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Research Article

Selinexor (KPT-330) in Combination with Immune Checkpoint Inhibition in Uveal Melanoma: A Phase 1B Trial

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ABSTRACT

Introduction: Uveal melanoma remains a disease with aggressive behavior and poor prognosis despite advances in clinical management. Because monotherapy with immune checkpoint inhibitors has led to limited improvement in response rates, combination with other agents that act on the biological basis of oncogenesis has been proposed as a possible therapeutic strategy. **Methods:** We designed a phase 1b trial to test the safety and tolerability of selinexor in combination with immune checkpoint inhibitors in patients with advanced uveal melanoma. Patients received selinexor 60 mg PO twice weekly with standard of care, commercially available immune checkpoint inhibitor of the investigator's choice. In one patient receiving nivolumab and ipilimumab as the immunotherapy backbone, selinexor 60 mg PO was given once weekly. **Results:** We included 10 patients with uveal melanoma who received treatment with either selinexor plus pembrolizumab ($n = 9$) or selinexor plus nivolumab and ipilimumab ($n = 1$). The most common adverse events of any grade were neutropenia, thrombocytopenia, leukopenia, and anemia. Additional common nonhematological toxicities included hyponatremia, nausea, and vomiting. Dose reductions were required in six patients (60%). Among nine patients with evaluable disease, eight had stable disease as the

best response. The median progression-free and overall survival were 6 months (95% CI: 4, not reached and 17 months (95% CI: 7, not reached), respectively. **Conclusion:** The combination of selinexor and immunotherapy was safe and showed a side effect profile consistent with previous reports. Clinical benefit was achieved in most patients and should be validated in larger phase 2 trials. ClinicalTrials.gov ID: NCT02419495.

Keywords: clinical trial, phase I, uveal melanoma, checkpoint inhibitor, selinexor

INTRODUCTION

Metastatic uveal melanoma is a life-threatening cancer that originates in the uvea of the eye. Despite being generally rare, it is ranked as the most common intraocular malignancy in adults.[1] Similar to cutaneous melanoma, melanocytes are the cells of origin in uveal melanoma; however, the difference in genetic profile and tumors biology makes uveal melanoma and skin melanoma two distinct entities.[2] Despite advances in clinical management, prognosis remains generally poor, and the proportion of patients who eventually develop metastatic disease is quite high.[3,4] Nearly half of patients develop metastasis commonly affecting the liver despite successful treatment of primary disease with surgical enucleation or radiotherapy.[5,6] Once metastasized, the median overall survival (OS) usually drops to less than 1 year.[4,7] The response to treatment is usually limited, and even with advances in cancer immunotherapy, response rates remain remarkably low.[8–10] Nivolumab plus ipilimumab combination therapy results in marginally higher response rates compared with immune checkpoint inhibitor monotherapy or the T-cell redirection bispecific molecule tebentafusp. However, the objective response rate is still below 20%.[11–14]

Therefore, newer therapeutic options, including possible combinations of available drugs, are critically needed. One possible option is combining with selinexor, which is a selective inhibitor of exportin 1 (XPO1) that physiologically plays a critical role in the nuclear export of different proteins, including tumor-suppressor proteins. In cancer, dysregulation of XPO1 has been described in various malignancies as a possible driver of oncogenesis and a potential therapeutic target.[15,16] By blocking XPO1, selinexor prevents the export of tumor-suppressor proteins to the cytoplasm, thus leading to their accumulation within the nucleus that enables suppression of cancer cell growth. The United States Food and Drug Administration (FDA) has approved the use of selinexor in combination with bortezomib and dexamethasone to treat adult patients with multiple myeloma who have received at least one prior therapy. Selinexor has also received accelerated approval in diffuse large B-cell lymphoma.[17] Preclinical data from multiple other tumor types suggested that selinexor can sensitize tumors to chemotherapy and targeted therapy.[18]

To further explore the potential clinical use of selinexor in patients with nonhematological solid tumors, a phase 1b trial (ClinicalTrials.gov Identifier: NCT02419495) was done to assess the use of selinexor (KPT-330) with multiple standard chemotherapy or immunotherapy regimens in the treatment of patients with advanced cancers. Because patients with uveal melanoma derive clinical benefits from various immunotherapeutic agents, we tested the hypothesis that combining selinexor with immunotherapy would be safe and effective in patients with uveal melanoma. Multiple preclinical studies have suggested the role of selinexor in enhancing the immune response against cancer. For example, selinexor combined with anti-PD1, anti-PD-L1, or anti-CTLA4 antibodies showed in vivo activity in melanoma mice models. In human melanoma cell lines, there was an increase in leukocyte *PDCD1* and *CTLA4* gene expression and induction of *CD274* gene expression.[19] Similar data have also been shown for other tumor types.[20,21] Herein, we report on the safety and efficacy of investigational selinexor (KPT-330) when combined with immunotherapy in patients with uveal melanoma.

METHODS

We designed a phase 1b trial of selinexor in combination with chemotherapy or immunotherapy (NCT02419495) in patients with advanced solid tumors. Institutional review board approval was obtained from The University of Texas MD Anderson Cancer Center before starting the study, and informed consent was obtained from all included participants. The study was conducted per the International Council for Harmonisation standards. The study had multiple arms with disease- and combination-specific cohorts. Reports from other cohorts with safety and efficacy data were previously published.[22–26] Patients with advanced or metastatic cutaneous and uveal melanoma were enrolled to receive selinexor with either pembrolizumab (arm L) or nivolumab or ipilimumab (arm O). The results from patients with nonuveal melanoma were reported separately.[27] In the uveal melanoma cohort, we included patients 18 years or older with histologically confirmed uveal melanoma who started treatment between February 2019 and November 2020. Eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1),[28] a life expectancy of 12 weeks or more, and normal blood counts and laboratory tests. Patients with central nervous system (CNS) involvement were only allowed if CNS disease had been treated and clinically stable. Patients with prior treatment with an XPO1-targeting agent were excluded.

For the uveal melanoma cohort included in this analysis, patients received selinexor 60 mg orally (PO) twice weekly with pembrolizumab given at a dose of 200 mg intravenously (IV) every 3 weeks. In one patient receiving

nivolumab and ipilimumab as the immunotherapy backbone, selinexor 60 mg PO was given once weekly. Nivolumab was given at a dose of 3 mg/kg IV every 3 weeks for 4 cycles, then 3 mg/kg every 4 weeks, and ipilimumab was given at a dose of 1 mg/kg IV every 3 weeks for 4 cycles. Patients received treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death. Toxicities were managed according to the standard of care clinical practice.

The primary endpoint of this phase 1b study was the incidence of adverse events. Patients had toxicity monitored during participation, and adverse events were graded and reported according to Common Terminology Criteria for Adverse Events version 5.0.[29] Dose-limiting toxicity (DLT) was defined as grade 3 or more toxicity occurring in the first 21 days at any dose, which was considered at least possibly related to selinexor or selinexor plus immunotherapy. Detailed definitions of DLTs are included in the Supplement, available online. Secondary endpoints included response according to RECIST 1.1,[28] progression-free survival (PFS), time to treatment discontinuation (TTD), and OS. Patients had restaging scans every three cycles using the same imaging modality that was used at baseline assessment.

Statistical analysis was performed using SAS 9.4 and R 4.1.2. The baseline categorical and continuous characteristics were summarized. Fisher's exact test was used to compare the best response in the treatment-naïve and prior PD-1 groups. Analyses of OS, PFS, and TTD were performed. OS was defined as the time from first treatment to death or last contact. PFS was defined as the time from first treatment to progression or death, whichever occurred first. Patients who came off treatment due to toxicity or consent withdrawal were censored for progression at the time of last known status of being alive, progression-free, and not on another anticancer therapy. TTD was defined as the time from first treatment to treatment discontinuation. The distributions of OS, PFS, and TTD were estimated by the Kaplan-Meier method.[30]

RESULTS

Patient Characteristics

We included 10 patients with uveal melanoma who had a median age of 61.1 (range 31–67). Nine patients received treatment with selinexor plus pembrolizumab, and one received treatment with selinexor plus nivolumab and ipilimumab. Six patients (60%) were treatment naïve, and four patients (40%) had received prior treatment with PD1-based therapy for metastatic disease (Table 1). In the four pretreated patients, three (75%) had a PD-1 therapy backbone as the most recent treatment before trial enrollment.

By the time of data cutoff in August 2023, nine patients (90%) were off treatment. Reasons for treatment discontinuation included disease progression ($n = 5$; 56%), toxicity ($n = 3$; 33%), and consent withdrawal ($n = 1$; 11%).

Table 1. Characteristics of patients included in this study

Characteristic	*n* (%)
Sex	
Male	6 (60)
Female	4 (40)
Age, y	
Median	61.1
Race	
White	10 (100)
Other	0
No. of prior systemic therapies	
0	6 (60)
1	2 (20)
2	0
3	2 (20)
Site of metastasis	
Hepatic only	1 (10)
Extrahepatic only	1 (10)
Hepatic and extrahepatic	8 (80)
Treatment	
Selinexor in combination with pembrolizumab	9 (90)
Selinexor in combination with nivolumab + ipilimumab	1 (10)

Safety

All 10 included patients (100%) had treatment-related adverse events, including seven patients with grade 3 or more toxicity. None of the nine patients on selinexor plus pembrolizumab had DLT, and one patient on selinexor plus nivolumab/ipilimumab had DLT in the form of grade 3 transaminitis, probably related to nivolumab/ipilimumab that was the reason for treatment takeoff. The most common adverse event of any grade was neutropenia ($n = 7$; 70%), thrombocytopenia ($n = 6$; 60%), leucopenia ($n = 5$; 50%), and anemia ($n = 5$; 50%). In addition, other common toxicities occurring in 30% or more of patients included hyponatremia ($n = 4$; 40%), nausea ($n = 4$; 40%), and vomiting ($n = 3$; 30%). The most common grade 3 or more toxicity was decreased neutrophil count ($n = 5$; 50%) (Table 2). Dose reductions of selinexor were required in six patients (60%) (Table 3).

Efficacy

By the time of data cutoff in August 2023, nine patients were evaluable for response. One patient was not evaluable because of early discontinuation due to toxicity before sufficient dosing. Among the nine patients with evaluable disease, all were treated with selinexor in combination with pembrolizumab, and the best response was stable disease (SD) in eight patients (89%) and progressive disease (PD) in one patient (11%) (Table 4; Fig. 1). In patients with non-PD, the duration of stable disease ranged from 1–30 months, with a median of 5 months (Supplementary Fig. 1). Five patients (55%) experienced tumor regression in their target lesion(s) (Fig. 1).

At a median follow-up of 32 months in 9 patients with evaluable disease, the median PFS was 6 months (95% CI: 4, not reached). The 6-month PFS rate was 36.5% (95% CI: 12.4%, 100%), and the 12-month PFS rate was

Table 2. Adverse events reported in the included cohort ($N = 10$)

Adverse Event	Total		Grade 1-2		Grade 3-4	
	n	%	*n*	%	*n*	%
Neutrophil count decreased	7	70	2	20	5	50
Platelet count decreased	6	60	5	50	1	10
White blood cell decreased	5	50	4	40	1	10
Anemia	5	50	5	50	0	0
Hyponatremia	4	40	3	30	1	10
Nausea	4	40	4	40	0	0
Vomiting	3	30	3	30	0	0
Alanine aminotransferase increased	2	20	1	10	1	10
Anorexia	2	20	1	10	1	10
Aspartate aminotransferase increased	2	20	1	10	1	10
Hypokalemia	2	20	1	10	1	10
Constipation	2	20	2	20	0	0
Creatinine increased	2	20	2	20	0	0
Dizziness	2	20	2	20	0	0
Fatigue	2	20	2	20	0	0
Lymphocyte count decreased	2	20	2	20	0	0
Acute kidney injury	1	10	1	10	0	0
Cough	1	10	1	10	0	0
Dysarthria	1	10	1	10	0	0
Dysgeusia	1	10	1	10	0	0
Hypophosphatemia	1	10	1	10	0	0
Other nervous system disorders						
Neurocognitive impairment	1	10	1	10	0	0
Word finding difficulty and expressive aphasia	1	10	1	10	0	0
Stroke	1	10	1	10	0	0

Table 3. Dose detail among the patients who had dose reduction ($n = 6$)

Final Dosage	40 mg Twice Weekly	20 mg Twice Weekly	10 mg Once Weekly
No. of Patients	2	3	1

Note – Starting dose: 60 mg twice weekly.

18.2% (95% CI: 31.5%, 100%). Eight of nine evaluable patients discontinued therapy by the time of data cutoff with a median TTD of 6 months (95% CI: 3, not reached). Five and two patients were still on treatment 6 and 12 months after initiation, respectively. One patient remained on treatment with SD after 30 months of treatment. The median OS was 17 months (95% CI: 7, not reached). The 6-month OS rate was 77.8% (95% CI: 54.9, 100%), and the 12-month OS rate was 55.6% (95% CI: 31%, 99.7%).

Table 4. Best response in included patients with evaluable disease ($n = 9$)

	Stable Disease (n = 8)	Progressive Disease (*n* = 1)
No. of prior systemic therapies	8 (89%)	1 (11%)
0	5	0
1	1	1
2	0	0
3	2	0

All patients with prior therapy received an immune checkpoint inhibitor.

DISCUSSION

Metastatic uveal melanoma has been classically associated with poor prognosis.[3,4,7–9] Responses to monotherapy with immune checkpoint inhibition is generally below 5%, and combined PD-1/CTLA-4 blockade can debatably lead to responses up to 20%,[11–14] which is still relatively low. Indeed, the only FDA-approved therapy for HLA-A*02:01–positive metastatic uveal melanoma, tebentafusp-tebn, also demonstrated a low response rate of 9% but with a statistically significant improvement in OS compared with pembrolizumab in a randomized phase 3 trial.[10] In this phase 1b trial, we investigated the incidence of adverse events with selinexor in combination with immune checkpoint inhibition in patients with metastatic uveal melanoma. Hematological toxicities were the most frequently reported adverse events occurring in 70% of included patients. Most patients had the best response of SD with a median PFS at 6.6 months.

The reported side effect profile is consistent with the known toxicity profile of Selinexor, which was demonstrated in registrational studies in myeloma and lymphoma with hematological toxicities as the major adverse events.[31–33] Another phase 1 study in patients with solid tumors showed a higher incidence of fatigue, nausea, anorexia, and vomiting of grade 1 or 2, with thrombocytopenia, fatigue, and hyponatremia as the most common grade 3 or 4 toxicities.[34] It is not immediately clear why our data are more in line with data from studies in hematological malignancies; however, the small sample size and design differences might limit appropriate interpretations. Selinexor-induced thrombocytopenia has been shown to result from inhibition of thrombopoietin signaling and stem cell differentiation to megakaryocytes via XPO1 blockade.[35] Platelet decrease with selinexor was previously shown to reach nadir between 28 and 42 days in the absence of interventions. Suggested nondose-related interventions that can be used for the management of thrombocytopenia events include platelet transfusion and thrombopoietin receptor agonists, none of which were needed in our study.[36]

Although the primary objective of this study was to measure the incidence of adverse events, the efficacy data are notable, with a median PFS of 6 months. In the first-line treatment setting, median PFS in the landmark phase 3 study of tebentafusp versus the investigator's choice was 3.4 months and 2.9 months, respectively.[10,37] Prolonged SD was observed in more than half of the patients in our study, and 23% are still deriving clinical benefits at 12 months; this might be a positive efficacy signal to be

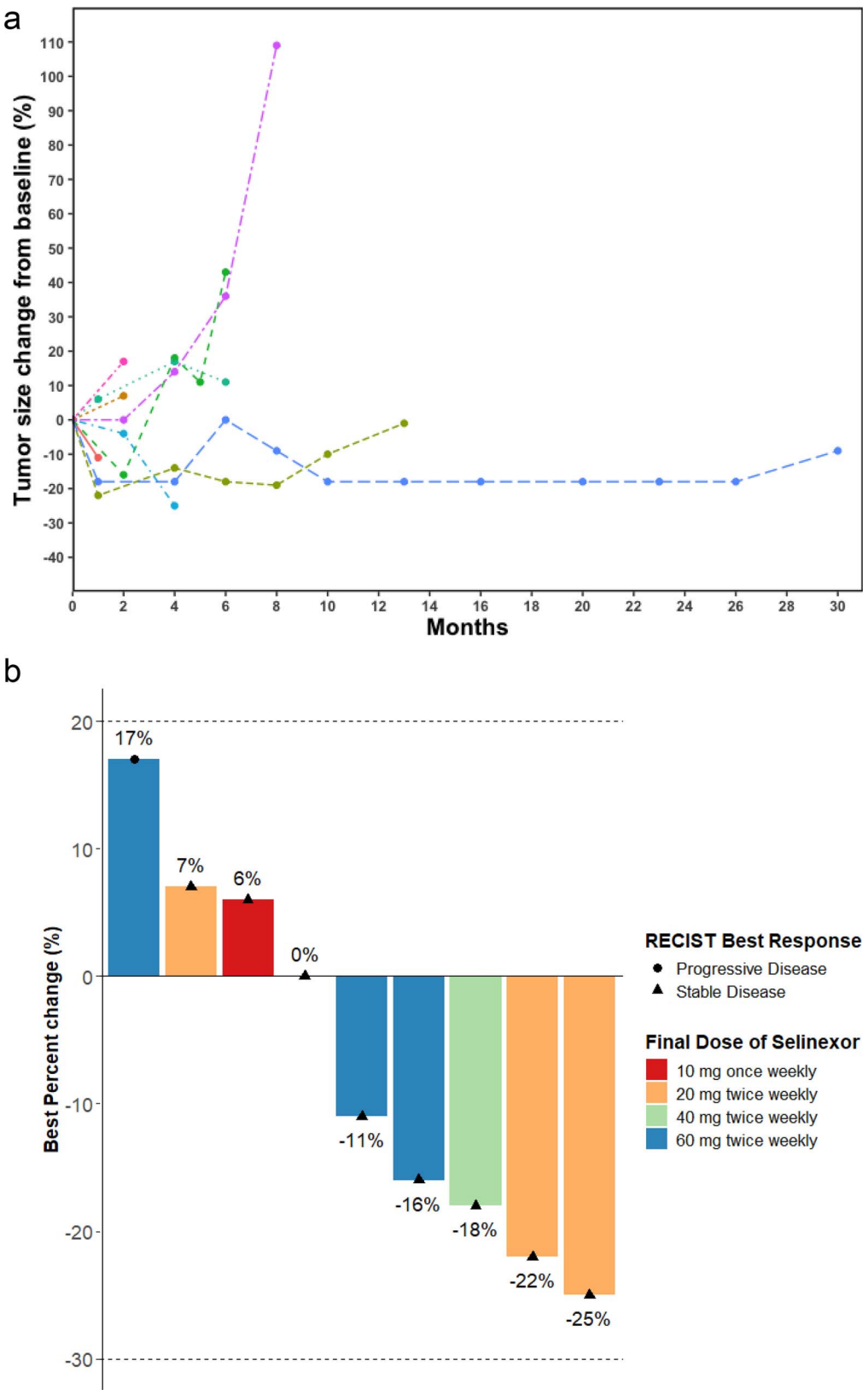

Figure 1. Response in patients with evaluable disease demonstrated in spider plot (**a**) and waterfall plot (**b**). * The patient with PD (in bluemost left) had RECIST measurement of +17%, which qualifies as SD but also had unequivocal progression of nontarget lesions.

confirmed in additional phase 2 studies. Whether prolonged SD may be considered a surrogate for OS remains an area of debate because observations of prolonged SD have been frequently reported with novel agents beyond the chemotherapy era. The fact that RECIST has been primarily developed based on data from clinical trials of chemotherapy that might not accommodate different mechanisms of action of newer therapeutic drugs remains arguable. However, there is at least some evidence in favor of using disease control rate and clinical benefit rate as possible endpoints in new cancer clinical trials, although regulatory considerations remain a challenge.[38,39] Efficacy data should be interpreted with caution given the small number of patients and the 0% objective response rate. However, this was a phase 1 trial with the primary objective of evaluating the safety of combined selinexor and immunotherapy treatment regimens. The safety of the combination should justify the exploration in a larger trial in the context of the lack of therapeutic options in uveal melanoma and the observed signal of activity in our patients.

Our study had several limitations. For example, the small sample size precludes definitive conclusions. Additionally, these results come from a single-center nonrandomized trial, which necessitates interpretation with caution. We have not had correlative biomarkers or pharmacodynamic analysis in this cohort, which could have been valuable in understanding the effects of the combination. Last, the racial difference in safety or efficacy was not feasible to assess, given the small number of patients who unintentionally belonged to one racial group. However, to the best of our knowledge, this is the first study to report the safety of selinexor in combination with immunotherapy in patients with uveal melanoma. Moreover, the combination led to prolonged clinical benefit in most patients with a paucity of immune-related adverse events. Further studies with enough power to assess efficacy and obtain biomaterial for translational studies are needed and may provide evidence on a possible treatment option in uveal melanoma.

CONCLUSIONS

The combined use of selinexor and immune checkpoint inhibition showed a side effect profile consistent with previous reports with no added safety signals. The combination led to promising antitumor activity that needs to be validated in larger phase II trials.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplemental Material

Supplemental materials are available online with the article.

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