A PHASE IB/II STUDY OF SELINEXOR PLUS PEMBROLIZUMAB IN CISPLATIN-INELIGIBLE OR CISPLATIN-REFRACTORY PATIENTS WITH ADVANCED UROTHELIAL CARCINOMA

Protocol Number:	UCDCC#289 (IST# xxxxx)
Indication:	Advanced Urothelial Carcinoma
Phase:	Ib/II
Funding Source:	Karyopharm Therapeutics, Inc.
Agent:	Selinexor (KPT-330), pembrolizumab
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IND Sponsor:	UC Davis Comprehensive Cancer Center
Protocol History:	Version 1.0 04/21/2020 Version 2.0 07/20/2020 Version 3.0 09/07/2020 Version 4.0 (06/03/2022)

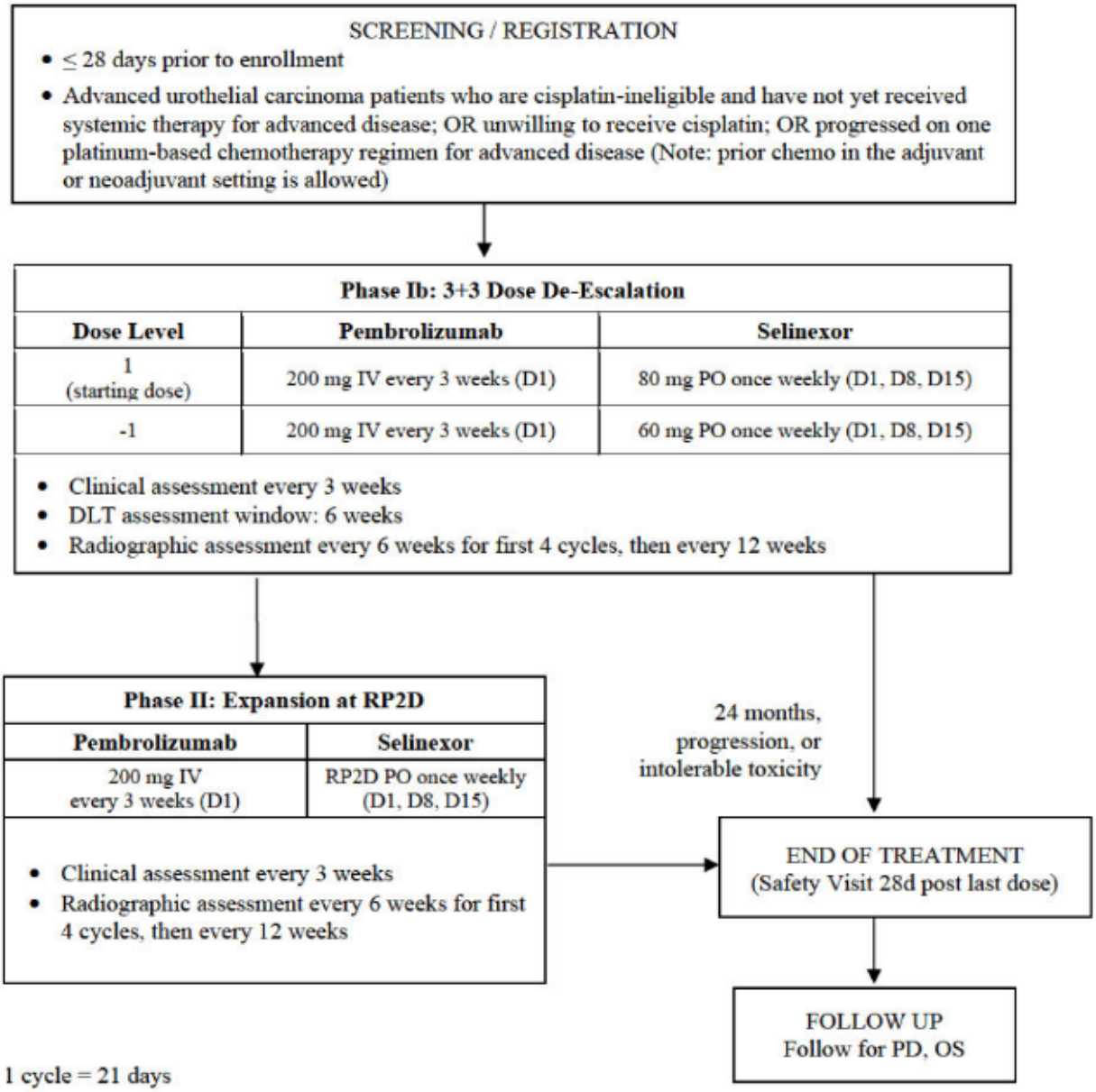
PROTOCOL SYNOPSIS

<table>
<tr><td>Study Title:</td><td>A Phase Ib/II study of selinexor plus pembrolizumab in cisplatin-ineligible or cisplatin-refractory patients with advanced urothelial carcinoma.</td></tr>
<tr><td>Protocol No.:</td><td>UCDCC#289</td></tr>
<tr><td>Phase of Dev.:</td><td>Ph Ib/II</td></tr>
<tr><td>Investigational Product, Dosage Form, Route, and Dose Regimen</td><td>Selinexor 60 mg or 80 mg orally (PO)
Pembrolizumab 200 mg intravenously (IV) once every 3 weeks
<table>
<tr><th>Dose Level</th><th>Pembrolizumab</th><th>Selinexor</th></tr>
<tr><td>1 (starting dose)</td><td>200 mg IV every 3 weeks (D1)</td><td>80 mg PO once weekly (D1, D8, D15)</td></tr>
<tr><td>-1</td><td>200 mg IV every 3 weeks (D1)</td><td>60 mg PO once weekly (D1, D8, D15)</td></tr>
<tr><td colspan="3">* Each cycle is 21 days</td></tr>
</table></td></tr>
<tr><td>Primary Objective:</td><td>• Ib: Identify Recommended Phase 2 Dose (RP2D) of selinexor in combination with standard dose pembrolizumab in patients with advanced urothelial carcinoma who are cisplatin-ineligible or cisplatin-refractory, as defined by dose-limiting toxicity
• II: Characterize the efficacy of selinexor at RP2D in combination with pembrolizumab by objective response rate as defined by RECIST criteria.</td></tr>
<tr><td>Secondary Objectives:</td><td>1. Evaluate the toxicity of the combination of selinexor with standard-dose pembrolizumab in patients with advanced urothelial carcinoma who are cisplatin-ineligible or cisplatin-refractory.
2. Evaluate progression-free survival in patients treated with the combination of selinexor with standard-dose pembrolizumab at the RP2D.</td></tr>
<tr><td>Exploratory Objectives:</td><td>1. Evaluate the frequency of positive XPO1 expression by IHC among patients with cisplatin-ineligible advanced urothelial carcinoma.
2. To evaluate the relationship between XPO1 expression by IHC and response to the combination of selinexor and pembrolizumab.
3. To evaluate the relationship between PD-L1 expression by IHC and response to the combination selinexor and pembrolizumab.
4. To analyze pre- and post-treatment blood samples/peripheral blood mononuclear cells (PBMCs) for changes in NK and T-cells.</td></tr>
<tr><td>Study Design and Investigational Plan/Methodology</td><td>This Phase Ib study will initially enroll 3 patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible and treatment-naïve in the advanced setting to receive selinexor 80 mg PO weekly and pembrolizumab 200 mg IV q3weeks (Dose Level [DL] 1). Using a 3+3 approach, the following dose de-escalation plan will proceed, and the RP2D will be the highest dose level at which 0/3 or 1/6 patients have DLT:
<table>
<tr><th>Number of Patients with DLT at a Given Dose Level</th><th>De-escalation Decision Rule</th></tr>
<tr><td>0 out of 3</td><td>Enroll 3 patients to same dose level</td></tr>
<tr><td>0 out of 6</td><td>RP2D</td></tr>
<tr><td>1 out of 3</td><td>Enroll 3 patients to same DL</td></tr>
<tr><td>1 out of 6</td><td>RP2D</td></tr>
<tr><td>2 out of 3</td><td>If DL 1, de-escalate one dose level
If DL -1, stop study</td></tr>
<tr><td>2 out of 6</td><td>If DL 1, de-escalate one dose level
If DL -1, stop study</td></tr>
</table></td></tr>
</table>

	Once the RP2D cohort is identified, a Phase II expansion cohort will be enrolled for a total of 27 evaluable patients to further evaluate toxicity, and to evaluate efficacy as defined by objective response rate. Patients will be assessed every 3 weeks clinically for toxicity, and the DLT assessment window during the Phase Ib portion of the study will be 6 weeks. Patients will be assessed every 6 weeks for response or progression to therapy for the first 12 weeks (after which they will undergo radiographic imaging every 12 weeks) and will continue on treatment until the time of unacceptable toxicity or until evidence of progressive disease by RECIST on radiographic imaging. Pre-treatment biopsy will be required for any patient who does not have archival tissue available. Pre-treatment blood samples will be drawn, and additional research blood draws will be performed on patients on trial and when patients come off study.
Study Population and Sample Size:	This study's population is patients with locally advanced or metastatic urothelial carcinoma, who are cisplatin-ineligible or who have progressed on one platinum-based chemotherapy regimen. Patients may have received systemic therapy in the neoadjuvant or adjuvant setting, and may have received intravesical therapy in the past. The sample size for this study will require 6-12 patients for the 3+3 portion, and an additional expansion to evaluate 27 patients at the RP2D, for a total enrollment of up to 33 patients. Assuming a response rate of 20% for pembrolizumab alone in this study population based on historical controls, a sample size of 27 evaluable patients will allow for detection of an improvement of ORR to 45% with 80% power at the 0.05 level (2-sided).
Eligibility Criteria	Patients will meet the following inclusion criteria: • Age ≥ 18 years • Histologically confirmed locally advanced, unresectable, or metastatic urothelial carcinoma who have measurable disease by RECIST 1.1 criteria • Will have archival tissue available or a willingness to undergo pre-treatment biopsy • ECOG performance status 0-2 • Not eligible to receive cisplatin-based chemotherapy due to renal dysfunction, peripheral neuropathy, ototoxicity or unwillingness of patient to receive cisplatin OR progressed on one platinum-based chemotherapy regimen. • May have had neoadjuvant or adjuvant platinum-based chemotherapy or intravesical therapy in the past • Adequate hematologic function - see Section 3.1 • Adequate organ function - see Section 3.1 Patients are ineligible if the following exclusion criteria are met: • Radiation treatment to a field considered part of the selected target lesions, received ≤ 14 days prior to enrollment • Systemic cancer therapy received ≤ 21 days prior to enrollment • Concomitant diagnosis of additional malignancy in the past 2 years, with the exception of prostate cancer with demonstrated PSA < 4 or not requiring systemic therapy, and of cutaneous malignancies which have been resected such as basal cell carcinoma or squamous cell carcinoma of the skin, and cancers that have been treated with curative intent and are in clinical remission for at least 2 years. • Autoimmune disorder requiring active therapy as defined by corticosteroids at a dose ≥ 10 mg oral prednisone or the equivalent or requiring immunosuppressive therapy. • Use of corticosteroids at dose of ≥ 10 mg oral prednisone or the equivalent per day ≤ 14 days prior to enrollment.

	• Received any prior immune checkpoint inhibitor therapy (anti-PD-1, anti-PD-L1, or anti-CTLA4 directed therapy)
Endpoints:	Primary endpoint: • Recommended Phase 2 Dose as defined by Dose-Limiting Toxicity • Objective response rate (ORR), i.e. patients with complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) by RECIST criteria Secondary endpoint: • Grade 3 or higher adverse events (AEs) as defined by NCI CTCAE criteria • Progression-free survival Exploratory endpoint: • XPO1 expression by IHC of tumor specimens • PD-L1 expression by IHC of tumor specimens • Pre- and post-treatment NK and CD4+, CD8+ cells
Statistical Considerations	To establish the RP2D, a 3+3 de-escalation design is employed; this will require a minimum of 6 patients and up to 12 patients. Additional patients will be enrolled at RP2D for a total of 27 evaluable patients to further characterize toxicity and to evaluate efficacy. Assuming a response rate of 20% for pembrolizumab alone in this study population, based on historical controls, a sample size of 27 patients will allow for detection of an improvement to ORR of 45%.
Correlatives:	Exploratory objectives will require pre-treatment tissue, either archival or collected prior to treatment on trial, and pre-treatment research blood sample as well as research blood samples for all patients on treatment and when patients come off study. Research blood samples will be banked.

STUDY SCHEMA



1 cycle = 21 days

LIST OF ABBREVIATIONS AND TERMS

Abbreviation/Term	Definition
°C	degrees Celsius
µM	Micromolar
AE	adverse event
ANC	absolute neutrophil count
ALT	alanine transaminase
AST	aspartate transaminase
CLIA	Clinical Laboratory Improvement Amendments
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
IRB	institutional review board
IV	Intravenous
Ki	inhibitory constant
lbs	Pounds
LDH	lactate dehydrogenase
m^2	square meters
mg	Milligram
Min	Minute
mL	Milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mUC	metastatic urothelial carcinoma
NCI	National Cancer Institute
OCR	Office of Clinical Research
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PI	principal investigator
PR	partial response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SRC	Scientific Review Committee
UCD	University of California, Davis (UC Davis)
UCDCCC	UC Davis Comprehensive Cancer Center
US	United States

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 2
STUDY SCHEMA 5
LIST OF ABBREVIATIONS AND TERMS 6
TABLE OF CONTENTS 7
LIST OF TABLES 9
LIST OF FIGURES 9
1.0 STUDY OBJECTIVES 10
1.1 Primary Objective 10
1.2 Secondary Objectives 10
1.3 Exploratory or Correlative Objectives 10
2.0 BACKGROUND 10
2.1 Scientific Rationale 11
2.1.1 Pembrolizumab 11
2.1.2 Selinexor 11
2.1.3 Selinexor and Pembrolizumab Combination 12
2.2 Disease 13
2.2.1 Treatment Options 13
2.3 Investigational Product Name and Description 13
2.3.1 Selinexor 13
2.3.2 Pembrolizumab 14
2.4 Summary of Nonclinical Data 14
2.4.1 Pharmacology 14
2.4.2 Toxicology 15
2.5 Summary of Clinical Data 16
2.5.1 Pharmacokinetics and Product Metabolism 16
2.5.2 Summary of Clinical Safety 17
2.5.3 Risks 18
3.0 SUBJECT SELECTION 19
3.1 Inclusion Criteria 19
3.2 Exclusion Criteria 20
4.0 STUDY DESIGN 22
4.1 Phase Ib 22
4.1.1 Definition of Dose Limiting Toxicity 23
4.1.2 Definition of RP2D 23
4.2 Phase II Expansion at RP2D 23
5.0 TREATMENT OF SUBJECTS 24
5.1 Study Treatment Administration 24
5.2 Selinexor 24
5.2.1 Dosing and Administration 24
5.2.2 Formulation, Packaging, and Handling 25
5.2.3 Preparation 25
5.2.4 How Supplied 25
5.3 Pembrolizumab 25
5.3.1 Formulation, Packaging, and Handling 26
5.3.2 Preparation 26
5.3.3 How Supplied 26

5.3.4 Disposal and Destruction 26
5.4 Monitoring 26
5.5 Dose Modification and Management of Toxicity 27
5.5.1 Dose Delay and Discontinuation 27
5.5.2 Toxicities Necessitating Dose Modification or Delay 27
5.5.3 Selinexor Dose Modifications 30
5.5.1 Criteria to Resume Treatment 35
5.6 Instructions for Initiation of Each Cycle 36

6.0 TREATMENT DURATION 36
6.1 Discontinuation Criteria 36
6.1.1 Discontinuation from Study Treatment 36
6.1.2 Discontinuation Due to AEs 37
6.2 Duration of Follow Up 37
6.3 Termination of Treatment and Study Participation 37

7.0 CONCOMITANT AND EXCLUDED MEDICATION 38
7.1 Concomitant Therapy 38
7.2 Excluded Therapy 38
7.3 Permitted Therapy 38

8.0 STUDY CALENDAR 39

9.0 STUDY EVALUATIONS 40
9.1 Screening Phase 40
9.2 Treatment Phase 40
9.3 End of Treatment Visit 40
9.4 Follow-up Phase 40
9.5 Efficacy 41
9.5.1 Response Criteria 41
9.6 Safety 43
9.6.1 Adverse Events 43

10.0 CORRELATIVES 44
10.1 Blood 47
10.2 Tissue 47

11.0 STATISTICAL CONSIDERATIONS 48
11.1 Sample Size 48
11.2 Statistical Analysis Plan 48
11.3 Safety 49
11.4 Efficacy 49
11.5 Subject Course 50

12.0 SAFETY AND REPORTING REQUIREMENTS 50
12.1 Adverse Events 50
12.1.1 Severity of Adverse Events 50
12.1.2 Causality (Attribution) of Adverse Events 51
12.1.3 Serious Adverse Events 51
12.1.4 Laboratory Test Abnormalities 52
12.2 Procedures for Handling Special Situations 52
12.2.1 Pregnancy and Breastfeeding 52
12.2.2 Overdose 53
12.2.3 Abuse, Misuse, or Medication Error 54
12.3 Procedures for Reporting Adverse Events 54
12.3.1 Methods and Timing for Assessing and Recording Safety Variables 54
12.3.2 Adverse Event Reporting Period 54

12.3.3 Procedures for SAE Reporting 55

13.0 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES 57
13.1 Ethics and Good Clinical Practice 57
13.2 Institutional Review Board 58
13.3 Patient Information and Informed Consent 58
13.4 Patient Confidentiality 58
13.5 Study Registration 58
13.6 Protocol Compliance and Deviations 59
13.7 Record Retention 59
13.8 Quality Assurance and Control 59

14.0 OVERSIGHT AND MONITORING 59
14.1 Data and Safety Monitoring 59
14.2 Investigator Monitoring Guidelines 60

15.0 REFERENCES 61

16.0 APPENDICES 63
16.1 ECOG and Karnofsky Performance Status Scores[1,2] 63
16.2 Cockcroft-Gault Estimation of CrCl 64
16.3 Study Registration 64
16.4 Data Collection Forms 65
16.5 NCI CTC Version 5.0 66
16.6 Pill Diary for Selinexor 67
16.7 Correlative Sample Collection and Handling 68

LIST OF TABLES

Table 1. Rules for Dose De-escalation 22
Table 2. Dose Levels 22
Table 3: Dose Forms of Study Treatments 24
Table 4. Dose Modification Due to Immune-Mediated Toxicity 28
Table 5. Dose Modification Due to Non-Immune Mediated Toxicity 29
Table 6. Pre-specified Dose Modifications for AEs Related to Selinexor Treatment 31
Table 7. Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor 31
Table 8. Best Overall Response Evaluation 42
Table 9. Correlative Studies 44
Table 10. Phenotypic Markers for Analysis of Various Immune Cells 45

LIST OF FIGURES

Figure 1: T24 Bladder Cancer Cell Line Treated with Selinexor 250 nM for 2 Days; PDL1 Expression by qPCR ..12

1.0 STUDY OBJECTIVES

1.1 Primary Objective

There are co-primary objectives in this study. The primary objective of the Phase Ib portion of the study is to determine the recommended Phase 2 dose (RP2D) of selinexor in combination with standard-dose pembrolizumab in patients with advanced urothelial carcinoma who are cisplatin-ineligible or platinum-refractory. The primary objective of the Phase II portion of the study is to determine the objective response rate (ORR) of selinexor in combination with pembrolizumab in patients with advanced urothelial carcinoma who are cisplatin-ineligible or platinum-refractory.

1.2 Secondary Objectives

1. To further evaluate the toxicity profile of the combination of selinexor with pembrolizumab in patients with advanced urothelial carcinoma.
2. To further evaluate the efficacy of the combination of selinexor with pembrolizumab in patients with advanced urothelial carcinoma as defined by progression-free survival (PFS).

1.3 Exploratory or Correlative Objectives

1. To evaluate the frequency of positive XPO1 expression by IHC among patients with cisplatin-ineligible advanced urothelial carcinoma.
2. To evaluate the relationship between XPO1 expression by IHC and response to the combination of selinexor and pembrolizumab.
3. To evaluate the relationship between PD-L1 expression by IHC and response to the combination of selinexor and pembrolizumab
4. To analyze pre- and post-treatment blood samples/peripheral blood mononuclear cells (PBMCs) for changes in NK and T-cells.

2.0 BACKGROUND

The advent of immune checkpoint inhibitor therapies has resulted in new options for bladder cancer patients who have progressed after cisplatin-based therapy or are cisplatin-ineligible. Yet, various FDA approved anti-PD-1 and anti-PD-L1 antibody therapies have demonstrated modest objective response rates (ORR) ranging from 16-35% [8-13]. Thus, there remains a need for

improvement of the response of checkpoint inhibition in patients with metastatic urothelial carcinoma (mUC).

The nuclear exportin-1/chromosome region maintenance 1 (XPO1) protein is implicated in the transport of numerous tumor suppressor proteins (TSPs) and cell cycle regulators including RB, p53, BRCA1, and p21, out of the cell nucleus, and thus could play a key regulatory role in tumor cell proliferation [14-15]. Preclinical data gathered at UC Davis indicate that XPO1 is overexpressed in urothelial carcinoma compared to normal bladder tissue. XPO1 inhibition in bladder cancer cell lines arrested cell cycle progression [23]. Thus, XPO1 is a target that could have potential benefit in patients with mUC.

2.1 Scientific Rationale

2.1.1 Pembrolizumab

Pembrolizumab is a selective, humanized anti-PD1 monoclonal antibody. It was studied in two major trials in mUC. In the first Phase III study, platinum pre-treated patients were randomized to receive either pembrolizumab or chemotherapy (paclitaxel, docetaxel or vinflunine) [8]. The study met its primary endpoints, demonstrating a median overall survival (OS) benefit of pembrolizumab compared to chemotherapy (10.3 vs 7.4 months), though there was no significant difference in progression-free survival (PFS). In the second Phase II trial, 370 cisplatin-ineligible patients with advanced or metastatic UC, were treated with pembrolizumab until progression, with an overall response rate (ORR) of 24% [9]. The response rate was higher (~35%) amongst patients with PD-L1 expression $\geq$ 10%.

2.1.2 Selinexor

Selinexor (KPT-330) is an orally bioavailable, first-in-class inhibitor of XPO1, and has demonstrated a tolerable safety profile in both solid tumors and hematologic malignancies, and shown encouraging efficacy in a variety of hematologic malignancies [16-22]. It was recently approved by the FDA for the treatment of refractory multiple myeloma. To date, it has not been studied clinically in urothelial carcinomas.

Work from the Mudryj lab (UC Davis) has evaluated the effect of selinexor in high-grade bladder malignancies [23]. By evaluating ONCOMINE datasets of normal bladder tissue and tissue from bladder tumors, XPO1 transcript levels were shown to be higher in tumor tissue than in normal bladder. In four muscle-invasive bladder cancer cell lines, selinexor led to decreased cell viability and decreased XPO1 levels. In all cell lines tested, XPO1 inhibition retarded cell cycle progression by decreasing S phase, inducing G1 arrest, or inducing G2/M arrest. In several models of bladder cancer treated with selinexor *in vitro*, the lab also observed increased apoptosis, evaluated by changes in PARP cleavage. In mouse xenograft models, oral gavage of

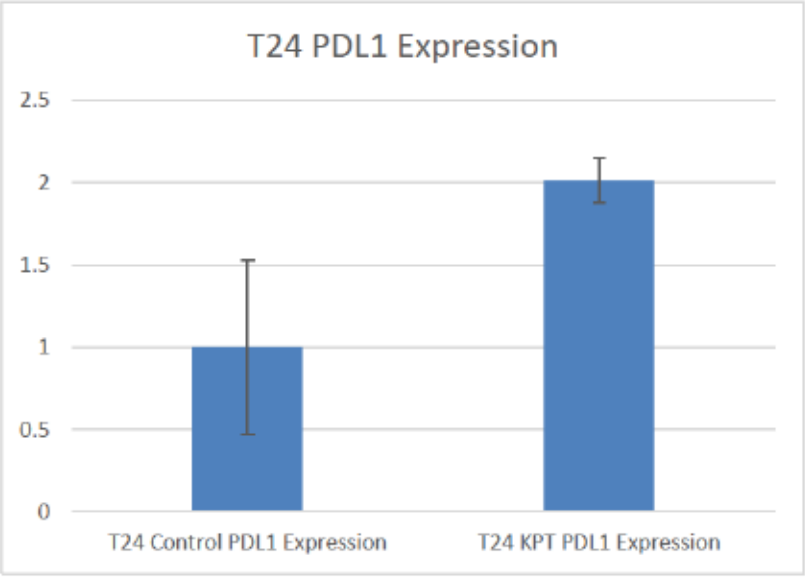
selinexor resulted in decreased tumor growth compared to control. Also demonstrated in these models were XPO1 inhibition, increased expression of p27, and decrease of cyclin A [23].

On the whole, these results suggest that selinexor has potential efficacy in patients with mUC.

2.1.3 Selinexor and Pembrolizumab Combination

Data suggest that the combination of immune checkpoint inhibition with selinexor may enhance the activity of selinexor. A preclinical trial of selinexor demonstrated increased CTLA4 and PDCD1 (which encodes PD-1) gene expression in leukocytes, and in melanoma models selinexor in combination with anti-PD-1 or with anti-PDL-1 antibodies decreased tumor growth rates [24]. In fact, the combination also increased NK cells and CD4+ T cells. In addition, Dr. Mudryj's lab also evaluated the effect of selinexor on 4 bladder cancer cell lines; in three of these cell lines, PD-L1 and PD-L2 expression was increased by selinexor (*unpublished data, example in Figure 1 below*), further supporting the combination of selinexor with pembrolizumab in treatment of urothelial carcinomas.

Figure 1: T24 Bladder Cancer Cell Line Treated with Selinexor 250 nM for 2 Days; PDL1 Expression by qPCR



2.2 Disease

Approximately 79,000 new cases of bladder cancer are diagnosed annually, with nearly 17,000 patients dying due to the disease every year [1]. The prognosis for patients who develop distant disease remains poor, with 5-year survival currently estimated at 5.2%. Cisplatin-based combination chemotherapy regimens have been the mainstay for metastatic urothelial carcinoma (mUC) for decades; while response rates are encouraging, only 10-15% of patients survive long term from these treatments [2-7]. Moreover, nearly half of patients with mUC cannot be treated with cisplatin-based chemotherapy due to comorbidities or poor performance status.

2.2.1 Treatment Options

The current treatment options for patients with platinum-refractory urothelial carcinoma is treatment with an anti-PD-1 or anti-PD-L1 agent, but response rates are generally around 20% [8, 10-12]. In the last year, erdafinib has been approved for use in patients with advanced urothelial carcinoma who have progressed after platinum-containing chemotherapy if they have a susceptible FGFR3 or FGFR2 genetic alteration. While the response rate in these patients is promising at ~40%, a limited number of patients have this genetic alteration.

2.3 Investigational Product Name and Description

2.3.1 Selinexor

Selinexor is a first-in-class, selective inhibitor of nuclear export (SINE) compound. It functions by binding with, and inhibiting, the nuclear export protein, XPO1.

2.3.1.1 Mechanism of Action

XPO1 is overexpressed in a large variety of malignancies including multiple myeloma (MM), osteosarcoma, pancreatic cancer, ovarian cancer, glioma, leukemia, and lymphoma and correlates with advanced disease, resistance to therapy, and poor survival. XPO1 exports tumor suppressor proteins (TSPs; eg, p53, p73, pRb, FOXOs, APC, PTEN) and growth regulatory proteins (GRPs; eg, p21, p27, survivin) out of the nucleus. These protein cargos mediate their cell cycle checkpoint/tumor suppression functions within the nucleus. Therefore, nuclear to cytoplasmic transport of these proteins by XPO1 leads to their functional inactivation. XPO1 also regulates the cytoplasmic localization and, in turn, translation of key proto oncogenic mRNAs (eg, Myc, BCL2, BCL6 and cyclin D) that complex with the XPO1 cargo protein, eukaryotic initiation factor 4E (eIF4E). In addition, XPO1 is involved in regulating nuclear levels of the glucocorticoid receptor (GR).

Inhibition of XPO1 by selinexor promotes apoptosis in malignant cells by blocking each of the above XPO1-mediated mechanisms. Because these mechanisms are relevant to any neoplastic

cell, selinexor has the potential to effectively treat a range of malignancies. Normal cells undergo reversible cell cycle arrest following inhibition of XPO1 and recover when the block is removed.

Selinexor is (2*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,24-triazol-1-yl}-*N*'-(pryazin-2—yl)prop-2-enehydrazide. It is a white to off-white powder and has the molecular formula $C_{17}H_{11}F_6N_{70}$ and a molecular mass of 443.31 g/mol. Each selinexor tablet contains 20 mg of selinexor as the active ingredient. Selinexor tablets are blue, round, bi-convex, film-coated tablets with "K20" debossed on one side and nothing on the other side. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate.

2.3.2 Pembrolizumab

Pembrolizumab is a monoclonal IgG4 kappa antibody blocking the PD-1 receptor. The antibody has an approximate molecular weight of 149 kDa. It is produced in recombinant Chinese hamster ovary (CHO) cells. It is an intravenous therapy administered at a dose of 200 mg intravenously (IV) over 30 minutes every 3 weeks, provided as a 100 mg/4 mL solution in a single-dose vial. It is approved for use in the treatment of patients with advanced urothelial carcinoma.

Pembrolizumab for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg) and sucrose (140 mg). may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab injection is also produced as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and water for injection, USP.

2.4 Summary of Nonclinical Data

2.4.1 Pharmacology

2.4.1.1 Selinexor

In nonclinical studies, selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nuclear, reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. Selinexor demonstrated pro-apoptotic activity in vitro in multiple myeloma cell lines and patient tumor samples, and in murine xenograft models. Selinexor exposure-response relationships and

the time course of pharmacodynamics responses are unknown. The effect of selinexor on QTc interval was evaluated in patients with heavily pretreated hematologic malignancies at a dose 2.2 times the approved recommended dose twice weekly, with no large effect on QTc interval at the therapeutic dose level.

2.4.1.2 Pembrolizumab

By binding to the PD-1 ligands, leading to PD-L1 and PD-L2 blockade, and to the PD-1 receptor found on T cells, pembrolizumab inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

2.4.2 Toxicology

2.4.2.1 Selinexor

Carcinogenicity studies have not been conducted with selinexor. It was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay and was not clastogenic in either the in vitro cytogenetic assay in human lymphocytes or in the in vivo rat micronucleus assay. Fertility studies in animals have not been conducted with selinexor. In repeat-dose oral toxicity studies, selinexor was administered for up to 13 weeks in rats and monkeys. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed in rats at $\geq$ 1 mg/kg, decreased ovarian follicles were observed in rats at $\geq$ 2 mg/kg, and single cell necrosis of testes was observed in monkeys at $\geq$ 1.5 mg/kg. These dose levels resulted in systemic exposures approximately 0.11, 0.28, and 0.53 times, respectively, the exposure (AUClast) in humans at the recommended human dose of 80 mg.

2.4.2.2 Pembrolizumab

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity. Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

In animal models, inhibition of PD-1 signaling resulted in an increased severity of some infections and enhanced inflammatory responses. M tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis

virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

2.5 Summary of Clinical Data

2.5.1 Pharmacokinetics and Product Metabolism

2.5.1.1 Selinexor

Following a single-dose administration of selinexor 80 mg, the mean (standard deviation) peak plasma concentration (Cmax) was 680 (124 ng/mL) and the mean AUC was 5386 (1116) ng-h/mL. Selinexor Cmax and AUC increased proportionally over doses from 3 mg/m^2 to 85 mg/m^2 (0.06 to 1.8 times the approved recommended dose based on 1.7 m^2 body surface area). No clinically relevant accumulation at steady state was observed. The Cmax is reached within 4 hours following oral administration of selinexor. Concomitant administration of high-fat meals did not affect the pharmacokinetics of selinexor to a clinically significant event. The apparent volume of distribution of selinexor is 125 L in patients with cancer.

The protein binding of selinexor is 95%. Following a single dose of selinexor, the mean half-life is 6 to 8 hours. The apparent total clearance of selinexor is 17.9 L/h in patients with cancer. Selinexor is metabolized by CYP3A4, multiple UDP-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs). No clinically significant difference in the PK of selinexor were observed based on age (18-94 years old), sex, ethnicity, mild to severe renal impairment (CLcr: 15-89 mL/min by Cockcroft-Gault). The effect of end-stage renal disease (CLcr<15 mL/min) or hemodialysis on selinexor PK is unknown. Mild hepatic impairment had no clinically significant effect on the PK of selinexor. The effect of moderate and severe hepatic impairment on selinexor PK is unknown. Selinexor is a substrate of CYP3A4 and of UGTs and GSTs. It inhibits OATP1B3 but does not inhibit other solute carrier (SLC) transporters. It is not a substrated of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K. Formal drug-drug interaction studies have not been performed.

2.5.1.2 Pembrolizumab

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma

concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

The geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%). Pembrolizumab clearance (CV%) is approximately 23% lower at steady state than that after the first dose; this decrease in clearance with time is not considered clinically important. The terminal half-life ($t_{1/2}$) is 22 days (32%). No clinically important effect on the CL of pembrolizumab was seen in regards to: age (range 15-94 years), sex, race (89% white), renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST >ULN or total bilirubin between 1-1.5x ULN and any AST), or tumor burden. The impact of moderate to severe hepatic impairment on the PK of pembrolizumab is unknown.

2.5.2 Summary of Clinical Safety

2.5.2.1 Selinexor

Selinexor was studied clinically at a dose of 80 mg in a Phase 2 study in combination with dexamethasone 20 mg, with both drugs given on Days 1 and 3 of every week. The median duration of selinexor treatment was 8 weeks (1-60 weeks). The median dose was 115.4 (36-200 mg) per week. The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the selinexor dose and 65.3% had a dose interruption. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received selinexor included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%. The most common (≥10% of patients) adverse reactions Grade ≥ 3 reported in patients with relapsed and refractory multiple myeloma who received selinexor and dexamethasone included thrombocytopenia, anemia, hyponatremia, and neutropenia (see Investigator's Brochure).

2.5.2.2 Pembrolizumab

The safety of pembrolizumab was investigated in KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible. Patients received pembrolizumab 200 mg IV every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression. The median duration of exposure to pembrolizumab was 2.8 months (1 day-15.8 months).

Pembrolizumab was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with pembrolizumab experienced sepsis which led to death, and three patients (0.8%)

experienced pneumonia that led to death. Adverse reactions leading to interruption of pembrolizumab occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥ 40 mg oral prednisone equivalent.

2.5.3 Risks

2.5.3.1 Selinexor

Based on findings in animal studies and its mechanism of action, selinexor can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose. Pregnant women must be advised to the risks to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production, thus women are advised not to breastfeed during treatment with selinexor and for 1 week after last dose. Safety and effectiveness have not been established in the pediatric population. Patients ≥ 75 years old had a higher incidence of discontinuation due to adverse reactions (44% vs 27%), higher incidence of SAEs (70% vs 58%) and higher incidence of fatal AEs (17% vs 9%) compared to younger patients.

2.5.3.2 Pembrolizumab

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. No available human data is available informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. Human IgG4 are known to cross the placenta. There are no data on the presence of pembrolizumab in either animal or human mild or its effect on the breastfed child or on milk production; women are advised not to breastfeed during treatment and for 4 months after final dose administration.

3.0 SUBJECT SELECTION

Subjects will be recruited from the UC Davis Comprehensive Cancer Center.

3.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

1. Pathologically confirmed locally advanced or metastatic urothelial carcinoma by histology.
2. Measurable disease by RECIST v1.1 criteria.
3. Not eligible to receive cisplatin-based chemotherapy due to renal dysfunction (defined as CrCl $\leq$ 60 mL/min), > Grade 2 peripheral neuropathy, or ototoxicity (defined as $\geq$ Grade 2 hearing loss); OR unwillingness of patient to receive cisplatin; OR progressed on one platinum-based chemotherapy regimen for advanced disease.
4. May have had neoadjuvant or adjuvant platinum-based chemotherapy or intravesical therapy in the past
5. Men and women ≥18 years of age.
6. ECOG performance status score of 0, 1 or 2 (see Appendix).
7. Life expectancy ≥ 3 months.
8. Hematology parameters defined by:
    a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L,
    b. Platelet count $\geq 75 \times 10^9$/L (patients for whom <50% of bone marrow nucleated cells are plasma cells) or $\geq$50,000/mm^3 (patients for whom ≥50% of bone marrow nucleated cells are plasma cells), and
    c. Hemoglobin ≥ 9 g/dL (may have been transfused)
9. Blood chemistry levels defined by:
    a. Total bilirubin level $\leq 1.5 \times$ the upper limit of normal (ULN) range (except patients with Gilbert's syndrome who must have a total bilirubin of $<3 \times$ ULN)
    b. AST and ALT levels $\leq 2.5 \times$ ULN, or AST and ALT levels $\leq 5 \times$ ULN (for subjects with documented metastatic disease to the liver)

c. Creatinine clearance ≥ 30 mL/min by Cockcroft-Gault formula

10. Subjects with active hepatitis B virus (Hep B) are allowed if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/mL prior to first dose of trial treatment. Subjects with untreated hepatitis C virus (HCV) are allowed. Subjects with Human Immunodeficiency Virus (HIV) who have CD4+ T-cell counts ≥ 350 cells/μL and no history of AIDS-defining opportunistic infections in the last year are allowed.

11. Willingness to undergo mandatory pre-treatment biopsy (unless there is adequate archival tumor specimen available for PD-L1 IHC evaluation).

12. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Or, female subjects of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to the first study drug administration.

13. Male and female subjects who are of reproductive potential must agree to use highly effective method of birth control (e.g., implants, injectables, birth control pills with two hormones, intrauterine devices [IUDs], complete abstinence or sterilized partner, and female sterilization) and a barrier method (e.g., condoms, vaginal ring, sponge, etc.) during the period of therapy and for 4 months after the last dose of study drug.

14. Ability to understand and willingness to sign an informed consent form.

15. Ability to adhere to the study visit schedule and other protocol requirements.

16. Must be able to swallow study drug.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

1. Receiving radiation ≤ 14 days prior to enrollment to the site of selected target lesions.

2. Systemic therapy for cancer ≤ 21 days prior to enrollment.

3. Autoimmune disorder requiring active therapy as defined by corticosteroids at a dose ≥ 10 mg oral prednisone or the equivalent or requiring chronic immunosuppressive therapy.

4. Use of corticosteroids ≤ 14 days prior to enrollment at a dose of ≥ 10 mg oral prednisone or the equivalent per day.

5. Received immune checkpoint inhibitor therapy (anti-PD-1, anti-PD-L1, or anti-CTLA4 directed therapy) on a prior clinical trial.
6. Has received selinexor or another XPO1 inhibitor previously.
7. Any active gastrointestinal dysfunction that could interfere with absorption of study treatment in the opinion of the investigator.
8. Pregnant or lactating women.
9. Any condition that would prohibit the understanding or rendering of informed consent.
10. Any condition including additional malignancies, laboratory abnormalities, or psychiatric illness that in the opinion of the investigator would interfere with the patient's safety or compliance while on trial.
11. Severe infection that in the opinion of the investigator would interfere with patient safety or compliance on trial within 4 weeks prior to enrollment.

4.0 STUDY DESIGN

This is a Phase Ib/II study using a 3+3 de-escalation design to identify the RP2D of selinexor in combination with fixed dose pembrolizumab during the Phase Ib portion. Due to toxicity observed at the currently approved dose of selinexor in patients with refractory multiple myeloma, the study will initiate with a lower dose of selinexor that has been previously established to be well-tolerated, with allowance for one dose level de-escalation.

4.1 Phase Ib

Patients with platinum-refractory or cisplatin-ineligible advanced urothelial carcinoma with measurable disease (as defined by RECIST v1.1), will be enrolled to this trial if they meet all other eligibility criteria (see Sections 3.1, 3.2).

Archival tissue will be required prior to treatment on the study. Following a 3+3 study design, initially 3 patients will be enrolled, with the proposed dose de-escalation plan shown in Table 1 and dose levels shown in Table 2. The RP2D will be the highest dose level at which 0/3 or 1/6 patients have DLT.

Table 1. Rules for Dose De-escalation

Number of Patients with DLT at a Given Dose Level	De-escalation Decision Rule
0 out of 3	Enroll 3 patients to same DL
0 out of 6	RP2D
1 out of 3	Enroll 3 patients to same DL
1 out of 6	RP2D
2 out of 3	If DL 1, deescalate one dose level If DL -1, stop study
2 out of 6	If DL 1, de-escalate one dose level If DL -1, stop study

Table 2. Dose Levels

Dose Level	Pembrolizumab	Selinexor
1 (Starting Dose)	200 mg IV every 3weeks (D1)	80 mg PO once weekly (D1, D8, D15)
-1	200 mg IV every 3weeks (D1)	60 mg PO once weekly (D1, D8, D15)
* Each cycle is 21 days		

Each treatment cycle will be 21 days in duration. Subjects will receive combination therapy for up to 24 months or until progression or intolerable toxicity. Patients will be assessed for toxicity every 3 weeks with clinical and lab monitoring, and the period for assessing dose-limiting toxicity (DLT) will be the first 6 weeks of treatment.

4.1.1 Definition of Dose Limiting Toxicity

Dose-limiting toxicity is defined as any clinically significant Grade 3 or higher non-hematologic toxicity requiring intervention as defined by NCI CTCAE version 5.0 and any Grade 4 or higher hematologic toxicity as defined by NCI CTCAE version 5.0 with the exception of the following:

- Immune-related Grade 3 or higher adverse event (AE) that resolves to Grade 2 or less within 21 days with glucocorticoids
- Grade 3 or higher endocrinopathies that resolve to Grade 2 or less with or without pharmacologic intervention within 21 days
- Grade 3 or higher nausea, vomiting that resolves to Grade 2 or less with pharmacologic intervention within 7 days
- Grade 3 hyponatremia that resolves within 7 days

Subjects who are not evaluable for toxicity will be replaced for DLT assessment. If subjects are unable to receive at least 75% of the intended selinexor dose for reasons other than toxicity and did not experience a DLT, those subjects will be replaced to allow for more accurate DLT assessment. Subjects who receive at least one dose of pembrolizumab are evaluable for DLT. Holding drug due to toxicity does not meet the definition of DLT as long as the subject receives at least 75% of the intended selinexor dose.

4.1.2 Definition of RP2D

The Recommended Phase 2 Dose (RP2D) is the highest dose of selinexor in combination with pembrolizumab at which there are 0 or 1/6 DLTs observed during the DLT assessment window (first 2 cycles).

4.2 Phase II Expansion at RP2D

After identification of the RP2D, an expansion cohort will be enrolled to receive combination therapy at the established RP2D. Additional patients will be enrolled in the Phase II portion of the study to accrue a total of 27 patients at the RP2D to further evaluate toxicity and to evaluate efficacy as defined by objective response rate. Combined selinexor and pembrolizumab will continue for 24 months or until progression or unacceptable toxicity.

Subjects will be assessed every 3 weeks clinically for toxicity. Subjects will be assessed every 6 weeks for response or progression to therapy for the first 12 weeks (after which they will undergo radiographic imaging every 12 weeks) and will continue on treatment until the time of unacceptable toxicity or until evidence of progressive disease by RECIST v1.1 on radiographic imaging.

Blood samples will be drawn on Day 0, Day 8 (±3 days) and Day 21 (±3 days) of Cycle 1, and when subjects come off study (±7 days).

5.0 TREATMENT OF SUBJECTS

5.1 Study Treatment Administration

Table 3: Dose Forms of Study Treatments

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg (single use vial)	Lyophilized Powder for Injection
Pembrolizumab 100 mg/4mL (single use vial)	Solution for Injection
Selinexor 20 mg	Oral tablets

5.2 Selinexor

5.2.1 Dosing and Administration

Selinexor starting dose for this study will be 80 mg (four 20 mg tablets) on Day 1, Day 8, and Day 15 of a 21-day cycle. Selinexor and pembrolizumab must be administered on Day 1, but the sequence of administration is at the discretion of the treating physician.

Selinexor tablets should be taken orally with at least 120 mL (4 ounces) of water at approximately the same time each day. It can be taken with or without food. Selinexor tablets should be swallowed whole (not crushed) to prevent an increased risk of dermatologic toxicity if the powder comes in contact with skin.

All patients will be given a diary to record the timing of taking selinexor over 21 days (see Appendix); the patient diary will be reviewed at each clinic visit.

In order to minimize nausea, all patients should receive 5-HT3 antagonists (ondansetron 8 mg or equivalent), unless contraindicated, approximately 30 minutes prior to and continued 2-3 times daily for 3 days after selinexor dosing. Alternative antiemetic agents may be used if the patient

does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonist. In addition, patients should receive olanzapine 2.5 mg oral QHS starting on Day 1 for at least the first 2 cycles. The olanzapine dose may be reduced to daily PRN due to side effects or stopped after 2 months if nausea is well controlled.

Missed or Vomited Doses

If a patient misses a dose of selinexor, then that dose should be replaced if the subject remembers within a 3 day window (within 72 hours of missed dose). Otherwise, patients should take the next dose the following week, without compensating for the missed dose. Do not double dose. Missed doses should be recorded in the eCRF. If a patient misses an infusion of pembrolizumab, dose may be replaced within 3 days.

If a dose of selinexor is vomited within 1 hour of ingestion, it may be replaced, but subject will need to notify study team. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose and the dose cannot be replaced

5.2.2 Formulation, Packaging, and Handling

Selinexor is formulated as a blue, round, bi-convex, film-coated immediate release 20 mg tablet with "K20" debossed on one side and nothing on the other side. Selinexor 20 mg tablets for oral administration will be packaged in wallet-sized child-resistant blister packs. Each blister pack has 12 tablets (see IST Pharmacy Manual for more information). Tablets should be stored at or below 30° C (86° F).

5.2.3 Preparation

Refer to the IST Pharmacy Manual for details of selinexor formulation, preparation, and administration.

5.2.4 How Supplied

Selinexor will be supplied by Karyopharm at no cost to study patients.

5.3 Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg as an IV infusion over 30 minutes on D1 (± 3 days) of a 21-day cycle provided both study drugs are taken on the same day.

Delayed infusions: If a patient misses an infusion of pembrolizumab, then that dose should be replaced within 3 days. Otherwise, this will be considered a missed dose.

5.3.1 Formulation, Packaging, and Handling

Pembrolizumab for injection as a clear to slightly opalescent, colorless to slightly yellow solution is packaged in a carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02). Vials should be stored under refrigeration at 2-8ºC (36-46º F) in original carton to protect from light. The vials should not be frozen and should not be shaken.

5.3.2 Preparation

Refer to the Pembrolizumab prescribing information for additional guidance on study drug storage, preparation and handling.

5.3.3 How Supplied

Pembrolizumab is commercially available and will be locally sourced from commercial, standard of care supplies.

5.3.4 Disposal and Destruction

Responsibility for drug accountability is on the investigator and the assigned pharmacist or designee. Drug supply will be disposed of according to institutional standard operating procedures. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the Drug Log.

5.4 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the Study Calendar. Patients will be followed for protocol-related toxicity for 30 days following the last dose of study treatment, whichever comes first. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Study Calendar for the list and timing of study assessments). **All serious adverse events (SAEs) will be reported in an expedited fashion**. In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

5.5 Dose Modification and Management of Toxicity

5.5.1 Dose Delay and Discontinuation

Toxicity necessitating dose modification or delay is based on NCI CTCAE v5.0 Toxicity Grade. The Investigator will assess whether each AE is related or not to each of the study drugs. Events that are judged definitely, probably or possibly related are considered related AEs. Events that are considered unlikely or definitely not related are considered not related AEs. Factors to be taken into consideration include the temporal relationship between administration of study drug and the onset of the AE, other potential causes of the AE including the subject's underlying medical condition and concomitant medications, whether the AE is consistent with known AEs previously attributed to a study drug, whether the AE decreases or resolves upon withholding or reducing the dose of the study drug, or whether the AE recurs upon reintroduction of the study drug.

5.5.2 Toxicities Necessitating Dose Modification or Delay

The following action in Table 4 and Table 5 should be taken for any study drug-related toxicity outlined below, divided into immune-mediated AEs (Table 4) and non-immune mediated AEs (Table 5).

Table 4. Dose Modification Due to Immune-Mediated Toxicity

Adverse Reaction	Severity	Dose Modification
Immune-mediated pneumonitis	Grade 2	Withhold pembrolizumab
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue pembrolizumab
Immune-mediated colitis	Grades 2 or 3	Withhold pembrolizumab and selinexor until resolution
	Grade 4	Permanently discontinue pembrolizumab. Continue selinexor at one dose level lower.
Immune-mediated hepatitis	AST or ALT greater than 3 but no more than 5 times the ULN or total bilirubin greater than 1.5 but no more than 3 times the ULN	Withhold pembrolizumab
	AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN	Permanently discontinue pembrolizumab
Immune-mediated endocrinopathies	Grade or 4	Withhold pembrolizumab until clinically stable, continue selinexor
Immune-mediated nephritis	Grade 2	Withhold pembrolizumab, continue selinexor
	Grade 3 or 4	Permanently discontinue pembrolizumab, continue selinexor
Immune-mediated skin adverse reactions	Grade 3 or suspected Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold pembrolizumab and selinexor until resolution. Resume selinexor at same dose level.
	Grade 4 or confirmed SJS or TEN	Permanently discontinue pembrolizumab, resume selinexor at one dose level lower.
Other immune-mediated adverse reactions	Grade 2 or 3 based on the severity and type of reaction	Withhold pembrolizumab, can continue selinexor if AE is not related to selinexor
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue pembrolizumab
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grade 3 or 4	Permanently discontinue pembrolizumab. Hold selinexor until resolution of symptoms, then resume.
Inability to taper corticosteroid	Requirement for $\geq$ 10 mg per day prednisone or equivalent for more than 12 weeks after last dose of pembrolizumab	Permanently discontinue pembrolizumab. Continue selinexor.
Infusion-related reactions	Grade 1 or 2	Interrupt or slow rate of infusion of pembrolizumab. Continue selinexor.
	Grade 3 or 4	Permanently discontinue pembrolizumab, continue selinexor

Table 5. Dose Modification Due to Non-Immune Mediated Toxicity

Adverse Reaction	Occurrence	Action*
Hematologic Adverse Reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL	Any	Reduce selinexor by 1 dose level
Platelet count 25,000 to less than 75,000/mcL with concurrent bleeding	Any	- hold selinexor and pembrolizumab - resume pembrolizumab and resume selinexor at 1 dose level lower after resolution of bleeding
Platelet count less than 25,000/mcL	Any	- hold selinexor and pembrolizumab - resume pembrolizumab and resume selinexor at 1 dose level lower after platelet count > 50,000/mcL
Neutropenia		
Absolute neutrophil count of 0.5- 1.0 x 10^9/L without fever	Any	Reduce selinexor by 1 dose level Continue pembrolizumab
Absolute neutrophil count less than 0.5 x 10^9/L OR febrile neutropenia	Any	Hold selinexor Monitor until neutrophil count returns to 1.0 x 109/L or higher Resume selinexor at one dose level lower Continue pembrolizumab
Anemia		
Grade 3	Any	Administer blood transfusions Reduce selinexor by one dose level Continue pembrolizumab
Grade 4	Any	Discontinue selinexor Hold pembrolizumab until AE $\leq$ Grade 2, then resume
Hyponatremia		
Sodium level <130 mmol/L	Any	Hold selinexor and pembrolizumab Monitor until sodium levels return to 130 mmol/L or higher Resume selinexor at 1 dose level lower, resume pembrolizumab
Fatigue		
Grade 2 lasting greater than 7 days or Grade 3		Hold selinexor and pembrolizumab Monitor until fatigue resolves to Grade 1 or baseline Resume selinexor at 1 dose level lower; resume pembrolizumab
Nausea and Vomiting		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) OR Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	Continue selinexor and pembrolizumab, add additional anti-nausea medications.

Grade 3 nausea or Grade 3 or higher vomiting	Any	Hold selinexor. Monitor until symptoms resolve to Grade 2 or lower Add additional anti-nausea medications Resume selinexor at one dose level lower
Diarrhea		
Grade 2	1st occurrence without supportive care	Continue selinexor and pembrolizumab Add supportive care
	2nd and additional occurrence with optimal management	Reduce selinexor by one dose level, continue pembrolizumab Continue supportive care
Grade 3 or higher	Any	Hold selinexor; hold pembrolizumab if any suspicion of colitis Add supportive care Monitor until resolution to Grade 2 or less Resume selinexor at one dose level lower, continue pembrolizumab
Weight loss and Anorexia		
Weight loss of 10% to less than 20% OR anorexia associated with significant weight loss or malnutrition	Any	Hold selinexor, continue pembrolizumab Monitor until weight $\geq$ 90% of baseline weight Resume selinexor at one dose level lower
Weight loss of >20%	Any	Discontinue
Infections		
Active uncontrolled or suspected infections	Any	Hold until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose (see section 5.5.3.1)

*study drugs can be held for up to 12 weeks, after which patient must come off study

5.5.3 Selinexor Dose Modifications

Dose reductions due to intolerable toxicity are allowed per Section 5.5.2 above. Schedule modifications are allowed in some cases per treating investigator. For some AEs, dose interruption and/or reduction is recommended. See Table 6 for pre-specified dose modifications for AEs related to study treatment and see Table 5 for dose reduction and interruption recommendations.

While drug-related major organ toxicities are not prominent, thrombocytopenia and a number of constitutional side effects can limit dosing with selinexor. Therefore, patients should also be treated with supportive care to reduce toxicities. In addition, it should be noted that the constitutional side effects often attenuate over the first 4 to 6 weeks of dosing. Finally, some patients with rapid tumor responses experience significant fatigue, nausea, malaise and/or asthenia after one or more doses of selinexor. This effect has not been associated with typical

markers of TLS, but if suspected, assessment of tumor response is strongly recommended in order to better inform treatment recommendations.

The CTCAE v5.0 is used for grading the severity of AEs; the therapy modifications described in Table 6 are applied according to this severity grading. Toxicity will be documented as described in Section 12. If more than one type of toxicity occurs concurrently, the most severe grade will determine the modification.

Each dose modification or treatment delay, as well as the reason, must be documented.

Table 6. Pre-specified Dose Modifications for AEs Related to Selinexor Treatment

Selinexor Dose Level[1]	Selinexor Dose Schedule
Dose level 1	80 mg once per week[2]
Dose level -1	60 mg once per week[2]
Dose level -2	40 mg once per week[2]

1. For some AEs, dose interruption rather than reduction is recommended. See Table 5 for specific recommendations.
2. On Days 1, 8, and 15.

Table 7. Supportive Care and Selinexor Dose Adjustment Guidelines for AEs Related to Selinexor

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[1,2]
Fatigue	
Grade 1	Maintain dose. Rule out other causes. If found to be anemic and symptomatic, consider transfusing even with hemoglobin >8 g/dL (anemia Grade <3). Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Grade 2 lasting ≤7 days	As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.
Grade 2 lasting >7 days or Grade ≥3	Rule out other causes. If found to be anemic and symptomatic, consider transfusions for hemoglobin >8 g/dL (Grade <3); transfusions usually indicated for Hb <8 g/dL (Grade ≥3). Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level. Patients with significant fatigue after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation. As per NCCN guidelines, consider stimulants such as methylphenidate 5mg QD in the morning only.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[1,2]
Anorexia or Weight Loss	
Grade 1 anorexia	Maintain dose. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®). For persistent symptoms, initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 1 weight loss Grade 2 anorexia	Initiate appetite stimulants, such as olanzapine (2.5 to 5 mg PO every morning) or megesterol acetate (400 mg QD), as per NCCN guidelines.
Grade 2 weight loss Grade 3 anorexia, or Grade 3 weight loss	Interrupt selinexor dosing until improved to Grade 1 or baseline and weight stabilizes. Reduce selinexor by 1 dose level. Rule out other causes. Consider nutritional consultation and use nutritional supplements (eg, Ensure®, Boost®) Initiate appetite stimulants as above,
Nausea, Acute	
Grade 1 or 2	Maintain dose. Rule out other causes. Use standard additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists. If persistent, use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia.
Grade 3	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonist(s). Olanzapine 2.5 to 5 mg PO every morning, as per NCCN guidelines, can mitigate nausea and anorexia. Interrupt selinexor dosing until resolved to Grade ≤2 or baseline and reduce selinexor by 1 dose level. Patients with significant nausea/vomiting after several doses of selinexor may have an antitumor response. Consider an unscheduled assessment of tumor response as part of the patient's evaluation.
Hyponatremia	
Grade 1 (sodium levels < Normal to 130 mmol/L)	Maintain dose. Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). Treat hyponatremia per institutional guidelines including dietary review. Provide supplemental oral and/or intravenous fluids if dehydration is present. Consider addition of salt tablets to patient's diet.
Grade 3 with sodium levels <130-120 mmol/L without symptoms	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose >150 mg/dL). If (corrected) sodium is Grade ≤3 and continues to be asymptomatic, then patient may continue current dosing without interruption provided that IV saline and/or salt tablets are provided and patient is followed closely. If Grade 3 is persistent or worsens or does not respond to treatment, interrupt selinexor dosing until resolved to Grade 1 or baseline and reduce selinexor by 1 dose level.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[1,2]
Grade 3 with sodium levels <130-120 mmol/L with symptoms or Grade 4 (<120 mmol/L)	Rule out other causes including drug (e.g., diuretic) effects. Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL). Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level.
Diarrhea	
Grade 1	Maintain dose. Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals, such as loperamide.
Grade 2	Rule out other causes including drug effects. Treat per institutional guidelines with anti-diarrheals. Interrupt selinexor dosing until resolved to Grade 1 or baseline. For first occurrence, restart selinexor at current dose. For ≥ second occurrence, reduce selinexor by 1 dose level.
Grade 3 or 4	Interrupt selinexor dosing until resolved to Grade 1 or baseline and patient is clinically stable. Reduce selinexor dose by 1 dose level.
Thrombocytopenia	
Grade 1 or 2	Maintain dose. Rule out other causes including drug effects.
Grade 3 without bleeding	Rule out other causes including drug effects. For first occurrence: skip 1 dose and reduce selinexor by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents such as romiplostim 5 to 10 µg/kg SC weekly (preferred) or eltrombopag 100 to 150 mg QD. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, due to prior marrow-toxic therapy), or if there is thrombocytopenia Grade 2 to 4 at baseline, the Investigator in consultation with the Sponsor investigator may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored. Thrombopoietin stimulating agents are recommended.
Grade 4 without bleeding	Rule out other causes including drug effects. Interrupt selinexor until patient recovers to Grade 2 or baseline. Selinexor dosing may be reduced by 1 dose level (it is recommended to have only 1 dose modification per cycle) If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above. In cases where there is significant disease involvement in the bone marrow or pre-existing compromised marrow function (eg, due to prior marrow-toxic therapy), the Investigator in consultation with the Sponsor investigator may decide to continue selinexor dosing without dose reductions and/or interruptions as specified above, provided that platelet counts and bleeding symptoms/signs are closely monitored.
Grade ≥3 with bleeding	Interrupt selinexor dosing and check platelet counts weekly until the bleeding has stopped, patient is clinically stable and the platelets have recovered to Grade 2 or baseline. When resuming selinexor, reduce by 1 dose level. If recurrent, unless contraindicated, initiate treatment with moderate to high doses of thrombopoietin stimulating agents as above.

Toxicity and Intensity	Supportive Care and Dose Adjustment Guidelines[1,2]
Neutropenia	
Grade 3 or 4 neutropenia (afebrile) OR Febrile neutropenia	Institute colony stimulating factors and prophylactic antibiotics as clinically indicated per institutional guidelines. Interrupt selinexor and check neutrophils at least weekly until recovers to Grade 2 or baseline and without fever (if febrile) and the patient is clinically stable. Reinitiate selinexor therapy and colony stimulating factors per institutional guidelines. If recurrent, continue colony stimulating factors, interrupt selinexor until neutrophil counts improve to Grade ≤2 or baseline levels, and reduce dose of selinexor 1 dose level.
Anemia	
Treat per institutional guidelines including blood transfusions and/or erythropoietins. Consider transfusing for symptoms with hemoglobin >8 g/dL (Grade <3) or for any Grade 3 (hemoglobin <8 g/dL). If possible, maintain selinexor dose as long as patient is clinically stable, but if a dose reduction or interruption is desired, consult with the Sponsor-Investigator.	
Tumor lysis syndrome	
If TLS risk factors are identified, provide prophylactic IV hydration and regular monitoring of hydration (especially when increasing the dose of selinexor), renal function, urine output, and clinical laboratory measures of interest for TLS (e.g., phosphorus, potassium, calcium, LDH, uric acid). Consider administration of hypouricemic agents to reduce the risk of TLS. Hold selinexor in patient with hyperkalemia (≥7.0 mmol/L) and/or symptoms of hyperkalemia, an increase in uric acid, or other changes in biochemical blood parameters suggestive of TLS. Start IV hydration, and consider hypouricemic agent until levels return to normal. Selinexor can be reintroduced at the normal or reduced dose.	
Other selinexor-related adverse events	
Grade 1 or 2	Rule out other causes. Maintain dose. Start treatment and/or standard supportive care per institutional guidelines.
Grade 3 or 4	Rule out other causes. Interrupt selinexor until recovers to Grade 2 or baseline and reduce selinexor by 1 dose level. Isolated values of Grade ≥3 alkaline phosphatase do NOT require dose interruption. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5'-nucleotidase, or other liver enzymes should be performed.

IV: intravenous; NCCN: National Comprehensive Cancer Network; QD: once daily; PO: oral; SC: subcutaneous: TLS: tumor lysis syndrome.

1. For all Grade ≥3 hematologic or non-hematologic AEs that are NOT selinexor related, after consultation with the Sponsor investigator and at the discretion of the Investigator, selinexor dosing may be maintained.
2. For all selinexor-related AE's, if the below prescribed dose reductions/interruptions result in a stabilization of ≥4 weeks, a re-escalation may be considered after approval from the Sponsor-Investigator.

All dose modifications should be based on the worst preceding toxicity.

Note: When toxicities due to selinexor have returned to baseline levels or the patient has stabilized, the dose of selinexor may be re-escalated in consultation with the Sponsor-Investigator.

5.5.3.1 Selinexor Dose Adjustment in the Setting of Infection

Patients with active uncontrolled or suspected infections should have treatment withheld until the infection has clinically resolved and/or the patient is clinically stable. When ready to resume dosing, treatment may continue at the original dose. Missed doses will not be replaced. Patients may continue antibiotics for prolonged periods while re-initiating their treatment at the discretion of the Investigator.

5.5.3.2 Conditions Not Requiring Selinexor Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. Selinexor does not need to be interrupted or reduced in the following cases:

- Alopecia of any grade
- Electrolyte or serum analyte (eg, urate) abnormalities except for hyponatremia that are reversible with standard interventions
- Isolated values of Grade ≥3 alkaline phosphatase. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed.

5.5.1 Criteria to Resume Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) outlined in Table 4 and Table 5 resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects who have experienced a Grade 3 drug-related skin AE that is deemed to require treatment hold may resume treatment in the presence of Grade 2 skin toxicity.
- Drug-related pulmonary toxicity that is deemed to require treatment hold must have resolved to baseline before treatment is resumed.
- Any exception outlined in Table 4 and Table 5
- Subjects may resume pembrolizumab if study drug is held due to selinexor-attributable toxicity. Patients can continue selinexor if held due to pembrolizumab-attributable toxicity.

5.6 Instructions for Initiation of Each Cycle

Each cycle of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1000/mm³;
- The platelet count is ≥ 75,000/mm³ (patients for whom <50% of bone marrow nucleated cells are plasma cells) or ≥50,000/mm³ (patients for whom ≥50% of bone marrow nucleated cells are plasma cells);
- No evidence of life-threatening infection.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

6.0 TREATMENT DURATION

Subjects will receive combination therapy for up to 24 months unless one of the following criteria applies:

- Confirmed disease progression per RECIST v1.1
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Patient withdrawal from study (patient choice)
- Pregnancy
- Patient receives alternative cancer-directed treatment
- Study termination
- Physician Discretion

6.1 Discontinuation Criteria

6.1.1 Discontinuation from Study Treatment

Patients will be discontinued from study treatment due to disease progression per RECIST v1.1 criteria, due to unacceptable toxicity either in the opinion of the investigator or the patient, or if the patient withdraws consent.

6.1.2 Discontinuation Due to AEs

Patients will discontinue study treatment due to unacceptable toxicity per section 4.1.1 at any time while on study treatment, but patients will continue clinical follow-up until disease progression or initiation of new treatment. In the case of AEs Grade > 3, if in the opinion of the investigator or the patient, the patient can no longer be assessed clinically due to severity of illness, the patient will be discontinued from the trial, but will be included in the toxicity evaluation for the study.

6.2 Duration of Follow Up

All patients will be followed for 30 days after the last dose of treatment or until all treatment related toxicities resolve to baseline or Grade ≤ 1. Adverse events with attribution of possible, probable, or definite will be reported following guidelines for adverse event reporting, and all SAEs will be reported for 30 days after the last dose.

Patients will be followed every 3 months per SOC for documented progression, PFS, until death, loss to follow up, consent withdrawal, or study termination.

Patients who discontinue study treatment early will be followed for progression free survival (PFS) every 3 months as part of their routine SOC management.

6.3 Termination of Treatment and Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for safety, behavioral or administrative reasons.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the End of Treatment Visit.

Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to institutional, federal, and any other committees and/or funding source as appropriate.

7.0 CONCOMITANT AND EXCLUDED MEDICATION

7.1 Concomitant Therapy

Prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents prior to and during treatment with selinexor will be administered. Alternative treatment may be provided if the patient does not tolerate 5-HT3 antagonists. Intravenous hydration may also be offered to patients while on therapy.

No concomitant therapy is required during treatment with pembrolizumab.

7.2 Excluded Therapy

Patients must not take prednisone at a dose of greater than 10 mg PO daily (or equivalent dose of any other corticosteroid).

Patients are prohibited from taking immunosuppressive agents such as cyclosporine, methotrexate, mycophenolate mofetil, infliximab.

7.3 Permitted Therapy

Prednisone is permitted at a dose $\leq$ 10 mg PO per day.

8.0 STUDY CALENDAR

Evaluation	Pre-Treatment		Treatment Cycles (3-week cycles)	End of Treatment[9]	Post-Treatment[11]
	Screening[1] (# days prior to first dose)		All Cycles[3]		Safety Visit
Scheduling Window (days)	≤ 28	≤ 14	± 3		± 7
History					
Medical History	X		X		X
Clinical/Laboratory/Assessments					
Physical Exam		X	X		X
Vital Signs		X	X		X
AE and Concomitant Medications			Continuously		
Hematology (CBC with Differential)		X	X		X
Serum Chemistry (CMP)[12]		X	X		X
TSH		X	X		X
HepB/C, HIV	X				
Pregnancy Test (if applicable)[6]		X			
Chest/Abdomen/Pelvis CT Imaging[2]	X		X		
Correlatives					
Pre-treatment Tissue Biopsy	X[4]				
Blood Sample		X	X[5]		
Study Treatment Administration					
Selinexor[7]			X		
Pembrolizumab[8]			X		

1. Screening: Screening clinical safety laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed ≤ 14 days prior to first dose.
2. Imaging will be accepted if performed ≤ 60 days prior to first dose. CT imaging assessment will be performed every 6 weeks for first 4 cycles of treatment, then every 12 weeks.
3. DLT assessment window is 6 weeks.
4. Pre-treatment tissue biopsy is required only if patient does not have available archival tissue. See Section 10.0.
5. Blood samples for correlative studies will be obtained on Day 0, Day 8 (±3 days) and Day 21 (±3 days) of Cycle 1, and when subjects come off study (±7 days).
6. For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. During trial treatment, urine pregnancy tests should be performed as clinically indicated.
7. Selinexor is taken on Day 1, Day 8, and Day 15 of each cycle.
8. Pembrolizumab is administered on D1 of each cycle. Pembrolizumab should taken on the same day as Selinexor.
9. End of Treatment is at the time the decision is made to take the subject off study treatment.
10. Safety Visit: 28 days after subject is taken off study treatment.
11. Follow up: Every 3 months from End of Treatment per standard of care for survival follow up and PFS. PFS will be assessed using RECIST 1.1 criteria.

12. Determination of liver versus bone etiology should be made, and evaluation of gamma-glutamyl transferase, 5' nucleotidase, or other liver enzymes should be performed (see section 5.5.3.2).

9.0 STUDY EVALUATIONS

9.1 Screening Phase

The screening phase is defined as the time interval between when the subject signs the informed consent (ICF) and the time of registration.

During Screening, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Study Calendar. Screening procedures will be performed ≤ 28 days prior to first dose, unless otherwise specified. Imaging will be accepted if performed ≤ 60 days prior to first dose. Screening clinical safety laboratory evaluations can be used for Cycle 1 Day 1 assessments if performed ≤ 14 days prior to first dose.

9.2 Treatment Phase

One cycle of treatment is 21 days in which the subject will receive the combination therapy, and the treatment phase is up to a total of 24 months.

The Treatment Phase will begin at Cycle 1 Day 1 and will continue until the study drug is discontinued. The last measurements taken on Day 1 of Cycle 1 before administration of the study drug or at screening (whichever value was last) will be defined as the baseline values.

9.3 End of Treatment Visit

An end-of-treatment (EoT) visit should be at the time the decision is made to take the subject off study treatment. If a subject is unable to return to the site for the EoT visit, the subject should be contacted to collect AEs that occurred within 30 days after the last dose of study drug.

9.4 Follow-up Phase

The safety follow-up phase is the interval between the end of treatment visit and scheduled safety follow up visit which will occur 28 (±7 days) days after discontinuation of combination therapy. Patients will be followed every 3 months per SOC for documented progression, PFS, until death, loss to follow up, consent withdrawal, or study termination. Patients who discontinue study treatment early will be followed for progression free survival (PFS) every 3 months as part of their routine SOC management.

If the subject starts on a new anticancer drug before 30 (±7 days) days after discontinuation of study drugs, the safety follow up visit should be prior to the start of new therapy. If the subject discontinues treatment without disease progression, the subject will be followed every 3 months (or patient standard of care schedule) by imaging to monitor disease status. Once the subject starts a new therapy or has progression of disease, the subject's survival status should be followed with chart review, telephone, or email until death or withdrawal of consent.

9.5 Efficacy

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [1]. Changes in the largest diameter (unidimensional measurement) of the tumor lesion is used in the RECIST criteria [25].

9.5.1 Response Criteria

9.5.1.1 Evaluation of Target Lesions by RECIST 1.1

- **Complete Response (CR)**: Disappearance of the target lesion
- **Partial Response (PR)**: At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD)**: At least a 20% increase in the sum of the LD of target lesion, or the appearance of one or more new lesions
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

9.5.1.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8. Best Overall Response Evaluation

Best Overall Response Evaluation		
Target Lesion	**New Lesion**	**Overall Response**
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue.

When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.5.1.3 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For reporting the study outcomes the response rate and confirmed response rate will be made clear. To be assigned the status of confirmed responses must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol. For PD all results should be confirmed as described in section 6.2.

9.5.1.4 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

9.5.1.5 Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started. The clinical

relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

9.5.1.6 Objective Response Rate

ORR is defined as the percentage of patients that achieve PR or CR.

9.5.1.7 Disease Control Rate (DCR)

DCR is defined as the percentage of patients that achieve an objective tumor response or have stable disease to therapy confirmed by imaging 6 weeks apart.

9.5.1.8 Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration, or failure to complete all prescribed study therapy, does not result in exclusion from the analysis of the response rate. All conclusions should be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). The reasons for excluding patients from the analysis should be clearly reported.

9.6 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, and the regular monitoring of vital signs, and physical condition as shown in corresponding tables. For details on AE collection and reporting, refer to the Safety section in the protocol (Section 12).

9.6.1 Adverse Events

Potential AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) beginning at initiation of study treatment and

ending 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. Investigators will determine if the events are recorded as AEs. AEs will be followed by the investigator as specified in Section 12.

10.0 CORRELATIVES

We hypothesize that (1) XPO1 expression will be associated with responses to therapy on this trial, (2) the frequency of CD4+ T-cells and INF-gamma+ producing CD4 T cells will increase with treatment with pembrolizumab and Selinexor.

In this study, pre-treatment tumor biopsy or archival FFPE tissue will be required for evaluation of correlative studies. In addition, blood samples will be collected for optional immunologic and molecular correlative studies on Day 0, Day 8 (±3 days) and Day 21 (±3 days) of Cycle 1, and when subjects come off study (±7 days). Pre-treatment tumor biopsy and pre- and post-treatment blood samples will be obtained as outlined in Section 10.1 & 10.2. Blood and tumor tissue will be banked for correlative studies.

Table 9. Correlative Studies

Biomarker Name[a] AND Lead PI and Site	Assay (CLIA: Y/N)	Use (Integral, Integrated, or Exploratory)AND Purpose [b]	Tissue/Body Fluid Tested and Timing of Assay	Mandatory /Optional	Funding Source(s)
CD4+ and CD8+ T cells	Flow cytometry CLIA: N	Integrated Assess absolute increase in CD4 due to Selinexor + pembrolizumab	PBMC D0, 8, 21, off study	O	Karyopharm-pending
CD4+ and CD8+ T cells/INF-gamma producing	Flow cytometry CLIA: N	Integrated Assess increase in INF-producing CD4 due to Selinexor + pembrolizumab	PBMC D0, 8, 21, off study	O	Karyopharm-pending
INF-gamma	ELISA CLIA: N	Integrated Assess absolute increase in INF due to Selinexor + pembrolizumab	PBMC D0, 8, 21, off study	O	Karyopharm-pending
NK, T cell and monocyte functional assays	Various techniques CLIA:N	Exploratory Assess the effect of Selinexor + pembrolizumab on T and NK cell function	PBMC D0, 8, 21, off study	O	Karyopharm-pending
NK cell killing assay	ADCC assay CLIA:N	Exploratory Assess the effect of Selinexor and pembrolizumab on NK cell function	PBMC D0, D8, D21, off study	O	Karyopharm-pending

Distribution, phenotype, and frequency of mononuclear cell subsets, serum and T-cell specific cytokines will be examined at the indicated time points summarized in the table above. After preparation of PBMCs via standard procedure, cells will be analyzed using a multi-parameter, Hi-D FACS to determine the frequency and phenotype of mononuclear subsets including: B cells, helper T cells, cytotoxic T cells, regulatory T cells, naïve T cells, memory T cells, NKT cells, NK cells (and subtypes).

Table 10. Phenotypic Markers for Analysis of Various Immune Cells

Cell Subset		Phenotype Marker
T cell	$CD4^+$ helper T cell	$CD3^+CD4^+$ (+/- INF)
	$CD8^+$ cytotoxic T cell	$CD3^+CD8^+$ (+/- IFN)
	Regulatory T cells	$CD3^+CD4^+CD25^+Foxp3^+$
	Naïve T cell	$CD4^+/CD8^+CD45RA^+CD11a^+$
	Memory T cell	$CD4^+/CD8^+CD45RO^+CD11a^+$
	NK T cell	$CD3^+CD56^+CD16^+$
	iNKT cell	$CD3^+CD56^+CD16^+6B11^+CD1d^+$
		$CD4^+$,& $CD8^+$ /PD-1^+, & PDL-1^+
		$CD4^+$, & $CD8^+$ Tim-3^+,& Lag-3^+
NK cell		$CD3^-CD56^+CD16^+$ +/_ Granzyme B
B cell	B2 cell	$CD19^+IgD^+CD11b^-CD5^-$
	B1a cell	$CD19^+IgM^+CD11b^+CD5^+$
	B1b cell	$CD19^+IgM^+CD11b^+CD5^-$

Functional Analysis

NK, T, and monocyte function will be assayed at indicated timepoints. Assay of PBMC's for T cell and monocyte activation: PBMC's will be purified from blood using ficol/hypaque and (1x105cells/well in 200 µL culture media) will be cultured in quadruplicate 96-well U-bottom plates for each condition: culture medium alone or medium supplemented with CD3/CD28 mAb (0.5 µg/ml), or PHA (5 µg/ml) for T cell activation and LPS (1 mcg/ml) for monocyte activation. Cells will be incubated for 3-5 days at 37°C, 5% CO2. The culture supernatants will be collected and stored at -70°C. The supernatants will be assayed for several cytokines/chemokines (e.g. IL-2, IFN-γ, IL-17, IL-10, IL-4, TNF-α, TGF-β) using the Multiplex Bead-based Luminex®

Technology, Cytokine Human 10-Plex Panel (or if batched with other samples, the Cytokine Human 25-Plex Panel) (Invitrogen, Carlsbad, CA), see below.

NK functional assay: Human NK cells will be identified as described NK (CD3-CD56+CD16+), NKT (CD3+CD56+CD16+) and iNKT cells will be sorted from blood. The sorted NK/NKT cells will be stimulated with poly IC for 12 and 24 h. iNKT cells will be stimulated with iNKT cell-specific ligand, α-GalCer. Supernatants will be collected to analyze the levels of IFN-gamma, IL-6 and IL-8 using the BD cytometric bead array kit per the manufacturer's recommendations. IFN-gamma and IL-4 will be measured by CBA kit or intracellular staining. Sera cytokine will be measured by CBA kit.

NK Cell Killing Activity: NK cells bind to, and kill K562 cells (a human myelogenous cell line, ATCC) thus forming the basis of this functional killing assay; this flow cytometric assay can detect binding and killing.

K562 cells. Spontaneous lysis will be tested at each time point using equivalently cultured K562 cells in the absence of effectors. If we encounter any problems with this assay, a standard 51Cr-release assay will be done, testing groups equivalent to those described above.

Serum biomarkers: Serum will be archived from patients prior to, during and after treatment with Selinexor and pembrolizumab.

Multiplex Bead-based Luminex® Technology: The microbead multiplex detection system developed by Invitrogen) enables detection of numerous cytokines simultaneously in a single reaction container. In this technology, molecular reactions take place on the surface of microscopic plastic beads (2 um). For each reaction, capture molecules (i.e., mono-specific antibodies) are covalently attached to the surface of internally color-coded microbeads. The assigned color-code identifies the reaction in a specific microbead population throughout the test. Multiplex capability involves mixing several populations of microbeads, each with a specific capture molecule, into one reaction vessel at the start of the test. The magnitude of the biomolecular reaction is measured using a reporter molecule which signals the extent of the reaction by attaching to the test molecules captured on the microbeads. To perform a test, the color-coded microbeads, reporter molecules, and sample (e.g., tumor cell lysate) are mixed and then injected into the Luminex flow cytometer where lasers illuminate the colors inside and on the surface of each microbead. This method is rapid, sensitive, and quantitative, and lends itself to high-throughput in an economical fashion.

Serum Cytokines: The Luminex assay for immunologic analytes will include 37 different cytokines and growth factors (including IL-1, 2, 4, 5, 6, 7, 10,12, 17, TNF, INF-γ, TGF-beta, GM-CSF, PDGF, and VEGF) (Invitrogen). This test will allow for the ultrasensitive determination of cytokines in the serum of patients before and during treatment with Selinexor

and pembrolizumab. This will allow for the identification of potential biomarkers that might predict a response to the combination of Selinexor and pembrolizumab.

INF-gamma producing CD4+ and CD8+T cells: PBMCs isolated at indicated time points will be assessed for IFN-gamma production form both CD8+ and CD4+ T cells using intracellular flow cytometry. Approximately 10^6 PBMC's will be stained with fluorochrome-conjugated antibody for detection of CD4 and CD8 (Dako) for 30-60 minutes and washed with fixation/permeabilization solution (eBioscience). Cells will be then washed with permeabilzation buffer after centrifugation, blocked with 2% rat/mouse serum followed by adding the recommended amount of anti-INF-gamma flurochrome-conjugated antibody (Dako) for 30 minutes. Cells will be washed twice with permeabilization buffer followed by resuspension in Flow Cytometry Staining buffer (eBioscience) and analyzed by flow cytometry (BD Coulter). Data will be collected using a FACS ARIA (BD Biosciences) and analyzed by "Flowjo" flow cytometry data analysis software (Tree Star Inc, Ashland, OR).

10.1 Blood

One 10 mL EDTA tube of whole blood will be collected at screening and processed by the Molecular Pharmacology Shared Resource (MPSR). Whole blood will be centrifuged at 2000 x g for 15 minutes to separate plasma from buffy coat and red blood cells (RBC). Plasma will be discarded, and buffy coat will be collected ~2 mL and mixed well and placed into 2 x 1 mL cryotubes, stored at -80°C until delivery to Dr. Maverakis's lab. Tubes will be labeled with study, study ID, date and time of collection. (See above for studies intended)

10.2 Tissue

Tissue will be collected from a pre-treatment biopsy or archival specimen if the latter is available. Urothelial carcinoma tissue will be collected from FFPE blocks processed by the standard protocols of the Department of Pathology. A board certified pathologist will identify tumor on the clinical H&E slides. Paraffin sections and cores will be prepared by the Biorepository shared resource. We will request 5 FFPE slides sectioned at 5 microns or 3mm x 5mm cores (if possible) based on tumor volume. Planned studies include PD-L1 expression by IHC and XPO1 expression by IHC. Using institutional standards, XPO1 IHC analysis standards will be validated prior to performing this study's analysis. Using established Department of Pathology guidelines, PD-L1 expression by IHC analysis will also be performed.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size

To establish the RP2D, a 3+3 de-escalation study design is employed; this will require a minimum of 6 patients and up to 12 patients. Only two dose levels are included in this trial. These were chosen because the first dose level is a reduced dose from the FDA-approved level that has been reported to be well-tolerated in patients with multiple myeloma. We anticipate it to be well-tolerated in combination with pembrolizumab, but have included one dose level reduction in the event that unexpected toxicity is observed. Our hypothesis is that a dose level reduction below 60 mg weekly of selinexor would indicate that the combination of selinexor and pembrolizumab is not well-tolerated and should not be further developed. Once RP2D is established, additional patients will be enrolled for a total of 27 patients at the RP2D evaluable for response assessment. This will provide further evaluation of true toxicity- for example, if the true AE rate is 10%, then the probability of observing at least one adverse event as a function of true rate and number of patients on trial is 47% with a 6 patient cohort as would be obtained in the 3+3 dose-de-escalation. The inclusion of an additional, at minimum, 12 patients would improve the probability of observing at least one AE as a function of true rate and number of patients to 85% if the true AE rate is 10%.

Assuming a response rate of 20% for pembrolizumab alone in this study population based on historical controls, a sample size of 27 patients will allow for detection of an improvement to ORR of 45% with 80% power, at the 0.05 level (2-sided) based on this single stage Phase II design.

11.2 Statistical Analysis Plan

The RP2D is defined in Section 4.1.2. Dose limiting toxicities will be listed according to dose level. All enrolled patients who initiate combination therapy will be considered, unless the patient stops therapy during the DLT assessment period for a reason other than DLT.

Separately by dose level and the expansion cohort (as well as for the total RP2D cohort), AEs will be summarized as number of patients according to NCI CTCAE term and grade, where grade is the maximum across a patient's treatment period. Grade 3 and higher AEs will be listed, according to dose level and patient. The number (%) of patients who experience $\geq$ 1 Grade 3-5 AEs will be reported, as well as the proportion with exact binomial 95% CI

For reporting of AEs, the safety-evaluable patients are those who received at least one dose of both selinexor and pembrolizumab.

Objective response rate (ORR) will be reported as a primary endpoint for all evaluable patients-evaluable patients are considered patients who received at least one dose of the RP2D of selinexor and standard-dose pembrolizumab and had at least one imaging assessment after enrollment. Objective response rate, calculated as the total number of patients with a confirmed CR or PR, will be reported as a percentage of total evaluable patients. Disease control rate, calculated as the total number of patients with a confirmed CR, PR or stable disease, will be reported as a percentage of total evaluable patients at the RP2D. Each will be reported with exact binomial 95% CI. Progression-free survival (PFS) will be reported as defined as time from enrollment to trial to time of disease progression or death from any cause, and will be reported with exact binomial 95% CI.

Exploratory analyses of tumor tissue sample will be undertaken upon completion of study follow-up. Tumor tissue will be analyzed for XPO1 expression by IHC (per Pathology Department validated assay); those patients with IHC 2+ will be reported as positive. The frequency of XPO1 expression positivity among patients in this study will be reported with 90% CI. A descriptive table evaluating XPO1 expression (positive or negative) versus objective response (yes or no) will be produced without formal statistical testing. Similar analysis will be undertaken to evaluate the relationship between PD-L1 expression and objective response. Using flow cytometry, analyzing PBMCs derived from blood samples, baseline and post-treatment NK, CD4, and CD8 T-cell levels will be measured for each patient. Pre- and post-treatment T-cell levels will be reported descriptively (quantitatively and as a % change between pre- and post-treatment) and graphically first for all patients on trial, and then separately among those who have an objective response rate, and those who do not have an objective response rate. These studies will be conducted once accrual and follow-up is complete, assuming availability of adequate resources.

11.3 Safety

NCI CTCAE v5.0 criteria will be used to document safety data by patient and by dose level.

11.4 Efficacy

As a primary endpoint, all responses will be reported using RECIST 1.1 definitions. Objective response rate will be summarized by exact binomial confidence intervals. Progression-free survival will be captured as a secondary endpoint, with a Kaplan-Meier plot and estimate of median PFS with 95% confidence interval.

11.5 Subject Course

Information regarding the subject's course such as completing the study treatment, dose delays, premature discontinuation and major protocol violation will be tabulated and summarized.

12.0 SAFETY AND REPORTING REQUIREMENTS

12.1 Adverse Events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

12.1.1 Severity of Adverse Events

The severity of an AE is graded as follows:

Grade 1 (Mild):	The event causes discomfort that affects normal daily activities.
Grade 2 (Moderate):	The event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Grade 3 (Severe):	The event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Grade 4 (Life-threatening):	The patient was at risk of death at the time of the event.
Grade 5 (Fatal):	The event caused death.

12.1.2 Causality (Attribution) of Adverse Events

The investigator is to assess the causal relation of all AEs (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Probably Related:	The AE is likely related to investigational product.
Related:	The AE is clearly related to use of the investigational product.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

12.1.3 Serious Adverse Events

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization**
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.

- Is a **medically important event or reaction**. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

12.1.4 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures.

12.2 Procedures for Handling Special Situations

12.2.1 Pregnancy and Breastfeeding

Pregnant patients are not permitted to enroll in this trial. During screening for enrollment, all women of reproductive potential will undergo urine pregnancy testing and will be excluded from participation if found to be pregnant. If a patient becomes pregnant during treatment, the patient will have to discontinue study treatment immediately, but would continue with follow-up assessment per study.

Note: Pregnancy per se is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

Female patients of childbearing potential and fertile male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use highly effective contraception listed below (i.e., results in a low failure rate when used consistently and correctly) during the dosing period and for a period of at least 4 months after the end of treatment.

A list of highly effective methods of contraception is provided in the Appendix.

A pregnancy test will be performed on each premenopausal female patient of childbearing potential $\leq$ 3 days prior to the first dose of study drug. During trial treatment, urine pregnancy tests should be performed as clinically indicated. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor Sponsor investigatorof this event and record the Pregnancy on the Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm's Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm Pharmacovigilance.

The pregnancy should be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

All pregnancies occurring within 4 months after the patient's last dose of study drug must be reported to Karyopharm, regardless of whether the patient received the Karyopharm study drug or other study drugs, withdraws from the study, or the study is completed. Patients should be instructed to inform the Investigator regarding any pregnancies.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs (described in Section 9.2.3).

A pregnancy in a female partner of a male patient must be reported to Karyopharm Pharmacovigilance within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a selinexor-containing regimen. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether selinexor passes into the breast milk. Mothers should not breastfeed while being treated with a selinexor-containing regimen.

12.2.2 Overdose

An overdose is a deliberate or accidental administration of any Karyopharm study drug to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, Karyopharm Pharmacovigilance should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be recorded. Information regarding the overdose is to be recorded on Karyopharm's SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

As selinexor is metabolized by GSH conjugation, it is possible, but not demonstrated, that hepatic GSH depletion might occur in case of extreme overdose. Therefore, in overdose cases, if patients develop liver function test abnormalities, supportive measures such as SAM or other drugs that can replace GSH might be considered as part of the overall management plan.

12.2.3 Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the Karyopharm study drug which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with the Karyopharm study drug are to be recorded on Karyopharm's SAE report form and sent to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

12.3 Procedures for Reporting Adverse Events

12.3.1 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the IRB and to the FDA in accordance with CFR 312.32 (IND Safety Reports).

12.3.2 Adverse Event Reporting Period

- AE will be reported and recorded from the time of the first dose of study drug through 30 days after the last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.
- SAEs will be reported to Karyopharm from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. All SAEs must also be reported to Karyopharm Pharmacovigilance

Investigators are not obligated to actively seek information regarding the occurrence of new SAEs beginning after the 30-day post last dose period. However, if the investigator learns of such an SAE and that event is deemed relevant to the use of study treatment, he/she should promptly document and report the event.

12.3.3 Procedures for SAE Reporting

12.3.3.1 Initial and Follow up Reports

Every SAE, regardless of the causal relationship to the Karyopharm study drug, occurring after the patient has signed informed consent until at least 30 days after the patient has stopped the Karyopharm study drug must be reported to the Karyopharm Pharmacovigilance Department within 24 hours of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department
Karyopharm Therapeutics Inc.
Email: pharmacovigilance@karyopharm.com
Fax: +1-617-334-7617 (USA)
+49-89-9218-5650 (Germany)

Karyopharm will report applicable SAEs to other applicable regulatory authorities and Investigators utilizing selinexor, as may be required.

12.3.3.2 Additional Investigator Responsibilities on Follow-up of SAEs

The investigator and supporting personnel responsible for patient care should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include extra clinical laboratory tests, physical examinations or consulting an appropriate specialist. If a patient dies during the follow-up period for the SAE, the event causing the death will be reported as part of that SAE. The relationship between the SAE and the death should be specifically addressed.

12.3.3.3 Additional Reporting Requirements for IND Holders

For Investigator Sponsored IND Studies there are some additional reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 312.32.

Sponsor-investigators of studies conducted under an IND are required to report all serious, unexpected, and related adverse events directly to the FDA on a MedWatch Form FDA 3500A within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

The Sponsor-Investigator will notify the FDA according to the following timelines:

- within **7 calendar days** of any unexpected fatal or life-threatening adverse event with possible relationship to study drug;
- within **15 calendar days** of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

FDA fax number for IND Safety Reports: **(800) FDA-0178** or **(800) 332-0178**

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report to the FDA. For adverse events that are either serious but don't meet the criteria for expedited reporting or are not serious, the FDA will be notified at the time of the IND Annual Report.

MedWatch Form FDA 3500A Reporting Guidelines

In addition to completing appropriate demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch Form FDA 3500A:

- Treatment regimen (dosing, frequency, combination therapy)
- Protocol description (include number if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive diagnostic and laboratory results
- Investigator's assessment of the relationship of the SAE to each investigational product and suspect medication

Follow-up information:

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch Form FDA 3500A and submitting it as follow-up
- Adding supplementary summary information and submitting it as follow-up with the original MedWatch Form FDA 3500A

Summarizing new information and submitting it with a cover letter including subject identifiers (i.e., DOB, initials, subject number), protocol description and number, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted

12.3.3.4 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Comprehensive Cancer Center's (UCDCCC) Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

Participating site(s) will report adverse events per institution's IRB guidelines.

13.0 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

13.2 Institutional Review Board

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board (IRB).

13.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

13.4 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCDCCC OCR. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.5 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. After verifying the eligibility, the OCR coordinator will register the patient onto the study and assign a patient accession. Administration of study drug may not be initiated until the patient is registered (See Appendix).

13.6 Protocol Compliance and Deviations

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies. Any departures from the protocol must be fully documented in the source documents.

13.7 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

13.8 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan. Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

14.0 OVERSIGHT AND MONITORING

14.1 Data and Safety Monitoring

In addition to the requirements for adverse event reporting, this protocol is also subject to the UC Davis Comprehensive Cancer Center's (UCDCCC) Data and Safety Monitoring Plan. The UCDCCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCCC to fulfill its mission in conducting high quality clinical cancer research.

As per UCDCCC Office of Clinical Research (OCR) standard operating procedures the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events, and to determine if dose de-escalation is warranted, when applicable.

According to the UCDCCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCCC Scientific Review Committee (SRC) determines if a UCDCCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information, and dose de-escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

14.2 Investigator Monitoring Guidelines

Investigators will conduct continuous review of patient safety. Patients will be monitored monthly during the study. All patients on active treatment will be discussed at weekly conferences that are held at the University of California, Davis. Per Cancer Center guidelines, a trial cannot proceed to the next dose level until a DLT meeting is conducted to comprehensively review all toxicity data and approve the dose de-escalation. The discussion will include for each dose level: the number of patients, significant toxicities as described in the protocol, doses adjustments, and responses observed.

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16.0 APPENDICES

16.1 ECOG and Karnofsky Performance Status Scores[1,2]

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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16.2 Cockcroft-Gault Estimation of CrCl

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

(**Males**)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

(**Females**)

16.3 Study Registration

Once signed, informed consent has been obtained; patients will be entered on study. To register a patient, the study coordinator must complete the Eligibility Checklist. The study coordinator will register the patient onto the study and assign a unique patient number.

16.4 Data Collection Forms

All data will be collected using UC Davis data collection forms. Any and all source documentation shall be maintained.

16.5 NCI CTC Version 5.0

Toxicity will be scored using NCI CTC Version 5.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 5.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC version.

16.6 Pill Diary for Selinexor

Protocol Number: UCDCC#289

PATIENT NAME: _____ **MEDICAL RECORD #:** _____

CYCLE#: _____ **START DATE:** _____ **DOSE:** _____

Instructions to Patients: In the table below, please provide time, date, and number of tablets for each dose taken. Doses should be taken around the same time each day. Selinexor tablets should be swallowed whole with water; the tablet must not be broken, chewed, crushed or divided. If a dose is missed, then that dose should be replaced within a 3 day window (within 72 hours of missed dose). Otherwise, patients should take the next dose the following week, without double dosing, and leave cell blank; confirm with study coordinator upon return of pill diary.

Take selinexor once daily on Day1, Day 8, and Day 15 of a 21-day cycle. Selinexor will be provided as 20 mg tablets for oral administration. Tablets must be swallowed whole. Subjects should take their dose in the morning with or without food.

Day	1	2	3	4	5	6	7
	_____ Time: _____ Date: _____ # Pills:						
Day	**8**	**9**	**10**	**11**	**12**	**13**	**14**
	_____ Time: _____ Date: _____ # Pills:						
Day	**15**	**16**	**17**	**18**	**19**	**20**	**21**
	_____ Time: _____ Date: _____ # Pills:						

Patient Signature: _____ Date: _____

Date Returned	# of pills left	Collector's Initials	Returned to Pharmacy
			Yes or N/A

16.7 Correlative Sample Collection and Handling

Blood samples will be collected pre- and post-treatment and will be stored in the UC Davis Biorepository, with assistance from Anthony Martinez.