong[2], Bulent Yilmaz[2], Julie Chambers[2], Selma Sulovic[2], Ida John[1], Tarin Hennegan[1], Siqing Fu[2], Apostolia M. Tsimberidou[2], Filip Janku[2], Daniel D. Karp[2], Funda Meric-Bernstam[2], Aung Naing[2]

[1]Melanoma Medical Oncology, [2]Investigational Cancer Therapeutics, [3]Biostatistics

The University of Texas MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Background

•The introduction of checkpoint inhibitors (CPI) into the clinic has revolutionized the treatment options for cancer patients among different tumor types. In melanoma, single agent anti-PD1 therapy leads to response rates of up to 40% in treatment naïve melanoma patients with unresectable stage III or IV disease. Combining anti-PD1 with anti-CTLA-4 leads to upfront response rates of 58%, however, at a price of significant toxicities, with 59% of patients experiencing grade 3 or 4 toxicities, which is in stark contrast to the ~10% of grade 3 or 4 toxicities observed with single agent anti-PD1.
•Despite these success, multiple areas of unmet need exist. For treatment naïve patients, combination of anit-PD1 with a different agent that leads to similar response rates like the combo of anit-PD1/TLA-4, but with significant grade 3 or 4 toxicities would represent a attractive options for patients, potentially especially for patients who would not be able to tolerate this combination. Furthermore, it is currently unclear how to best salvage patients who progress on either single PD-1 or anti-PD1/CTLA-4 combo. Finally, patients with uveal melanoma (UM) have very limited treatment options, as prior trials have not shown encouraging overall outcomes.
•Selinexor is a selective inhibitor of nuclear export used as an anti-cancer drug. It works by binding to exportin 1 and thus blocking the transport of several proteins involved in cancer-cell growth from the cell nucleus to the cytoplasm, which ultimately arrests the cell cycle and leads to apoptosis (Fig 1) It is the first drug with this mechanism of action.
•The hypothesis that using the combination of Selinexor with pembrolizumab (an anti-PD1 CPI) is well tolerated by patients and will induce overall response rates that are comparable to the combination observed with anti-PD1/CTLA-4, and to be able to salvage patients who progressed on prior CPI, and to induce response in patients with UM.

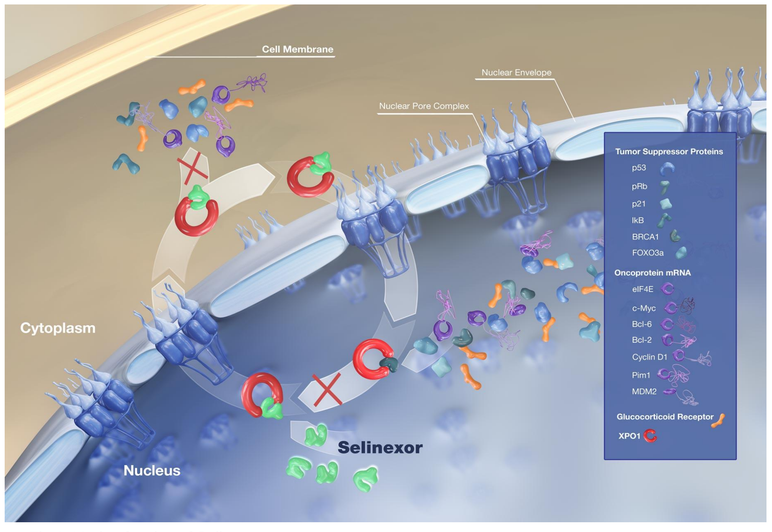

Fig.1: Mode of action of Selinexor

Methods

This open label, single center Phase IB combination therapy study in metastatic or locally advanced cancers enrolled either treatment naïve (t/n) pts or pts who relapsed on prior therapies (r/p). The addition of SEL to multiple standard chemotherapy and CPI regimens was tested in parallel (13 arms total), with ARM L using PEM (240mg IV q3 weeks) in combination with SEL (starting dose 60mg PO twice/week).
Primary objective was to establish the safety and tolerability of SEL/PEM.
Secondary endpoints included response rate (RR) and progression free survival (PFS).
Analyses of OS and PFS were performed. OS was defined as from the time of first treatment to the time of death or to the time of last contact. PFS was defined as from the time of first treatment to the time of progression or death, whichever occurred first or to the time of last contact. The distributions of OS and PFS were estimated by the Kaplan-Meier method [1]. All analyses were performed in SAS 9.4 and R.

Conflict Statement, Sponsor and Contact

The first author has no conflict of interest to declare. The study was sponsored by Karyopharm Therapeutics Inc. 1st Author Contact: icglitza@mdanderson.org

Conclusion

Results

Here, we describe the **result for 25 patients** with metastatic melanoma that were treated with the combination of selinexor at a starting dose of 60mg PO twice weekly and pembrolizumab at 240mg I.V. every 3 weeks in ARM L.
Seventeen patients were treatment naïve.

Tab.1: Patient demographics and outcomes

Factor	Category	N (%)
Sex	Female	12 (48)
	Male	13 (52)
Race	Caucasian	23 (92)
	Hispanic	2 (8)
Diagnosis	Melanoma	19 (76)
	Uveal melanoma	6 (24)
No of prior systemic therapies	0	17 (68)
	1	1 (4)
	2	2 (8)
	3	2 (8)
	4	1 (4)
	6	1 (4)
	10	1 (4)
Off treatment/ Active	Active	13 (52)
	Off treatment	12 (48)
Reason for Off Treatment*	Progression	6 (50)
	Toxicity	3 (25)
	Patient request	2 (17)
	Dead	1 (8)

Adverse Events

There were 248 adverse events from 25 patients reported after the first treatment date, which were either possibly, probably or definitely related to treatment. If a patient experienced the same AE at different period of time or grade, only the maximum attribution with highest grade and highest attribution to selinexor would be counted.

All the twenty-five patients had a total of 246 AEs. Sixteen patients experienced twenty-nine grade 3 or above AEs (Table 2).

Three pts discontinued therapy due to adverse events.

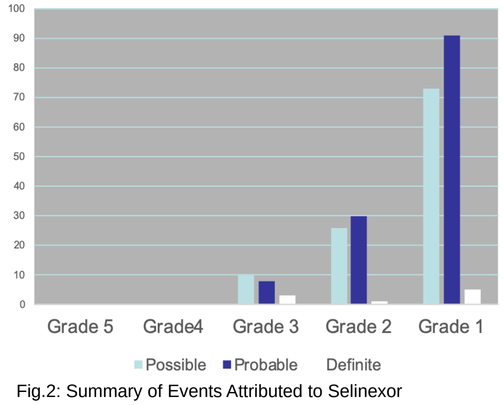

Fig.2: Summary of Events Attributed to Selinexor

Tab.2: Summary of grade 3 or above adverse events from 16 patients

AE Category	AE Term	Grade	SAE	Attribution to Selinexor	Attribution to Pembrolizumab
Laboratory	WBC ↓	3	No	Probable	Unrelated
Metabolism and nutrition	Anorexia	3	No	Definite	Unrelated
Laboratory	Neutrophil ↓	3	No	Definite	Unrelated
Metabolism and nutrition	Potassium ↓	3	No	Probable	Unrelated
Metabolism and nutrition	Sodium ↓	3	No	Probable	Unrelated
Gastrointestinal	Diarrhea	3	No	Unrelated	Definite
Laboratory	Anemia	3	Yes	Probable	Possible
Laboratory	Lymphocytes ↓	3	No	Possible	Possible
Gastrointestinal	Diarrhea	3	Yes	Possible	Possible
General	Fatigue	3	No	Possible	Possible
Investigations	ALT ↑	3	No	Probable	Unrelated
General	Fatigue	3	Yes	Probable	Probable
Gastrointestinal	Nausea	3	Yes	Probable	Unrelated
Laboratory	Anemia	3	No	Probable	Possible
Metabolism and nutrition	Sodium ↓	3	No	Possible	Possible
Metabolism and nutrition	Sodium ↓	3	No	Possible	Possible
Laboratory	Neutrophil ↓	3	No	Possible	Unrelated

Response

Total number of patients evaluable for response: 23

Withdrew consent: 1
Not reached restaging yet: 1

Median Follow up time:
4.83 months (range 01-14)

Median Age:
65.8 (range 31.4-83)

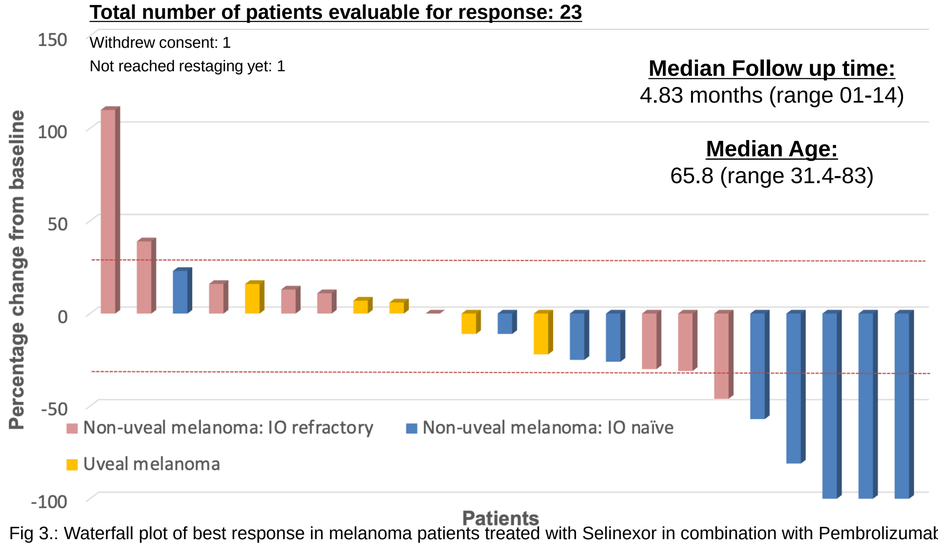

Fig 3.: Waterfall plot of best response in melanoma patients treated with Selinexor in combination with Pembrolizumab (n=23 evaluable patients)

Tab. 3: Responses based on prior IO status and uveal melanoma patients

	Number of evaluable patients	CR n (%)	PR n (%)	SD n (%)	PD n (%)	Objective Response n (%)
Non-Uveal melanoma: IO refractory	9	0	3 (33)	3 (33)	3 (33)	3 (33)
Non-Uveal melanoma: IO naïve	9	2 (22)	3 (33)	3 (33)	1 (11)	5 (56)
Uveal Melanoma	5	0	0	5 (100)	0	0
Total evaluable patients	23	2 (9)	6 (26)	11 (48)	4 (17)	8 (35)

Survival

•The median PFS for the entire cohort has not been reached
- 6-month PFS rate was 0.65 (95% CI: 0.475, 0.91).
- 9-month PFS rate was 0.57 (95% CI: 0.37, 0.87).

•**The median overall survival (OS) has not been reached**
- 6 months OS rate of .81 (95% CI: 0.63, 1).
- 22/25 pts are still alive.

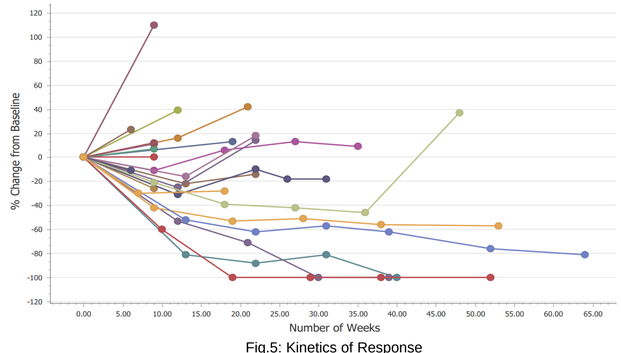

Fig.5: Kinetics of Response

Conclusion

Treatment with selinexor in combination with pembrolizumab is well-tolerated and shows significant clinical activity in t/n pts compared to historic single agent pembolizumab. The combination warrants further evaluation.

Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. Journal of the American statistical association, 53(282), 457-481. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomized dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109-17. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54. Robert C, Long GV, Brady B, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. N Engl J Med. 2015;372(4):320-330. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma [published correction appears in N Engl J Med. 2018 Nov 29;379(22):2185]. N Engl J Med. 2015;373(1):23-34. doi:10.1056/NEJMoa1504030