CLINICAL STUDY PROTOCOL

XPORT-MEL-033

A PHASE 2 OPEN-LABEL MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SELINEXOR IN COMBINATION WITH PEMBROLIZUMAB IN RECURRENT ADVANCED MELANOMA

Study Number:	XPORT-MEL-033
Study Phase:	Phase 2
Investigational Product:	Selinexor (KPT-330)
Indication:	Locally advanced unresectable or metastatic melanoma
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Protocol Date and Version:	20 January 2021, Version 1.0 22 March 2021, Version 2.0 22 July 2021, Version 3.0
CONDUCT In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.	
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PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study XPORT-MEL-033 dated 22 July 2021 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPD PPD

PPD **MD** **Date**

PPD

Karyopharm Therapeutics Inc.

PPD PPD

PPD **PhD** **Date**

PPD

Karyopharm Therapeutics Inc.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study XPORT-MEL-033 dated 22 July 2021 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practice, ICH E6, and applicable FDA regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Institution

_____

Date

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
BIW	twice weekly
CI	confidence interval
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CRR	complete response rate
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EoT	end of treatment
FDA	Food and Drug Administration
hCG	human chorionic gonadotropin
5-HT	5-hydroxytryptamine
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
irAE	immune-related adverse events
IRB	institutional review board
IRC	independent review committee

Abbreviation	Definition
iRECIST	immunotherapy Response Evaluation Criteria in Solid Tumors
IST	investigator-sponsored trial
IV	intravenous
LAG-3	lymphocyte antigen 3
MAPK	mitogen activated protein kinase
mITT	modified intent-to-treat
mAb	monoclonal antibody
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDn	pharmacodynamic
PFS	progression-free survival
PHI	protected health information
PO	per oral
PR	partial response
PT	preferred term
QW	once weekly
Q3W	every 3 weeks
Q6W	every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SINE	selective inhibitor of nuclear export
SoA	schedule of assessments
SOC	system organ class

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse events
ULN	upper limit of normal
XPO1	exportin 1 (also called CRM1)

3. PROTOCOL SUMMARY

3.1. Synopsis

Sponsor:	**Investigational Product:**	**Study Phase:**
Karyopharm Therapeutics Inc.	Selinexor	Phase 2

Title of Study: A Phase 2 Open-Label Multicenter Study to Evaluate the Safety and Efficacy of Selinexor in Combination with Pembrolizumab in Recurrent Advanced Melanoma

Protocol Number: XPORT-MEL-033

Study Location: Up to 20 sites in the United States

Study Rationale:

Selinexor (XPOVIO®) is a first-in-class oral selective inhibitor of nuclear export (SINE) compound, specifically inhibiting exportin-1 (XPO1). XPO1 has a key role in nuclear export of the proteins harboring a leucine-rich nuclear export sequence. Enhanced cytoplasmic accumulation of several tumor suppressor proteins has been suggested as an additional mechanism acquired by cancer cells to attain enhanced proliferative potential. XPO1 has been identified as 1 of 7 key candidate genes that may be therapeutic targets for melanoma; in addition, XPO1 mRNA is ~2-fold overexpressed in metastatic melanoma as compared with normal melanocytes and nevi.

XPO1-mediated nuclear export controls the localization of multiple proliferation-associated proteins including Rb p53, p21, p27, FOXO-3A transcription factors, mitogen-activated protein kinase/extracellular signal–regulated kinase (Mek), extracellular signal–regulated kinase (Erk) and Survivin further suggesting its potential deregulation in tumors and targetability. It has been demonstrated that XPO1 inhibition while reversing cytoplasmic Erk localization and inducing persistent Erk signaling hyperactivity induces multiple cell context–dependent molecular alterations that effect G1 arrest followed by melanoma cell apoptosis (Wu, 2019; Pathria, 2012).

Programmed cell death protein 1 (PD-1) is expressed on the surface of cytotoxic T cells, and its ligand programmed death ligand-1 (PD-L1) is expressed on both melanoma tumor and immune cells. The inhibition of interactions between PD-1 and PD-L1 by agents such as nivolumab and pembrolizumab (Robert, 2015) causes the reactivation of cytotoxic T cells, leading to the recognition and destruction of melanoma cells (Hodi, 2018; Robert, 2015; Jiang, 2019; Yang, 2020). Despite the impressive activity of anti-PD-1/L1 agents in melanoma, between 40%-65% of metastatic melanoma patients are shown to be resistant to checkpoint inhibitor (CPI) mono- or combination therapy (Fenton 2019).

Resistance to anti-PD-1/L1 therapy may be of three types:

- primary resistance defined by inability of immune cells to mount an antitumor response as noted by stable disease (SD) lasting for <6 months or no response to therapy.
- secondary or acquired resistance defined by confirmed objective response or prolonged SD ≥6 months but develop disease progression later.
- Disease progression after discontinuation of CPI in patients who are treated with either adjuvant or neoadjuvant therapy where duration of therapy is limited.

The LEAP-004 study evaluated the use of pembrolizumab with the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) lenvatinib, in patients who had progressive disease (PD) while on anti-PD-1 mAb. The objective response rate (ORR) in advanced melanoma patients with confirmed progression on CPI therapy was 21.4% (95% CI: 13.9, 30.5) with a disease control rate (DCR) of 66.0% (95% CI: 56.0, 75.1). The median progression free survival (PFS) was 4.2 months (95% CI: 3.8, 7.1) and the median overall survival (OS) was 14.0 months (95% CI: 10.8, not reached). The majority of patients (62 out of 103; 60.2%) had primary resistance to anti-PD-1 mAb in the

metastatic setting (Arance, 2021). Despite the improvement seen in patients with this combination, patients develop rapid disease progression and require improved treatment options.

Selinexor may overcome resistance to anti-PD-1/L1 mAbs by blocking nuclear export compounds which are implicated in regulating the inhibitory T cell receptor PD-1 and its ligand, PD-L1, such nuclear factor of activated T cells (NFAT)1c, signal transducer and activator of transcription (STAT)1 and STAT3. It is hypothesized that the retention of these regulatory compounds in the nucleus leads to an upregulation of T cell checkpoint molecule expression. This allows selinexor, when combined with anti-PD-1 mAbs, to enhance the antitumor activity (Farren, 2017).

Preclinical studies have shown that (1) XPO1 inhibitors kill malignant melanoma cells while sparing normal melanocytes and other normal cells (Pathria, 2012, Yang, 2014, Breit, 2014) (2) oral selinexor showed single agent anti-tumor activity at clinically relevant doses in immunocompetent mice bearing B16 melanoma tumors and did not impair anti-tumoral immunity (Tyler, 2017), (3) oral selinexor in combination with anti-PD-1 or anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mAbs showed synergistic activity in immunocompetent mice bearing aggressive syngeneic melanoma (Farren, 2017).

The preclinical results have been borne out in early clinical studies. In a Phase 1 clinical trial of single-agent oral selinexor in patients with advanced, heavily pretreated solid tumors (KCP-330-002), a total of 14 patients with melanoma received at least 1 dose of selinexor. The ORR in these heavily pretreated patients was 14.3% with 1 patient achieving a complete response (CR) and 1 patient achieving a partial response (PR) (Abdul-Razak, 2016).

Preliminary results from the ongoing investigator-sponsored trials study (NCT02419495) evaluating selinexor 60 mg twice weekly (BIW) in combination with pembrolizumab (200 mg IV [intravenous] once every 3 weeks [Q3W]) in patients with metastatic melanoma has shown promising anti-tumor activity. Amongst the 28 patients who were evaluable for efficacy, 22 patients were diagnosed with non-uveal melanoma; 9 of them naïve to prior CPI and the other 13 were refractory to CPI therapy. The ORR among patients with CPI-naïve and CPI-refractory melanoma was 67% and 31%, respectively, with 3 CRs. The longest duration of treatment for 1 CR patient who was CPI-naïve was 17 months, with the patient withdrawing from treatment due to the CR. The median PFS was 8.8 months (95% CI: 4.2, 30.7). The range was 0.13 to 54.4. The 3-month PFS rate was 0.76 (95% CI: 0.62, 0.93). The 6-month PFS rate was 0.66 (95% CI: 0.50, 0.85). The 9-month PFS rate was 0.47 (95% CI: 0.32, 0.70). The 12-month PFS rate was 0.44 (95% CI: 0.29, 0.67). The median follow-up time was 19.1 months. The median OS was 30.7 months (95% CI: 10.2, not reached). The range was 0.13 to 54.4. The 3-month OS rate was 0.93 (95% CI: 0.84, 1). The 6-month OS rate was 0.79 (95% CI: 0.66, 0.96). The 9-month OS rate was 0.72 (95% CI: 0.57, 0.91). The 12-month OS rate was 0.68 (95% CI: 0.53, 0.88). Adverse events (AEs) in the study were similar to those reported previously for selinexor and pembrolizumab with no clear overlapping toxicities. Adverse events attributed to both pembrolizumab and selinexor included hematological toxicities, fatigue, nausea, and low sodium. Hypokalemia and gastrointestinal AEs were attributed to selinexor (data on file).

An alternative dosing regimen for selinexor in combination with pembrolizumab has been explored in the study KCP-330-027: selinexor 80 mg once weekly (QW) each week plus 200 mg pembrolizumab once every 3 weeks in patients with advanced or metastatic microsatellite stable (MSS) colorectal cancer. This combination regimen was well tolerated in the first 12 patients treated in this study. Only 1 patient had a single dose interruption due to Grade 2 nausea and then resumed the treatment at the same dose level after nausea was resolved. These findings indicate that selinexor 80 mg QW with pembrolizumab 200 mg Q3W is a tolerable regimen in patients with advanced, heavily pretreated colorectal cancer (data on file).

The preclinical and preliminary clinical data of selinexor alone and in combination with pembrolizumab indicates anti-melanoma activity and tolerability that warrant further exploration. Based on the clinical activity and the patients' tolerability seen in the clinical study KCP-330-027

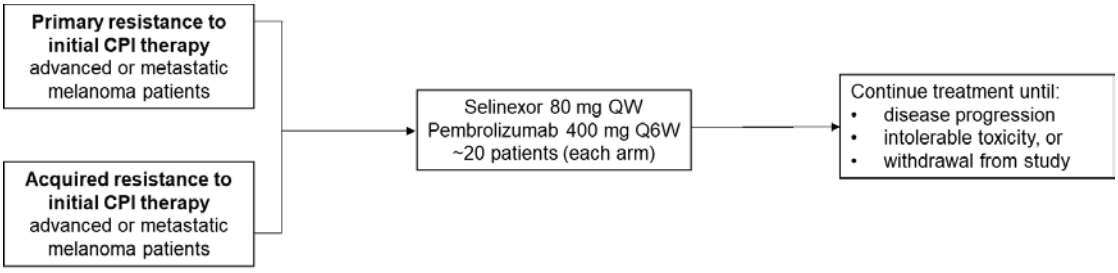
mentioned above, the regimen of selinexor 80 mg QW in combination with pembrolizumab will be explored in this study. In this study, we will be using the once every six weeks (Q6W) schedule of pembrolizumab due to the approved use of the 400 mg IV dosing schedule in the US. This open label Phase 2 study is aimed to evaluate the efficacy and safety of selinexor in combination with pembrolizumab in patients with unresectable locally advanced or metastatic (Stage III or IV) melanoma that demonstrated either primary resistance to anti-PD-1/L1 mAb or acquired resistance to anti-PD-1/L1 mAb.

Overall Study Design:

Approximately 40 patients with locally advanced or metastatic melanoma will be enrolled into one of the following 2 arms:

- **Primary resistance to initial checkpoint inhibitor (CPI) therapy (Arm A)**: Selinexor 80 mg orally (PO) QW+ Pembrolizumab 400 mg IV Q6W
- **Acquired resistance to initial CPI therapy (Arm B)**: Selinexor 80 mg PO QW + Pembrolizumab 400 mg IV Q6W

XPORT-MEL-033 Study Design



CPI: checkpoint inhibitor; Q6W: once every six weeks; QW: once weekly

Objectives and Endpoints: The primary efficacy endpoint for this signal finding study will be ORR assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 response criteria. Evaluation of the radiographic data for disease progression will be based on a scan review by the Investigator.

The objectives and endpoints for both arms to evaluate the treatment with selinexor plus pembrolizumab are the same and are listed below:

Objectives	Endpoints
Primary	
• To evaluate objective response rate (ORR) per RECIST v1.1 response criteria	• ORR defined as proportion of patients who achieved a complete response (CR) or partial response (PR).

Secondary	
• To evaluate progression-free survival (PFS) per RECIST v1.1 response criteria	• PFS defined as time from date of first treatment to the date of first confirmed progressive disease (PD), or death due to any cause, whichever occurs first.
• To evaluate overall survival (OS)	• OS defined as time to death, from the date of first treatment.
• To evaluate rates of CR	• Complete response rate (CRR), defined as proportion of patients who achieved a CR.
• To evaluate duration of response (DOR)	• DOR defined as the duration of time from first occurrence of response ≥PR until the first date of PD or death due to any cause, whichever occurs first.
• To evaluate disease control rate (DCR)	• Defined as the percentage of patients who have achieved CR, PR, and stable disease (SD).
• To evaluate the safety and tolerability of selinexor and pembrolizumab combination regimen.	• Safety and tolerability of study treatment will be evaluated based on adverse events (AE) reports, vital signs, clinical laboratory results, and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
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Number of Patients (planned):

Approximately 40 patients with advanced metastatic melanoma with disease resistant to CPI therapy will be enrolled.

Study Population: Eligible patients must fulfill all inclusion criteria and no exclusion criteria.

Inclusion Criteria

1. Age ≥ 18 years at the time of informed consent
2. Patient must have a histologically confirmed diagnosis of locally advanced unresectable stage III or metastatic stage IV melanoma not amenable to local therapy.
    a. Patients must have confirmed PD per RECIST on or within 12 weeks of the last dose of anti-PD-1/L1 monotherapy or combination therapy (including relatlimab or other anti-LAG-3 mAb) per Society for Immunotherapy in Cancer Guidelines (Kluger, 2020)
    b. Arm A (primary resistance): patient has disease progression after receiving at least 6 weeks of prior anti-PD-1/L1 mAb with the best response as PD, or SD<6months (patients with a PR or CR who have disease progression within 6 months will be considered to have primary resistance in this study).
    c. Arm B (secondary/acquired resistance): patient has disease progression after receiving at least 6 months of prior anti-PD-1/L1 mAb with the best response as CR, PR, or SD>6 months (patients who have disease progression after neoadjuvant or adjuvant therapy, will be considered to have secondary resistance in this study).
    d. Patients who progress on or within 12 weeks after elective discontinuation of anti-PD-1/L1 mono or combination treatment in the absence of PD or treatment limiting toxicity must have confirmed PD per RECIST.
3. Patients should have at least 1 prior line of CPI therapy but no more than 2.
4. Measurable disease according to RECIST v1.1.
5. Patients with stable previously treated brain metastases are permitted in this study.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤1

7. Adequate bone marrow function at screening, defined as:
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    b. Hemoglobin ≥ 10 gm/dL (≥6.2 mmol/L)
    c. Platelet count ≥100 × 10^9/L
8. Serum direct bilirubin ≤1.5 × ULN; AST and ALT ≤ 2.5 × ULN (with confirmed liver metastases: AST and ALT ≤ 5 × ULN)
9. Calculated creatinine clearance (CrCl) ≥15 mL/min based on the Cockcroft and Gault formula.
10. Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use highly effective methods of contraception throughout the study and for at least four months following the last dose of study treatment. Childbearing potential excludes: age >50 years and naturally amenorrhoeic for >1 year, or previous bilateral salpingo-oophorectomy, or hysterectomy.
11. Male patients who are sexually active must use highly effective methods of contraception throughout the study and for at least four months following the last dose of study treatment.Male patients must agree not to donate sperm during the study treatment period.
12. Written informed consent signed in accordance with federal, local, and institutional guidelines

Exclusion Criteria

1. Metastatic uveal or ocular melanoma.
2. Active central nervous system (CNS) metastases or other CNS (e.g., meningeal) involvement.
3. Patients must have resolution or improvement of immune-mediated treatment-related adverse reactions related to prior treatment(s) to Grade ≤ 1 without steroid maintenance therapy or his or her previous baseline prior to the corresponding CPI therapy
    a. History of immune-mediated treatment-related adverse reactions leading to discontinuation of prior anti-PD-1, anti-PD-L1, or anti-PD-L2 mAbs or severe hypersensitivity reaction to any mAb or any excipients which in the opinion of the Investigator precludes future use of anti-PD-1/PD-L1 therapy.
4. Concurrent systemic steroid therapy higher than physiologic dose (> 10 mg/day of prednisone or equivalent).
5. Previous treatment with selinexor or other XPO1 inhibitors.
6. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:
    a. Not recovered from major surgery ≤28 days prior to Day 1 dosing. Minor procedures, such as biopsies, dental work, or placement of a port or intravenous (IV) line for infusion are permitted.
    b. Have ongoing clinically significant anti-cancer therapy-related toxicities Common Terminology Criteria for Adverse Events (CTCAE) Grade >1. In specific cases, patients whose toxicity has stabilized or with Grade 2 non-hematologic toxicities can be allowed following documented approval by the Sponsor's Medical Monitor
    c. Had last dose of previous anti-cancer therapy ≤14 days prior to Day 1 dosing

d. Palliative radiotherapy >14 days prior to the study is allowed
e. Received investigational drugs in other clinical trials within 28 days, or 5 half-lives of the investigational drug (whichever is shorter), prior to C1D1

7. Live-attenuated vaccine (e.g., nasal spray influenza vaccine) ≤14 days prior to the intended C1D1
8. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of selinexor (e.g. vomiting, or diarrhea that is CTCAE v5.0 grade >1).
9. Life expectancy <4 months based on the opinion of the Investigator
10. Active pneumonitis requiring steroid therapy.
11. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 7 days prior to first dose of study treatment; however, prophylactic use of these agents is acceptable (including parenteral).
12. Any life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, prevent the patient from givinginformed consent, or being compliant with the study procedures.
13. Female patients who are pregnant or lactating.
14. Active hepatitis B virus treated with antiviral therapy for hepatitis B within 8 weeks with a viral load >100 IU/mL.
15. Untreated hepatitis C virus positive without documentation of negative viral load per institutional standard.
16. Human immunodeficiency virus positive with CD4+ T-cells ≤ 350 cells/uL, positive viral load per institutional standard, and a history of acquired immunodeficiency syndrome - defining opportunist infections in the last year.

Study Treatment Cohorts and Dosing

All patients will receive:

- selinexor 80 mg PO QW and
- pembrolizumab therapy, 400 mg IV Q6W on Day 1, per the Keytruda® USPI.

In order to minimize nausea, unless contraindicated all patients must receive 2 anti-emetics initially: a 5-hydroxytryptamine 3 (5-HT3) antagonist (ondansetron 8 mg or equivalent), starting 30-60 minutes before administration of selinexor and continued 2-3 times daily for at least 2 days after selinexor dosing. A neurokinin-1(NK-1) antagonist or another anti-emetic agent should be used as per the label per National Comprehensive Cancer Network (NCCN) Guidelines. Alternative or additional anti-emetic agents may be used if the patient does not tolerate or has inadequate anti-emetic effect with 5-HT3 antagonists.

Duration of Treatment and Follow-up:

Patients will receive study treatment until disease progression, toxicity or withdrawal from the study, whichever occurs first. Disease response or progression will be assessed Q9W for the first 6 months, then every 3 months thereafter. Note: per Investigator's discretion, and upon discussion with the Sponsor Study Director, patients with a prolonged response or stable disease can discontinue pembrolizumab after 24 months of treatment and continue with selinexor monotherapy.

Patients will be followed for survival after the end of treatment (EoT) visit every 3 months for 12 months, or until withdrawal of consent, death, or the end of study (i.e., when the last patient in the study has been followed up on study treatment for at least 1 year, or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up), whichever occurs first. End of treatment imaging will be performed ≤28 days after treatment discontinuation for patients who discontinue for reasons other than PD if their previous scan was performed >3 weeks before EoT.

After discontinuation of study treatment, patients will also be followed for safety 30 days after EoT and then every 3 months for 12 months and for PFS approximately every 3 months after EoT visit until PD, death or initiation of the subsequent anti-melanoma treatment (if a patient discontinues from the treatment due to reasons other than PD).

Statistical Methods:

Analysis Populations:

The modified intent-to-treat (mITT) population will consist of all patients who receive at least one dose of any study treatment.

The safety population will include all enrolled patients who receive at least 1 dose of both study drugs.

Efficacy Analyses:

The primary efficacy endpoint of ORR (proportion of patients who achieve CR or PR) will be analyzed for each arm separately on the modified intent-to-treat (mITT) population which consists of all enrolled patients who received any study treatment. Estimated ORR with 95% confidence interval (CI) will be summarized for each arm.

Analyses of other efficacy endpoints will be specified in Section 12 of the protocol and the Statistical Analysis Plan (SAP)

Safety Analysis:

Continual monitoring of safety data will be performed by the independent Data Safety Monitoring Board (DSMB). Adverse events and concomitant medications will be coded according to medical dictionary for regulatory activities (MedDRA) and WHO Drug, respectively. Safety analyses will be performed on the Safety Population and will be presented by actual treatment arm.

3.2. Schedule of Assessments

Table 1: Schedule of Assessments for Study XPORT-MEL-033 (42-Day Cycle)

Activity/Assessment	Screening[a]	Cycles* 1			Cycles* ≥2			EoT Visit	Follow-up Visit[b]	
	D -28 to -1	D1	D3±2D	D15/D29 ±3D	D1	D3±2D	D15/D29 ±3D	≤28 Days Post-Treatment Discontinuation	30 days after EoTVisit +7D	Every 3 months until 12 months ±14D
Procedures										
Informed Consent	X									
Inclusion/Exclusion	X									
Demographics	X									
Medical history	X									
Concomitant Medications Review	X	Continuous						X	X	X
Prior Melanoma Therapy	X									
Eligibility confirmation by Sponsor[c]	X									
ECOG Daily Living Performance Score	X	X			X					
Nutritional Counselling	X	Throughout, as needed								
Vital signs including weight	X	X			X			X		
Physical Exam – full	X							X		X
Physical Exam – symptom directed		X			X				X	
Adverse Events[d]		Continuous								
Telephone contact[e]			X						X	X
Collection of information regarding antineoplastic therapy after EoT									X	X
Laboratory										
Hematology and Serum Chemistry	X	X		X	X		X	X		

Activity/Assessment	Screening[a]	Cycles* 1			Cycles* ≥2			EoT Visit	Follow-up Visit[b]	
	D -28 to -1	D1	D3±2D	D15/D29 ±3D	D1	D3±2D	D15/D29 ±3D	≤28 Days Post-Treatment Discontinuation	30 days after EoTVisit +7D	Every 3 months until 12 months ±14D
LDH	X	X			X			X		
Pregnancy test[f]	X	X					X	X		
CCI										
Drug Administration										
Selinexor		Selinexor will be administered once weekly (Days 1, 8, 15, 22, 29, 36 of 42-day cycle)								
Pembrolizumab		Pembrolizumab will be administered on Day 1 once every 6 weeks								
Anti-tumor Activity										
Tumor assessment by CT or MRI Scan	X	Tumor assessment will be performed every 9 weeks for 6 months, then every 3 months thereafter						X		

CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; FU = follow-up; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PDn = pharmacodynamics

* Cycles are 6 weeks in length.

[a] Procedures that are performed as part of standard of care should not be repeated if they are within the screening window and are done prior to signing the ICF.

[b] After discontinuation of study treatment for reasons other than PD, disease assessments should continue to be performed every 3 months until progression, start of new therapy or withdrawal of consent.

[c] Eligibility form with past melanoma care, length of treatment, and best response will be reviewed and approved by Sponsor prior to randomization.

[d] AEs are recorded after first dose of study treatment and at any time the patient communicates an AE upon inquiry during each visit or phone call, or an AE is assessed by the Investigator, up until 30 days after EoT.

[e] Telephone contact will be made on C1D3 to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. After discontinuation of study treatment, follow-up phone calls will be performed 30 days after EoT visit and every 3 months until 12 months documenting startof new therapy and survival status.

[f] Female patients of childbearing potential must have a negative serum hCG pregnancy test within 3 days prior to first study dose on C1D1. A urine hCG test is allowed if serum hCG test is not available.

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4. INTRODUCTION

4.1. Melanoma

Melanoma is a malignant neoplasm of melanocytes derived from neural crest stem cells which produce melanin, and generally arises from UV exposure and genetic mutations (Byrne, 2017; Rebecca, 2020). While melanoma only accounts for about 1% of skin cancers, it is responsible for the majority of skin cancer mortality (Siegel, 2020). Over the past few decades, rates of melanoma have been rapidly increasing. In 2020, cases of newly diagnosed melanoma are estimated to be over 100,000, with 6,850 expected deaths (Siegel, 2020). Patients with stage IV melanoma have a median survival of 8 to 18 months after diagnosis, with metastasis to the brain as the most common complication (Balch, 2009; Rebecca, 2020).

Standard first line of treatment for patients with localized melanoma is surgical excision and complete lymphadenectomy for patients with involved regional nodes (Davis, 2019; Garbe, 2011). Until 2011, standard treatment for metastatic melanoma included, radiation therapy, surgery, and/or systemic therapy (i.e., other chemotherapy or interleukin-2 (IL-2)–based immunotherapy) (Agarwala, 2010). Unfortunately, response rates are poor with patients having a median overall survival (OS) between 5 to 11 months and a survival rate of 27% for one year. Advanced melanoma patients, as characterized by the American Joint Committee on Cancer stage IV have an overall 5-year mortality rate of 90% (Davis, 2019; Korn, 2008).

Treatment options for metastatic melanoma have improved and currently there are 3 immune approved checkpoint inhibitors (CPIs) available: nivolumab and pembrolizumab (anti-programmed cell death protein 1 [PD-1] antibodies), and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] antibody) (Davis, 2019). Antitumor responses in preclinical and clinical trials are observed with antibody blockade of either PD-1 or CTLA-4 (Okazaki, 2007; Peggs, 2008). When PD-1 and CTLA-4 are successfully inhibited in metastatic melanoma, 25%-50% of patients achieve 6 months progression-free survival (PFS) (Byrne, 2017). One-year survival rate of patients with melanoma was 62% when treated with nivolumab (Topalian, 2014). The estimated 5-year OS rate was 34% and the objective response rate (ORR) was 41% with pembrolizumab (KEYNOTE-001) (Hamid, 2019). Ipilimumab has demonstrated a median OS of 11.4 months with a 3-year survival rate estimated to be 22% (Schadendorf, 2015). Combination treatment of ipilimumab and nivolumab results in an ORR of 53% (Wolchok, 2013). An additional treatment option of relatlimab (anti-LAG-3 [lymphocyte antigen-3] antibody) and nivolumab showed an improved mPFS of 10.12 months (95% CI: 6.37, 15.74) as compared with nivolumab monotherapy at 4.63 months (95% CI: 3.38, 5.62) (HR 0.75 [95% CI: 0.62, 0.92]; p=0.0055 with the greatest improvement seen in patients with LAG-3 expression ≥1% (Lipson, 2021).

Melanoma has one of the highest mutational loads of all cancers, largely arising from somatic mutations. Of these, approximately 70% have mutations in mitogen activated protein kinase (MAPK) signaling pathways and approximately 50% have activating BRAF mutations − the most common being the V600E mutation (Davis, 2019; Byrne, 2017). In patients with $BRAF^{V600E/K}$ mutant melanoma, treatment with the BRAF inhibitor vemurafenib demonstrated a response rate of approximately 76% when treated with a combination of BRAF and MEK inhibitors, however over 95% will relapse (Schreuer, 2017; Rebecca, 2020). Cancers with high mutational loads like melanoma are associated with better responses to CPIs likely due to their poor capacity in repairing DNA damage (Byrne, 2017).

The safety profile of immune CPIs is well-established. The most common adverse events (AEs) of any grade with PD-1/L1 and CTLA-4 inhibitors were diarrhea, fatigue, pruritus and rash (Arnaud-Coffin, 2019). The most common treatment-related adverse events (TRAEs) in patients with melanoma receiving nivolumab were fatigue (32%), rash (23%), and diarrhea (18%), with 22% of patients experiencing Grade 3 or 4 TRAEs but no drug-related deaths (Topalian, 2014). Of the melanoma patients treated with pembrolizumab, 17% had grade 3 or 4 TRAEs, and only 10% had to discontinue treatment due to TRAEs (Hamid, 2019). Immune-related adverse events (irAEs) are from the excessive activation of the immune system and can lead to serious adverse events (SAEs), interruption or discontinuation of treatment (Bajwa, 2019). Patients with metastatic melanoma administered ipilimumab commonly have irAEs, the most common adverse events (AEs) being diarrhea, hepatotoxicity, hypophysitis, uveitis, pneumonitis, and neurotoxicity (Horvat, 2015). Patients taking the BRAF inhibitor, vemurafenib, most commonly experienced: cutaneous events, arthralgia, and fatigue; 38% of patients had AEs leading to dose interruption or modification (Chapman, 2011). Common irAEs in the combination of relatlimab and nivolumab include hypothyroidism/thyroiditis, rash, diarrhea/colitis, hyperthyroidism, hepatitis, adrenal insufficiency, pneumonitis, hypophysitis, nephritis/renal dysfunction, and hypersensitivity. Grade 3/4 TRAEs occurred in 18.9% of patients on relatlimab and nivolumab as compared with 9.7% of patients on nivolumab (Lipson, 2021).

4.2. Study Rationale

The frontline treatment of metastatic melanoma has evolved over the past decade and now centers around immune CPIs, such as pembrolizumab or nivolumab, which block PD-1, leading to augmentation of anti-tumor immune responses (Robert, 2015). These agents are approved alone or in combination with other therapies. While addition of the immune CPI, ipilimumab, which targets the immune checkpoint CTLA-4, to nivolumab leads to significantly improved PFS over nivolumab alone, the combination has substantially more toxicity and discontinuations due to AEs (Larkin, 2015). As a result, many physicians and patients prefer PD-1/L1 blockade alone (Jenkins, 2021). Attempts to improve ORR and PFS with PD-1/L1 monoclonal antibodies (mAbs) with other agents in BRAF-wild type melanoma have not yet been successful (Jenkins, 2021). Recent review of data from the RELATIVITY-047 study demonstrated improvement in mPFS using the combination of relatlimab with nivolumab over nivolumab monotherapy (Lipson, 2021). In BRAF-mutant melanoma, combined BRAF/MEK inhibitors plus PD-1/L1 mAbs show enhanced ORR and randomized trials to determine effects on OS and PFS are underway (e.g., NCT03455764, NCT03272464).

Taken together, despite the advances of BRAF/MEK, PD-1/L1, PD-1 with LAG-3, and CTLA-4 inhibitors, many patients experience relapse or remain refractory, leaving an unmet clinical need for beneficial long term and curative treatment for metastatic melanoma (Byrne, 2017).

The increased use of CPIs for the treatment of melanoma has changed the treatment paradigm due to the durable clinical benefits noted from this. The concerns have now become related to the majority of patients who either exhibit no response from anti-PD-1/L1 mAbs or those who have a response followed by disease progression (Kluger, 2020). These patients have few treatment options and represent an unmet medical need. Patients who have disease that is considered resistant to anti-PD-1/L1 therapy are broken down into 3 categories:

- Primary resistance

- Secondary or acquired resistance
- Progression after treatment discontinuation

Patients with primary resistance to PD-1/L1 inhibitors are defined by inability of their immune cells to mount an antitumor response as noted by stable disease (SD) lasting for <6 months or no response to therapy. The potential reasons for this include ineffective priming of T cell response, lack of tumor recognition due to defective antigen presentation, inability of T cells to eliminate tumor cells due to bypass pathways, an abundance of immune inhibitory cells like M2 macrophages, or other reasons that have yet to be identified. Patients with primary resistance typically are exposed to immunotherapies between 6 weeks and 6 months. In order to determine whether the patient has primary resistance, a confirmatory scan should be performed at least 4 weeks after the initial diagnosis of disease progression (Kluger, 2020).

Patients with secondary resistance to immunotherapies had a confirmed objective response or prolonged SD ≥6 months but develop disease progression. The types of resistance may involve adaptation of the tumor cells or due to epigenetic, transcriptomic, and/or proteomic changes to the tumor, alterations in antigen presentation, upregulation of alternative immune checkpoints, or changes in the tumor microenvironment, including numbers of regulatory T cells, myeloid-derived suppressor cells, and M2 macrophages. These are also referred to as acquired resistance to immunotherapies. In order to determine whether the patient has secondary resistance, a confirmatory scan should be performed to demonstrate that there was no presence of tumor flare (Kluger, 2020).

Disease progression after discontinuation of CPIs is often seen when patients are treated with either adjuvant or neoadjuvant therapy where duration of therapy is limited. Patients may develop a relapse once the therapy has stopped. This may be related to the inability of immunotherapies to eradicate malignant cells due to limited antigen presentation or due to PD-1 receptor decline that occurs over time. Adequate observation of disease progression is that which is seen within 6 to 12 weeks after the last dose of adjuvant therapy (Kluger, 2020).

The LEAP-004 study evaluated the use of pembrolizumab with the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) lenvatinib in patients who had progressive disease (PD) while on anti-PD-1 mAb. The ORR in advanced melanoma patients with confirmed progression on CPI therapy was 21.4% (95% CI: 13.9, 30.5) with a DCR of 66.0% (95% CI: 56.0, 75.1). The median PFS was 4.2 months (95% CI: 3.8, 7.1) and the median OS was 14.0 months (95% CI: 10.8, Not reached). The majority of patients (62 out of 103; 60.2%) had primary resistance to anti-PD-1 mAb in the metastatic setting (Arance, 2021).

Despite the improvement seen in patients with this combination, patients develop rapid disease progression and require improved treatment options in both the primary and acquired resistance groups. The activity of selinexor may allow patients to have reactivation of their tumor to CPI therapy.

4.3. Selinexor

Selinexor (XPOVIO®) is a first-in-class oral selective inhibitor of nuclear export (SINE) compound, specifically inhibiting exportin-1 (XPO1, also called Chromosome Region Maintenance protein 1/CRM1) and has been validated as a target for therapeutic intervention in cancer. Selinexor is FDA approved as a treatment (80 mg twice weekly [BIW]) in combination with low-dose

dexamethasone in patients with penta-refractory multiple myeloma, and as a monotherapy (60 mg BIW) for patients with relapsed or refractory diffuse large B-cell lymphoma after at least 2 prior lines of therapy. Selinexor also approved in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

XPO1is a nuclear export protein responsible for shuttling cargo from the nucleus to the cytoplasm (Senapedis, 2014). It is a member of the karyopherin β family of transport receptors that binds over 200 target proteins through a hydrophobic leucine-rich nuclear export signal (NES) present in the XPO1 cargo protein (Wang, 2019). XPO1 is the sole nuclear exporter of several major tumor suppressor proteins (TSPs) and growth regulatory proteins (GRPs), including p53, p75, Rb, p21, p27, STAT3, FOXO and IκB among others. XPO1 is upregulated in both hematologic malignancies and solid tumors (Senapedis, 2014). Overexpression of XPO1 correlates with a poor prognosis in many human cancers, indicating that changes in nuclear-cytoplasmic trafficking resulting in aberrant localization of key proteins can contribute to cancer development and progression. XPO1 has been identified as 1 of 7 key candidate genes that may be therapeutic targets for melanoma; in addition, XPO1 mRNA is ~2-fold overexpressed in metastatic melanoma as compared with normal melanocytes and nevi (Pathria, 2012; Yang 2014; Breit, 2014).

Programmed cell death protein 1 (PD-1) is expressed on the surface of cytotoxic T cells, and its ligand programmed death ligand-1 (PD-L1) is expressed on both melanoma tumor and immune cells. The inhibition of interactions between PD-1 and PD-L1 by agents such as nivolumab and pembrolizumab (Robert, 2015) causes the reactivation of cytotoxic T cells, leading to the recognition and destruction of melanoma cells (Hodi, 2018; Robert, 2015; Jiang, 2019; Yang, 2020). Despite the impressive activity of anti-PD-1/L1 agents in melanoma, between 40%-65% of metastatic melanoma patients are shown to be resistant to CPI mono- or combination therapy (Fenton 2019).

SINE compounds and selinexor demonstrated specific anti-melanoma activity in melanoma cell lines while sparing normal melanocytes and other normal cells. Anti-melanoma activity was demonstrated also in preclinical mouse models (Fragomeni, 2013; Breit, 2014; Farren, 2017). Oral selinexor showed single agent anti-tumor activity at clinically relevant doses (30 mg/m^2) in immunocompetent mice bearing B16 melanoma tumors and did not impair anti-tumoral immunity (Tyler, 2017). Oral selinexor in combination with anti-PD1, programmed death ligand 1 (PD-L1) or anti-CTLA-4 antibodies showed additive/synergistic activity in immunocompetent mice bearing aggressive syngeneic melanoma (Farren, 2017). Selinexor has also been shown to provide added benefit when combined with CPIs in colorectal and renal cancer xenograft models, while promoting an antitumor immune response (Trott, 2016; Elloul, 2016). Together, these data suggest that selinexor can potently kill melanoma cells while priming the tumor microenvironment to respond to cancer immune checkpoint inhibition.

In the Phase 1 clinical trial of single agent oral selinexor in patients with advanced, heavily pretreated solid tumors (KCP-330-002), amongst 14 patients with advanced metastatic melanoma, the ORR was 13% with 1 complete response (CR) and 1 partial response (PR). The patient who achieved CR had a duration of response (DOR) of 417 days and had received 2 prior immunotherapy regimens (interferon alfa-2B and ipilimumab) prior to enrollment in this study (Abdul Razak, 2016).

Preliminary results from the ongoing study of selinexor 60 mg BIW in combination with pembrolizumab (200 mg intravenous [IV] once every three weeks) have shown promising anti-tumor activity (NCT02419495). 22 patients were diagnosed with non-uveal melanoma; 9 of them naïve to prior CPI and the other 13 were refractory to CPI therapy. The ORR among patients with CPI-naïve and CPI-refractory melanoma was 67% and 31%, respectively with 3 CRs. The longest duration of treatment for 1 CR patient who was CPI-naïve was 17 months, with the patient withdrawing from treatment due to the CR. The median PFS was 8.8 months (95% CI: 4.2, 30.7). The range was 0.13 to 54.4. The 3-month PFS rate was 0.76 (95% CI: 0.62, 0.93). The 6-month PFS rate was 0.66 (95% CI: 0.50, 0.85). The 9-month PFS rate was 0.47 (95% CI: 0.32, 0.70). The 12-month PFS rate was 0.44 (95% CI: 0.29, 0.67). The median follow-up time was 19.1 months. The median OS was 30.7 months (95% CI: 10.2, not reached). The range was 0.13 to 54.4. The 3-month OS rate was 0.93 (95% CI: 0.84, 1). The 6-month OS rate was 0.79 (95% CI: 0.66, 0.96). The 9-month OS rate was 0.72 (95% CI: 0.57, 0.91). The 12-month OS rate was 0.68 (95% CI: 0.53, 0.88). Adverse events (AEs) in the study were similar to those reported previously for selinexor and pembrolizumab with no clear overlapping toxicities. Adverse events attributed to both pembrolizumab and selinexor included hematological toxicities, fatigue, nausea, and low sodium. Hypokalemia and gastrointestinal AEs were attributed to selinexor (data on file). The preclinical and preliminary clinical data of selinexor alone and in combination with pembrolizumab demonstrated anti-melanoma activity and tolerability that warrant further exploration. In the current study, one fixed pre-determined dosing schedule of selinexor, which has been shown to be adequately tolerated in patients with solid tumors, will be studied. This open-label phase 2 study is aimed to evaluate the safety and efficacy of selinexor in combination with standard anti-PD-1 therapy, pembrolizumab in patients with unresectable locally advanced or metastatic (Stage III or IV) melanoma.

Selinexor has exhibited linear and time independent pharmacokinetic (PK) over a dose range of 3 to 85 mg/m^2. Oral absorption is moderately rapid, with median t_{max} observed approximately 2 to 4 hours after administration and an apparent volume of distribution of 133 L, indicating good distribution to tissues beyond the central (vascular) compartment. The $t_{1/2}$ is approximately 5 to 7 hours, and, as expected based on the relatively short $t_{1/2}$, no accumulation has been observed following twice or thrice weekly dosing. Parent selinexor is the main moiety in plasma and the limited metabolism of selinexor is catalyzed by multiple enzymes, including CYP3A4, UDP-glucuronosyltransferases, and glutathione (GSH) S-transferases. Importantly, the primary metabolite of selinexor, KPT-375, has minimal biological activity. Other metabolites at lower levels include inactive N-dealkylation, glucuronidation, and GSH conjugations. Thus, the contribution of metabolites to the pharmacological activity of selinexor is negligible. Selinexor PK has been investigated in many different tumor types hematologic (including multiple myeloma, diffuse large B-cell lymphoma etc.) and solid tumors (including glioblastoma, ovarian cancer, sarcoma etc.), and PK is similar across different tumor types. There are no known clinically significant drug-drug interactions.

4.4. Dose Justification

Selinexor has been evaluated as a single agent or in combination with other anti-cancer agents in at least 3419 patients with hematologic or solid-tumor malignancies who received at least 1 dose of selinexor. Among these patients, 2310 were treated on company-sponsored trials and 1201 patients were treated on investigator-sponsored trials (ISTs). Based on the robust available clinical safety

and efficacy data from these clinical trials, selinexor shows a reasonably wide therapeutic range, with single agent activity ranging from ~6 mg/m^2 to ≥85 mg/m^2 BIW (approximately 10 mg to 145 mg orally [PO] BIW) which was initially observed from the two phase 1 studies and subsequently confirmed in multiple phase 2 and phase 3 clinical trials.

In dose escalation studies in patients with advanced hematologic and solid tumor malignancies (Studies KCP-330-001 and KCP-330-002, respectively), selinexor was dosed once weekly (QW) or BIW and exhibited linear PK and dose-proportional exposure (maximum plasma concentration and area under the concentration-time curve). In Study KCP-330-002 in solid tumors, the maximum tolerated dose was defined at 65 mg/m^2 using a BIW (Days 1 and 3) dosing schedule, which is approximately equivalent to 110 mg BIW for adult patients with solid tumors assuming the average adult body surface area of 1.7 m^2. However, analysis of prolonged dosing results in KCP 330-002 demonstrated that a dose of 35 mg/m^2 (~60 mg) BIW had acceptable efficacy and improved long-term tolerability. Based on the observation from this phase 1 study and several other phase 2 studies in solid tumors, the revised recommended Phase 2 dose of selinexor as single agent for many solid tumors is 60 mg BIW or 80 mg QW.

Selinexor dose of 80 mg QW is chosen for this study based on the following:

1. 80 mg once weekly dosing regimen for selinexor in combination with pembrolizumab 200 mg Q3W has been explored in the study KCP-330-027 (NCT04256707) in patients with advanced or metastatic colorectal cancer. This combination regimen was well tolerated in the first 12 patients treated in this study, with no dose limiting toxicities and no dose reduction in any patient. Nine patients are ongoing on the combination treatment as of November 2020. Median treatment duration is 2.5 cycles (21-day cycle) with the longest duration of treatment in 2 patients with KRAS and NRAS mutation (6 and 7 months, respectively, on the combination). Only one patient had a single dose interruption due to Grade 2 nausea and then resumed the treatment at the same dose level after nausea was resolved. These findings indicate that selinexor 80 mg QW with pembrolizumab 200 mg Q3W is a tolerable regimen in patients with advanced, heavily pretreated colorectal cancer.
2. Although the pharmacokinetic $t_{½}$ value of selinexor in humans is relatively short due to its covalent binding to XPO1, its mechanism of action and its pharmacodynamic (PDn) properties indicate that BIW dosing to QW dosing may be adequate to sustain its duration of action. Prior evaluations have exhibited robust killing of neoplastic lymphocytes at SINE compound concentrations <1 µM within 24 hours, as compared to concentrations of 5 to 10 µM for >38 to 72 hours required for killing normal lymphocytes (Lapalombella, 2012; Azmi, 2013). Additional in vitro and in vivo evaluations of selinexor have demonstrated similar findings (potent killing of malignant cells and minimal toxicity to normal circulating blood cells) (Etchin, 2013).
3. In study KCP-330-004 which evaluated the efficacy and safety of selinexor in patients with recurrent glioblastoma, 30 of the 68 study patients received the 80 mg QW dose, and 14 patients received 60 mg BIW. The six-month progression-free survival rate point estimation (6mPFS) in the 80 mg QW arm (Arm D) was 17%, while the PFS in the 60 mg BIW arm (Arm C) was 7.7%. The ORR was 10%, and the median OS was 10.2 months in the 80 mg QW arm versus 7.7% and 8.5 months in the 60 mg BIW arm, respectively. Grade 3 or above TEAEs are much lower in the 80 mg QW dosing (47%)

vs. 86% in 60 mg BIW dosing. The percentage of patients experiencing treatment-related adverse events (TRAEs) was lower in those receiving selinexor 80 mg QW than in those receiving 60 mg BIW (thrombocytopenia (23% versus 29%), nausea (60% versus 64%), fatigue (50% versus 71%), and decreased appetite (27% versus 71%).

4. 35 mg/m^2 (~ 60 mg) BIW and 50 mg/m^2 (~80 mg) QW dose regimen were evaluated in patients with ovarian cancer in study KCP-330-005 (NCT02025985). The ORR was 15% and 9.5% in 50 mg/m^2 QW arm (n = 20) and 35 mg/m^2 BIW arm (n = 21), respectively. Disease control rate was similar between 2 arms. However, grade 3 or above TEAEs are much lower in the QW dosing (65%) vs. 76% in BIW dosing. In addition, rate of at least one TEAE leading to discontinuation was 10% and 19% in QW and BIW dosing, respectively. The 50 mg/m^2 (~80 mg) QW dosing regimen provided better efficacy results and superior tolerability compared to 35 mg/m^2 (~60 mg) BIW dosing.
5. In an ongoing IST (NCT02419495), 31 melanoma patients were treated with combination of selinexor 60-120 mg total weekly dose (QW or BIW) and pembrolizumab 2 mg/kg or 200 mg IV Q3W. Of those, 28 patients were treated with selinexor 60 mg BIW. Nineteen (68%) out of 28 patients had selinexor dose reduction to a total weekly dose of 80 mg or less. Therefore, a lower dose (80 mg QW) is proposed in this study to further evaluate the safety and efficacy of selinexor in combination with pembrolizumab.

Modelling studies comparing the exposure of pembrolizumab 400 mg Q6W and 200 mg Q3W regimens indicated that the clinical efficacy and safety would be similar for the two dosing regimens (Lala, 2020).

4.5. Benefit/Risk Assessment

Broad antitumor activity has been observed with selinexor treatment in preclinical and clinical studies. The information about selinexor's mechanism of action and its efficacy from the IST (NCT02419495), indicates that selinexor 60 mg PO BIW and pembrolizumab at 200 mg IV Q3W have activity in metastatic melanoma; however, further investigation is warranted to elucidate clinical benefit. Adverse events in the study were similar to those reported previously for selinexor and pembrolizumab administered separately with no clear overlapping toxicities noted during the trial including hematological, fatigue, decreased appetite, nausea/diarrhea, pyrexia, constipation, low sodium attributed as possible/definite to either selinexor or pembrolizumab or possible with both treatments.

Early preclinical studies showed positive response rates and no obvious impact of immune CPI/selinexor combination treatment regimen on the overall body weight or general disposition of the mice (Farren 2017). In broad terms, this is consistent with the manageable toxicity profile that has been reported in recent selinexor clinical trials.

In addition, selinexor is currently being evaluated in combination with other agents (targeted therapies and chemo-/radiotherapy). As these clinical trials proceed, more data will become available to assess both the added efficacy and possible AEs resulting from these combinations to better inform potential trials combining selinexor with immune checkpoint blockade. In ongoing clinical studies, the most common non-hematologic AEs reported as related to selinexor have been

predominantly nausea, vomiting, diarrhea, fatigue, anorexia and weight loss, and these AEs were assessed as low-grade and manageable with dose modification or supportive care. Hyponatremia (typically asymptomatic), confused state and dizziness have also been reported. On the other hand, hematological AEs including thrombocytopenia, neutropenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies. Any potential overlapping toxicity including fatigue, decreased appetite, diarrhea, nausea, pyrexia, constipation, hyponatremia, and anemia will be monitored closely by careful physical examination and clinical laboratory testing on Days 1, 15, and 29 of Cycles 1 and 2 with dose adjustments as per prespecified dose modifications (see Table 5). Additional visits to manage AEs and telephone contact are also encouraged based upon the patient's condition.

A summary of the clinical trials, antitumor responses observed, and anticipated AEs of selinexor are found in the Investigator's Brochure.

5. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for both arms of this signal finding study are to evaluate the treatment with selinexor plus pembrolizumab are same as listed below:

Objectives	Endpoints
Primary	
• To evaluate objective response rate (ORR) per RECIST v1.1 response criteria.	• ORR defined as the proportion of patients who achieved a complete response (CR) or a partial response (PR).
Secondary	
• To evaluate progression-free survival (PFS) per RECIST v1.1 response criteria.	• PFS defined as time from date of first treatment to the date of first confirmed progressive disease (PD) or death due to any cause, whichever occurs first.
• To evaluate overall survival (OS).	• OS defined as time to death, from the date of first treatment.
• To evaluate rates of CR.	• Complete response rate (CRR), defined as proportion of patients who achieved a CR.
• To evaluate duration of response (DOR)	• DOR defined as the duration of time from first occurrence of response ≥PR until the first date of PD or death due to any cause, whichever occurs first.
• To evaluate the disease control rate (DCR)	• DCR is defined as the percentage of patients who have achieved CR, PR and stable disease (SD).
• To evaluate the safety and tolerability of selinexor and pembrolizumab combination regimen.	• Safety and tolerability of study treatment will be evaluated based on adverse event (AE) reports, vital signs, clinical laboratory results, and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

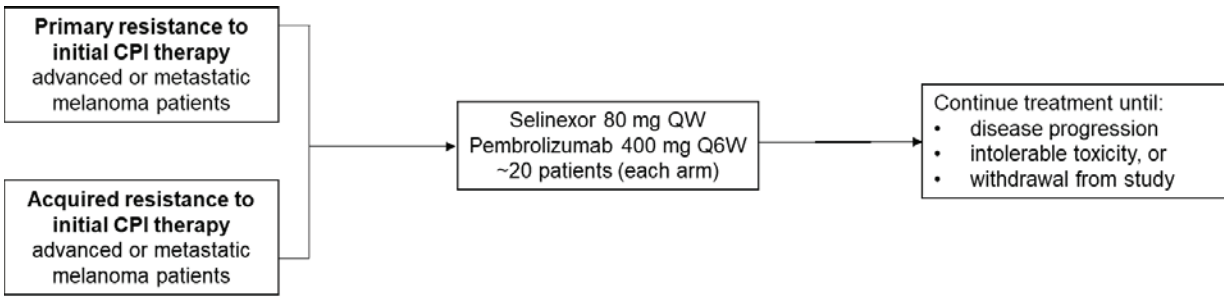
Objectives	Endpoints
Exploratory	
CCI	

6. STUDY DESIGN

6.1. Overall Design

This phase 2, open-label, multicenter study will evaluate the efficacy and safety of selinexor and pembrolizumab in patients with recurrent advanced or metastatic melanoma, and resistant to initial CPI therapy (Figure 1).

Figure 1: XPORT-MEL-033 Study Design



CPI: checkpoint inhibitor; Q6W: once every six weeks; QW: once weekly

Approximately 40 patients with locally advanced or metastatic melanoma will be enrolled, 20 patients with primary resistance to initial CPI therapy in Arm A and 20 patients with acquired resistance to initial CPI therapy in Arm B. Of note, patients who have disease progression after discontinuation of CPIs, especially in neoadjuvant or adjuvant therapy, will be considered to have acquired resistance in this study.

All eligible patients will be treated with selinexor 80 mg once weekly (QW) + pembrolizumab 400 mg once every six weeks (Q6W).

Primary efficacy will be assessed by ORR per RECIST v1.1 response criterion. Evaluation of the radiographic data for disease response or progression will be based on PI assessment. Safety will be assessed based on AE reports, physical examination results (including vital signs), and clinical laboratory results by the occurrence, nature, and severity of AEs.

Patients will receive study treatment until disease progression, intolerable toxicity, or withdrawal from the study. Disease response/progression will be based on assessments every 9 weeks for the next 6 months, and then every 3 months thereafter according to RECIST version 1.1, based on radiologic review and, as an CCI endpoint, on iRECIST (Seymour, 2017).

Per Investigator's discretion, patients with a prolonged response or stable disease can discontinue pembrolizumab after 24 months of treatment and continue with selinexor only.

6.2. End of Treatment

The end of treatment (EoT) visit will occur ≤28 days post-treatment discontinuation. After discontinuation of study treatment, patients will be followed for PFS approximately every 3 months after EoT visit until PD, death or initiation of the subsequent anti-melanoma treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit for 12 months or until withdrawal of consent, death, or the end of study (i.e., when the last patient in the study has been followed up on study treatment for at least 1 year or

completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up) whichever occurs first.

6.3. Safety Follow-Up Visit

A safety follow-up visit must be performed 30 days after EoT and then every 3 months for 12 months. The purpose is to assess patient status, and follow-up on any AEs that were not resolved at the EoT Visit.

Adverse events will be reported 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 new therapy, whichever occurs first. For events that are considered by the Investigator to be related to the study drug, the monitoring of the AE should be continued for at least 30 days following the last dose of study drug (30-Day Safety visit), or until the AE has resolved.

7. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Eligible patients must fulfill all inclusion criteria and none of the exclusion criteria for study entry.

7.1. Inclusion Criteria

1. Age ≥ 18 years at the time of informed consent
2. Patient must have a histologically confirmed diagnosis of locally advanced unresectable stage III or metastatic stage IV melanoma not amenable to local therapy.
    a. Patients must have confirmed PD per RECIST on or within 12 weeks of the last dose of anti-PD-1/L1 monotherapy or combination therapy (including relatlimab or other anti-LAG-3 mAb) per Society for Immunotherapy in Cancer Guidelines (Kluger, 2020)
    b. Arm A (primary resistance): patient has disease progression after receiving at least 6 weeks of prior anti-PD-1/L1 mAb with the best response as PD, or SD <6months (patients with a PR or CR who have disease progression within 6 months will be considered to have primary resistance in this study).
    c. Arm B (secondary/acquired resistance): patient has disease progression after receiving at least 6 months of prior anti-PD-1/L1 mAb with the best response as CR, PR, or SD>6 months (patients who have disease progression after neoadjuvant or adjuvant therapy, will be considered to have secondary resistance in this study).
    d. Patients who progress on or within 12 weeks after elective discontinuation of anti-PD-1/L1 mono or combination treatment in the absence of PD or treatment limiting toxicity must have confirmed PD per RECIST.
3. Patients should have at least 1 prior line of CPI therapy but no more than 2.
4. Measurable disease according to RECIST v1.1.
5. Patients with stable previously treated brain metastases are permitted in this study.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
7. Adequate bone marrow function at screening, defined as:
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    b. Hemoglobin ≥ 10 gm/dL (≥6.2 mmol/L)
    c. Platelet count ≥100 × 10^9/L
8. Serum direct bilirubin ≤1.5 × ULN; AST and ALT ≤ 2.5 × ULN (with confirmed liver metastases: AST and ALT ≤ 5 × ULN)
9. Calculated creatinine clearance (CrCl) ≥15 mL/min based on the Cockcroft and Gault formula.
10. Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use highly effective methods of contraception throughout the study

and for at least four months following the last dose of study treatment. Childbearing potential excludes: Age >50 years and naturally amenorrhoeic for >1 year, or previous bilateral salpingo-oophorectomy, or hysterectomy.

11. Male patients who are sexually active must use highly effective methods of contraception throughout the study and for at least four months following the last dose of study treatment. Male patients must agree not to donate sperm during the study treatment period.
12. Written informed consent signed in accordance with federal, local, and institutional guidelines.

7.2. Exclusion Criteria

1. Metastatic uveal or ocular melanoma.
2. Active central nervous system (CNS) metastases or other CNS (e.g., meningeal) involvement.
3. Patients must have resolution or improvement of immune-mediated treatment-related adverse reactions related to prior treatment(s) to Grade ≤ 1 without steroid maintenance therapy or his or her previous baseline prior to the corresponding CPI therapy.
    a. History of immune-mediated treatment-related adverse reactions leading to discontinuation of prior anti-PD-1, anti-PD-L1, or anti-PD-L2 mAbs or severe hypersensitivity reaction to any mAb or any excipients which in the opinion of the Investigator, precludes future use of anti-PD-1/PD-L1 therapy.
4. Concurrent systemic steroid therapy higher than physiologic dose (> 10 mg/day of prednisone or equivalent).
5. Previous treatment with selinexor or other XPO1 inhibitors.
6. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:
    a. Not recovered from major surgery ≤28 days prior to Day 1 dosing. Minor procedures, such as biopsies, dental work, or placement of a port or intravenous (IV) line for infusion are permitted
    b. Have ongoing clinically significant anti-cancer therapy-related toxicities Common Terminology Criteria for Adverse Events (CTCAE) Grade >1. In specific cases, patients whose toxicity has stabilized or with Grade 2 non-hematologic toxicities can be allowed following documented approval by the Sponsor's Medical Monitor
    c. Had last dose of previous anti-cancer therapy ≤14 days prior to Day 1 dosing
    d. Palliative radiotherapy >14 days prior to the study is allowed
    e. Received investigational drugs in other clinical trials within 28 days, or 5 half-lives of the investigational drug (whichever is shorter), prior to C1D1
7. Live-attenuated vaccine (e.g., nasal spray influenza vaccine) ≤14 days prior to the intended C1D1.
8. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of selinexor (e.g. vomiting, or diarrhea that is CTCAE v5.0 grade >1).
9. Life expectancy <4 months based on the opinion of the Investigator.

10. Active pneumonitis requiring steroid therapy.
11. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 7 days prior to first dose of study treatment; however, prophylactic use of these agents is acceptable (including parenteral).
12. Any life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, prevent the patient from giving informed consent, or being compliant with the study procedures.
13. Female patients who are pregnant or lactating.
14. Active hepatitis B virus treated with antiviral therapy for hepatitis B within 8 weeks with a viral load >100 IU/mL.
15. Untreated hepatitis C virus positive without documentation of negative viral load per institutional standard.
16. Human immunodeficiency virus positive with CD4+ T-cells ≤ 350 cells/uL, positive viral load per institutional standard, and a history of acquired immunodeficiency syndrome - defining opportunist infections in the last year.

7.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening.

8. STUDY TREATMENT

8.1. Study Treatment Administered

All study drugs must be dispensed only by a pharmacist or appropriately qualified site staff, including the Investigator.

Table 2: Study Treatment

Treatment Name	Selinexor (Xpovio™)	Pembrolizumab (Keytruda™)
Dose Formulation	Tablet	Solution
Unit Dose Strength	20 mg	25 mg/mL
Dosage Level	80 mg, single dose once weekly	400 mg once every 6 weeks on Day 1
Route of Administration	PO	IV

8.2. Dosing and Administration of Selinexor

8.2.1. Labeling

Medication labels for each blister pack of selinexor will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the randomization number, but no information about the patient.

8.2.2. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. Additional dispensing instructions will be provided in the Pharmacy Manual.

8.2.3. Dosing Information

Selinexor tablets should be taken orally with at least 120 mL (4 fluid ounces) of water. Selinexor can be taken with or without food. In order to avoid contact with skin, tablets must be swallowed whole and should not be crushed.

For additional details on drug formulation, preparation, and administration, please refer to the Pharmacy Manual and the Investigator's Brochure.

8.3. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study medications are provided in the Pharmacy Manual.

8.4. Study Treatment Compliance

Patient compliance with study treatment will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

8.5. Concomitant Medication

Concomitant medications include any prescription or over-the-counter preparation, including blood/blood products, vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study. Patients may continue their baseline medication(s). All concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s), and any clinical findings, if applicable.

8.5.1. Prohibited Concomitant Medications

Concurrent therapy with any approved or investigative anticancer therapeutic outside of those included in this study is not allowed. Use of any immunosuppressive agents during the study must be confirmed by the Sponsor. Refer to the full prescribing information for treatment of patients receiving pembrolizumab for the most current information on prohibited concurrent medications.

Elimination of selinexor is in part attributable to CYP3A4-mediated metabolism. Therefore, moderate and strong CYP3A inducer or inhibitor should be used with caution when co-administer with selinexor as it might result in decreased or increased selinexor exposure. A list of strong and moderate CYP3A inhibitors and inducers is provided in Appendix 3.

There are no restrictions on the use of acetaminophen (paracetamol) or acetaminophen-containing products in combination with study drug, except on days of selinexor dosing, when acetaminophen must not exceed a total daily dose of 1 gram.

8.5.2. Permitted Concomitant Medications

Patients will receive concomitant medications as prophylaxis and to treat symptoms, AEs and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed. Supportive measures for optimal medical care should be provided to all patients in this study. Supportive care per institutional guidelines and/or the National Comprehensive Cancer Network® (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) should be used as clinically indicated at the discretion of the Investigator. Should the treating physician choose to use different antiemetics than what is described in this section, the treating physician should consult the sponsor in order to ensure two different classes of antiemetics are administered prophylactically. Necessary supportive care such as appetite stimulants, and anti-diarrheals will be allowed.

8.5.2.1. Ondansetron

In order to minimize nausea, unless contraindicated all patients must receive 2 anti-emetics initially: a 5-HT3 (5-hydroxytryptamine 3) antagonist (ondansetron 8 mg or equivalent), starting 30-60 minutes before administration of study drug and continued 2-3 times daily for at least 2 days after dosing, as needed. A neurokinin-1 (NK-1) antagonist or another anti-emetic agent should be used as per the label per NCCN Guidelines Alternative or additional anti-emetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT3 antagonists.

8.6. Nutritional Counselling

Patients should be given documented nutritional consultation or counselling per local practice to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening period of the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional counselling, in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed, and per local guidance.

8.7. Dose Modification

8.7.1. Selinexor Dose Modifications

All dose modifications will be captured in the eCRF. Dose modifications should be associated in the eCRF with the AE requiring the modification.

If drug-related toxicity requires a treatment delay of more than 28 days, the patient will be taken off study treatment unless the investigator in consultation with the medical monitor believes that it is safe for the patient to resume therapy.

For all Grade ≥3 hematological or non-hematological AEs that are NOT selinexor related, after consultation with the Medical Monitor and at the discretion of the Investigator, selinexor dosing may be maintained.

8.7.2. Dose Modifications for Overlapping Toxicities

For general overlapping toxicities, the following guidance is recommended after ruling out alternative causes:

- If the non-hematological toxicity is attributable to selinexor, please follow the recommended management actions for the respective AE type, outlined in Table 5.
- If the toxicity is attributable to pembrolizumab, please refer to the pembrolizumab product insert for the management of the AE.
- The management of overlapping toxicities should include withholding pembrolizumab and starting corticosteroids until the toxicity is Grade ≤1 or at baseline before restarting at the next cycle:
    - The corticosteroid dosing for intolerable Grade 2 or Grade 3 toxicities is 0.5-1 mg/kg/day of prednisone or equivalent with a slow taper until the event is back to Grade ≤1.

- For Grade 4 toxicities or recurrent Grade 3 toxicities, the dose of corticosteroids is 1-2 mg/kg/day of prednisone or equivalent with a slow taper over 3-6 weeks until the event is back to Grade ≤1
- If the AE recurs again, stop pembrolizumab permanently

Table 3 summarizes the selinexor dose levels for modification; Table 4 describes supportive care and dose adjustment guidelines for hematologic adverse reactions. Table 5 describes dose adjustment guidelines for non-hematologic adverse reactions. Deviations from the guidelines are permitted after discussion between the Sponsor and the treating physician.

Table 3: Selinexor Dose Modification Steps for Adverse Reactions

Recommended Starting Dosage	First Reduction	Second Reduction	Third Reduction	Fourth Reduction
80 mg Once weekly	60 mg Once weekly	40 mg Once weekly	20 mg Once weekly	Discontinue

Table 4: Dose Modification for Hematologic Adverse Reactions

Adverse Reaction	Occurrence	Action
Thrombocytopenia		
Platelet count < 50,000 µL (Grade 3-4)	First Occurrence	Hold selinexor until platelets recover to ≥ 75,000 Restart selinexor at same dose level (see Table 3). Consider additional supportive care and discuss with Sponsor's Medical Monitor
	2nd and subsequent	Hold selinexor until platelets recover to ≥ 75,000 Reduce selinexor by 1 dose level (see Table 3). Consider additional supportive care and discuss with Sponsor's Medical Monitor
Platelet count < 50,000 µL *with* concurrent bleeding	Any	Hold selinexor until platelets recover to ≥ 50,000 and bleeding has resolved. Restart selinexor at 1 lower dose level (see Table 3) Consider additional supportive care and discuss with Sponsor's Medical Monitor
Neutropenia		
Absolute neutrophil count (ANC) of 0.5 to 1.0 x 10^9 /L (Grade 3)	First Occurrence	Hold selinexor until ANC recover to ≥ 1.0 Restart selinexor at same dose level (see Table 3). Consider additional supportive care and discuss with Sponsor's Medical Monitor

Adverse Reaction	Occurrence	Action
ANC of 0.5 to 1.0 x 10^9 /L (Grade 3)	2nd and subsequent	Hold selinexor until ANC recover to ≥ 1.0 Reduce selinexor by 1 dose level (see Table 3). Consider additional supportive care and discuss with Sponsor's Medical Monitor
ANC < 0.5 x 10^9/L (Grade 4) *OR* febrile neutropenia	Any	Hold selinexor until ANC recover to ≥ 1.0 Reduce selinexor by 1 dose level (see Table 3). Consider additional supportive care and discuss with Sponsor's Medical Monitor
Anemia		
Hemoglobin level less than 8.0 g/dL	Any	Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	Interrupt selinexor. Monitor hemoglobin until levels return to 8 g/dL or higher. Restart selinexor at 1 dose level lower (see Table 3). Administer blood transfusions and/or other treatments per clinical guidelines.
Overlapping anemia (due to combination of selinexor and pembrolizumab)		Interrupt selinexor Monitor hemoglobin until levels return to ≥8 g/dL or baseline Restart selinexor at 1 dose level lower (see Table 3).
[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.		

Table 5: Selinexor Dose Modification Guidelines for Non-hematologic Adverse Reactions

Adverse Reaction[a]	Occurrence	Action
Hyponatremia		
Grade 1 or 2 (sodium level < normal to 130 mmol/L	Any	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 Consider addition of salt tablets to patient's diet
Grade 3 (sodium levels 120 to 129 mmol/L) without symptoms	Any	Rule out other causes including drug (e.g., diuretic) effects Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150mg/dL) If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that IV saline and/or salt tablets are provided
Grade 3 (sodium levels 120 to 129 mmol/L) with symptoms *OR* Grade 4 (sodium levels < 120 mmol/L)	Any	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
Overlapping hyponatremia Grade 3 or 4 (due to combination of selinexor and pembrolizumab)	Any	Rule out other causes Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms Restart selinexor at 1 dose level lower (see Table 3).
Fatigue		
Grade 2 lasting greater than 7 days *OR* Grade 3	Any	Interrupt selinexor. Monitor until fatigue resolves to Grade 1 or baseline. Restart selinexor at 1 dose level lower (see Table 3).
Overlapping fatigue (due to combination of selinexor and pembrolizumab)	Any	Interrupt selinexor. Monitor until fatigue resolves to Grade 1 or baseline. Restart selinexor at 1 dose level lower (see Table 3).
Nausea and Vomiting		

Adverse Reaction[a]	Occurrence	Action
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	Maintain selinexor and initiate additional anti-nausea medications.
Grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher vomiting (6 or more episodes per day)	Any	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists In those patients in whom a 5-HT3 antagonist is contraindicated or not sufficient, use of olanzapine (2.5-5.0 mg po once daily in the morning) is recommended based on Investigator experience during Phase 1 selinexor studies. (Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care)). Interrupt selinexor dosing until resolved to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level (see Table 3).
Overlapping grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher due to combination of selinexor and pembrolizumab	Any	Rule out other causes. Interrupt selinexor. Monitor until nausea resolves to Grade ≤2 or baseline. Restart selinexor at 1 dose level lower (see Table 3). Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists In those patients in whom a 5-HT3 antagonist is contraindicated or not sufficient, use of olanzapine (2.5-5.0 mgpo once daily in the morning) is recommended Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis
Diarrhea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	Maintain selinexor and institute supportive care.

Adverse Reaction[a]	Occurrence	Action
	2nd and subsequent	Reduce selinexor by 1 dose level (see Table 3). Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	Interrupt selinexor and institute supportive care. Monitor until diarrhea resolves to Grade 2 or lower. Restart selinexor at 1 dose level lower (see Table 3).
Overlapping grade 3 or higher diarrhea due to combination of selinexor and pembrolizumab	Any	Interrupt selinexor and institute supportive care. Monitor until diarrhea resolves to Grade 2 or lower. Restart selinexor at 1 dose level lower (see Table 3). If the diarrhea is due to both selinexor and pembrolizumab, initiate steroid therapy and consider infliximab if the diarrhea is Grade ≥3
Weight Loss and Anorexia		
Weight loss of 10% to less than 20% *OR* anorexia associated with significant weight loss or malnutrition	Any	Interrupt selinexor and institute supportive care. Monitor until weight returns to more than 90% of baseline weight. Restart selinexor at 1 dose level lower (see Table 3).
Overlapping anorexia associated with significant weight loss or malnutrition due to combination of selinexor and pembrolizumab	Any	Interrupt selinexor and institute supportive care. Monitor until weight returns to more than 90% of baseline weight. Restart selinexor at 1 dose level lower (see Table 3).
Other Non-Hematologic Adverse Reactions		
Grade 3 or 4	Any	Interrupt selinexor. Monitor until resolved to Grade 2 or lower, restart selinexor at 1 dose level lower (see Table 3).
[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.		

8.7.3. Pembrolizumab Dose Modifications

For AEs related to pembrolizumab, refer to dose adjustment guidelines in the respective drug's prescribing information. If an AE requires interruption of pembrolizumab but not selinexor, selinexor treatment may continue.

Pembrolizumab dosing will be done on D1 of any given 21-day cycle. If an AE requires interruption of only pembrolizumab, but the AE does not require interruption of selinexor, then

pembrolizumab, may remain interrupted as long as is necessary to allow the patient to recover from the AE that caused the drug interruption. If it is determined that the patient should no longer receive pembrolizumab, the patient may continue treatment with single agent selinexor, at the discretion of the Investigator.

8.7.4. Missed or Vomited Selinexor Doses

If a dose was missed, the missed dose will be administered if the time for the next scheduled dose is ≥ 72 hours. The missed dose will not be administered if the time for the next scheduled dose is < 72 hours. The next dose will be taken as per the schedule.

If a dose must be skipped (e.g., due to recommendation of Investigator), the next dose will be taken as per the schedule. Doses should not be administered less than 72 hours apart and all missed and delayed doses should be documented.

If a dose is vomited within one hour of ingestion and all intact selinexor tablets are seen, it will be replaced. If vomiting occurs more than one hour after dosing, it will still be considered a complete dose.

9. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

9.1. Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

The Investigator must determine the primary reason for a patient's discontinuation of study treatment/withdrawal from the study and record this information on the eCRF.

The Investigator may remove a patient from study treatment for any of the following reasons:

- AEs or toxicity that cannot be managed by supportive care
- Misuse of study treatment (e.g., deliberate overdosing by patient)
- Any other medically appropriate reason or significant protocol violation, in the opinion of the Investigator.

The Investigator must remove a patient from study treatment for any of the following reasons:

- Patient withdraws consent to continue study treatment
- Pregnancy

9.2. Lost to Follow up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a scheduled study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

9.3. Early Termination of the Study

The study may be terminated at the sole discretion of the Sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. If this occurs, the Sponsor will notify independent ethics committees (IECs), institutional review boards (IRBs), Investigators, and regulatory authorities.

10. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (SoA).

- Immediate safety concerns should be discussed with the Sponsor's Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) that were obtained prior to signing of the informed consent form (ICF) may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All protocol defined assessments on clinic visit days (when study drug is given) should be completed prior to study drug dosing.

10.1. Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/research ethics board (REB)-approved informed consent (Section 13.3). Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in the protocol, unless performed as part of the patient's routine clinical management as mentioned above). The process of obtaining informed consent should be documented in the patient source documents.

10.2. Baseline Assessments

10.2.1. Demographics

Patient demographics (including date of birth, sex, race, ethnicity, and age at the time of consent) will be collected.

10.2.2. Medical History

A complete medical history will be obtained from each patient by at least the month and year. Medical conditions or symptoms experienced within 30 days of Screening as well as those ongoing at the time of Screening, any medical conditions that require medication will be documented. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) and type of melanoma will also be collected. All prior anti-cancer therapies, and disease management, length of care, and best overall response will be documented. including the start date, end date/ongoing. Data from standard-of-care procedures including whole blood or platelet transfusion will be part of the patient's medical history and may

be used for study purposes. In addition, a complete ophthalmic history and the smoking history of the patient will be recorded.

10.3. Efficacy Assessments

10.3.1. Response criteria

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)

Disease response is based on tumor measurement using CT scans or, MRI. Scans will be performed at Screening (Day -28 to Day -1) and every 9 weeks for 6 months, then every 3 months thereafter until confirmed PD, death or consent withdrawal occurs. Scans at the EoT visit should be performed for patients who discontinue for reasons other than documented PD, if previous imaging was more than 6 weeks old. The same scan modality should be used for all assessments.

10.3.1.1. RECIST

Disease response will be assessed according to the RECIST criteria v1.1 (Appendix 1).

10.3.1.2. iRECIST

Antitumor response based on assessment of changes in tumor burden will be assessed by iRECIST (Appendix 2). The RECIST 1.1 definitions will be used to determine “immune” response: PFS and ORR.

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10.5. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

10.5.1. Physical Examinations

The physical examination will be performed according to the standards at each institution.

Physical examination, including vital signs, will be performed on the scheduled days as indicated in the SoA. Physical examinations should include general appearance, dermatological, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdominal, lymph nodes, musculoskeletal, and neurological examinations. Full physical examinations will be performed prior to receiving first dose of study drug and as indicated in the SoA. All other physical examinations during the study should be limited, and symptom-directed examinations.

Height (without shoes) in centimeters and weight (indoor clothing without shoes) in kilograms (kg) will be measured during the physical examinations. Any new, clinically significant findings that occur after dosing with study treatment begins will be reported as AEs.

Information about the physical examination must be present in the source documentation at the study site. The result of the physical examination prior to the start of study treatment must be included in the Relevant Medical History/Current Medical Conditions eCRF. Clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE eCRF.

10.5.2. Vital Signs

Vital signs will include:

- Body temperature (°C or °F)
- Systolic and diastolic blood pressure. Pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. Blood pressure should be assessed on the same arm throughout the study.

10.5.3. ECOG Performance Status

The ECOG performance status (Oken, 1982) will be assessed at Screening to determine eligibility of the patient and also during the study as indicated in the SoA (Appendix 4).

10.5.4. Clinical Safety Laboratory Assessments

Clinical laboratory tests (hematology and serum chemistry) will be performed by the sites' local laboratories and conducted at times specified in the SoA (Table 6). More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion and these should be recorded on the eCRF.

Hematology and complete serum chemistry panel may not be repeated on C1D1 if performed within ≤7 days and those results are within required levels as specified in the protocol.

Table 6: Clinical Safety Laboratory Tests

Hematology		
Hemoglobin	WBC (with differential)	Platelet count
Serum Chemistry		
Sodium	Creatinine	ALT
Potassium	Glucose	AST
Chloride	Calcium	Alkaline phosphatase
Bicarbonate	Phosphate	Total bilirubin[a]
BUN/urea	Magnesium	Total protein
Creatine kinase	LDH	Albumin
Uric acid		

[a]If the total bilirubin concentration is >1.5 times ULN, total bilirubin should be differentiated into the direct and indirect bilirubin.

Blood chemistry will be analyzed at each study center by a certified laboratory. The Investigator or designee will review the laboratory report after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values.

The Investigator or designee will review the laboratory report to assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values.

At any time during the study, abnormal laboratory values that are clinically significant (e.g., require dose modification and/or interruption of study treatment, lead to clinical signs or symptoms, or require therapeutic intervention), whether specifically requested in the protocol or not, must be documented on the AE eCRF.

If any abnormal laboratory value or test result constitutes an AE, then these must be recorded on the AE eCRF. Values will be documented in the eCRF until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline. Any laboratory value that remains abnormal at the EoT visit that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline levels. For lab parameters included in the CTCAE, toxicity will be assessed using the NCI CTCAE, v. 5.0.

Karyopharm must be provided with a copy of the laboratory certification and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Karyopharm must be provided with a copy of the certification and normal ranges for that laboratory.

10.5.5. Adverse Events and Serious Adverse Events

Detailed information related to the collection and reporting of AEs and SAEs in Section 11.

All AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to study treatment or study procedures, or that caused the patient to discontinue study drug (Section 11.1.2).

10.5.6. Pregnancy Testing

Pregnancy testing will be performed only for females of childbearing potential as indicated in the SoA. A negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained at Screening (within 3 days before selinexor administration). A urine hCG test is allowed if serum hCG test is not available. Pregnancy testing may be performed if clinically indicated during the study.

10.6. Other Assessments

10.6.1. Collection of Information on Antineoplastic Therapy

Information on any antineoplastic therapies planned to be used or used after discontinuation of study treatment will be collected.

10.6.2. Telephone Contacts

A telephone call will be performed at C1D3 and at the Safety Follow-up. The purpose of this telephone call with the patient is to evaluate supportive care medications, concomitant medications, and AEs, and to adjust supportive care as appropriate. After discontinuation of study treatment, follow-up phone calls will be performed after 30 days after EoT visit and every 3 months until 12 months, start of new therapy, withdrawal of consent to assess the survival status, and collect information on any antineoplastic therapies used after discontinuation of study treatment.

11. ADVERSE EVENTS

11.1. Information on Reporting Adverse Events

11.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Life-threatening adverse event or life-threatening suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- *Treatment emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (See Section 11.2.3 for additional information about SAE reporting.)
- *Suspected adverse reaction*: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.
- *Unexpected adverse event or unexpected suspected adverse reaction*: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current

application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.2. Recording of Adverse Events

Adverse events will be reported and recorded in the eCRF from the time of the first dose of study treatment 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.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments.

An AE should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized.

11.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the AE eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin).

Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to baseline levels (as measured during the screening visit) or are deemed no longer clinically significant. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (considered to be severe per NCI CTCAE, v. 5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 11.1.1 and/or as per

the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRF.

11.1.3. Adverse Event Severity

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as a "serious" AE.

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Events that are not specifically defined in CTCAE v 5.0 should be assessed according to the guidance provided on page 2 of the CTCAE v 5.0 document.

11.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as defined below.

- Not related: These events will lack a strong temporal relationship of the event to the study treatment, making a causal relationship not reasonably possible. Exposure to other drugs, therapeutic interventions, or underlying conditions may provide a sufficient explanation for the event.
- Related: There is a temporal relationship of the event to the study treatment, and the event is more reasonably explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

11.2. Serious Adverse Events

See Section 11.1.1 for the definition of an SAE. Please note that SAEs that occur at any time between the signing of the Informed Consent Form up to the first dose of study treatment must be reported (in addition to SAEs that occur after the first dose of study treatment).

11.2.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate 24-hour urine collection) are not considered SAEs. A 'serious' hospitalization is defined as any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission as an inpatient to the hospital (e.g., undesirable effects of any administered treatment) and must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes) should NOT be reported as an SAE during the study or within the safety reporting period. Any sudden or unexplained death must be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy/disease, the finding should be reported as an AE or SAE, as appropriate.

11.2.2. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the time when the ICF is signed until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on the designated Sponsor's SAE Report Form in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator's site file.

All applicable sections of the SAE Report Form must be completed in order to provide a clinically thorough report. The Investigator must assess and record the relationship of each SAE to study treatment and complete the form in English.

See ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Attachment 1) for key data elements that are required for expedited reporting.

11.2.3. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance. The investigational site personnel must use the SAE Report Form (paper or electronic) provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department. The immediate report should be made by the investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE. After the 30-day follow-up period SAEs should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to the study treatment.

To complete the electronic SAE Report Form, a Log Line must first be completed in the AEs eCRF. The SAE will then be linked to an electronic SAE Report Form. It is then necessary to complete a Log Line in the corresponding SAE Report Form eCRF within 24 hours of learning of the SAE's occurrence. It is not necessary to submit a paper SAE Report Form if the SAE was originally declared using the electronic SAE Report Form.

If the SAE is to be reported via a paper SAE Report Form, 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)

Recurrent episodes, complications, or progression of the initial SAE must be reported, as follow-up to the original episode, within 24 hours of the Investigator receiving the follow-up information.

An SAE should be followed until its resolution or until it is judged to be permanent. An assessment should be made at each study visit (or more frequently, if necessary) of any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome of the event.

11.2.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions are SAEs that are unexpected and judged by the Investigator or Karyopharm to be related to the study treatment administered. All suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with the FDA's "Safety Reporting Requirements for Investigational New Drugs and Bioanalytical/Bioequivalence Studies" or as per national regulatory requirements in participating countries.

If required by local regulations, the Investigator is responsible for notifying his/her IRB or local ethics committee of all SAEs.

11.3. Procedures for Handling Special Situations

11.3.1. Pregnancy and Breastfeeding

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 EoT.

Highly effective methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

A pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, at screening, and again at treatment discontinuation during the

EoT. A negative serum hCG pregnancy test must be documented within 3 days prior to first study dose on C1D1.

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

The pregnancy should be followed up to determine the outcome, including any spontaneous or voluntary termination, details of the birth, and 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 selinexor 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 (e.g., 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 11.2.3)

A pregnancy in a female partner of a male patient must be reported to Karyopharm 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 selinexor-containing regimen.

11.3.2. Abuse, Misuse, Medication Errors, Overdose, and Occupational Exposure

All incidences of abuse, misuse, medication errors, overdose, and occupational exposure are required to be reported to Karyopharm Pharmacovigilance regardless of whether or not there is an associated AE or SAE. Reporting should be completed via the electronic SAE Report Form when technically possible. To complete the electronic SAE Report Form, a Log Line must first be completed in the Medication Error eCRF. The incident will then be linked to an electronic SAE Report Form. If electronic reporting is not possible, reporting should be completed via a paper SAE Report Form emailed to pharmacovigilance@karyopharm.com.

11.3.2.1. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment 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 any study treatment are to be recorded on an 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.

11.3.2.2. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm 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 documented in the patient's medical record and in the eCRF. Information regarding the overdose is to be recorded on an 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 as soon as possible.

11.3.2.3. Occupational Exposure

Occupational exposure is the exposure to a study treatment as a result of one's professional or nonprofessional occupation. For this protocol, please follow the instructions for preparation and administration of selinexor.

All occurrences of occupational exposure with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure 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. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be finalized prior to database lock. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the clinical study report.

12.1. General Considerations

Summary tabulations will be provided for disposition, demographic, baseline characteristics, efficacy, and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented.

For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized with Kaplan-Meier method using 50th (median) percentiles with associated 2-sided 95% CIs as well as percentage of censored observations if applicable.

12.1.1. Procedures for Handling Missing Data

In general, there will be no substitutions made to accommodate missing data points.

For time to event analyses, patients who have no efficacy evaluations will be considered as censored at date of first treatment.

For AEs, missing dates will be imputed per the rules outlined in the SAP. Each AE will be graded for severity according to NCI CTCAE. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

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12.3. Populations for Analyses

12.3.1. Modified Intent-to-treat Population

The modified intent-to-treat (mITT) population will consist of all patients who receive at least one dose of any study treatment. This population will be used for primary analyses of efficacy.

12.3.2. Safety Population

The safety population will consist of all enrolled patients who have received at least one dose of both study treatments. Patients will be analyzed according to treatment received.

12.4. Statistical Analyses

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections.

12.4.1. Efficacy Analyses

The primary efficacy analysis will be performed on the mITT population.

12.4.1.1. Primary Endpoint

The primary efficacy endpoint of ORR (proportion of patients who achieve CR or PR) will be analyzed for each arm separately on the mITT population which consists of all enrolled patients who received any study treatment. Estimated ORR with 95% confidence interval (CI) will be summarized for each arm.

12.4.1.2. Secondary Endpoints

- Progression-free survival is defined as time from date of first treatment to the date of first confirmed PD, or death due to any cause, whichever occurs first. Median PFS with 95% CI will be summarized for each treatment arm.
- Overall survival is defined as time to death, from the date of first treatment. Median OS with 95% CI will be summarized for each treatment arm.
- Complete response rate is defined as proportion of patients who achieved a CR. The point estimate and an 95% exact CI of CRR will be provided for each treatment arm.
- Duration of response is defined as the duration of time from first occurrence of response ≥PR until the first date of PD or death due to any cause, whichever occurs first. Median DOR with 95% CI will be summarized for each treatment arm.
- Disease control rate is defined as the percentage of patients who have achieved CR, PR or stable disease. The point estimate and an 95% exact CI of DCR will be provided for each treatment arm.

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12.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population, unless otherwise specified and will be presented by actual treatment arm. Details of the analyses will be described in the SAP.

The safety and tolerability of selinexor will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations. The grading of the severity of the AEs will be done according to CTCAE, v.5.0. Investigators will provide their assessment as either the AE is related or not related to study drug.

Treatment-emergent AEs, SAEs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment will be summarized by Arm and in the overall safety population. Treatment-emergent AEs will be those that start or worsen on or after the first day of study treatment, through 30 days after last dose (or the day before initiation of a new anti-neoplastic treatment, whichever occurs first). Related AEs will be those with an Investigator determination of related to study drug.

Laboratory data will be analyzed by summary statistics over time, as well as by shift tables based on severity.

Continual monitoring of safety data will be performed by the independent Data Safety Monitoring Board (DSMB). Adverse events and concomitant medications will be coded according to medical dictionary for regulatory activities (MedDRA) and WHO Drug, respectively.

12.4.2.1. Adverse Events

Adverse events will be coded using the MedDRA and displayed in tables and listings using MedDRA system organ class (SOC) and preferred term (PT).

In those instances where the AE only has a partial date recorded, the AE will be assessed using the available date information to determine if it is treatment emergent. For AEs in which the date is completely missing, the AE will be assumed to be treatment emergent. No formal hypothesis-testing of AE incidence rates will be performed.

Adverse events will be summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given AE (by PT). The number and percentage of patients with any TEAE will be summarized for each cohort, classified by SOC and PT. The number and percentage of patients with TEAEs assessed by the Investigator as related to treatment will also be tabulated. The number and percentage of patients with any Grade ≥3 TEAE will be tabulated in the same manner.

In the event a patient experience repeat episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

SAEs will be summarized in the same manner as TEAEs.

All AEs (treatment emergent and post-treatment) will be listed in by-patient data listings, classified by cohort, patient, and day on study. In addition, separate by patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

12.4.2.2. Laboratory Data

Clinical laboratory values will be expressed using SI units.

For each cohort, the actual value and change from baseline (Day 1, prior to the first administration of study drug) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology, and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the screening value will substitute as the baseline value.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE Grades ≥3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

12.4.2.3. Vital Signs and Physical Examinations

The actual value and change from baseline (Day 1, prior to the first administration of study treatment) to each on study evaluation will be summarized for vital signs.

By-patient listings of vital sign measurements will be presented in data listings.

Abnormal physical examination results at screening, and abnormal physical examination results (AEs) during the study, will be summarized. All physical examination findings will be presented in by-patient data listings.

12.4.2.4. Concomitant Medications

The use of concomitant medications will be included in by-patient data listings.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Ethical and Administrative Obligations

13.1.1. Regulatory and Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations (CFR) Title 21), and with the ethical principles that originate from the Declaration of Helsinki.

The protocol and the proposed ICF(s) must be reviewed and approved by a properly constituted IRB/IEC before study start. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Karyopharm monitors, auditors, designated agents of Karyopharm, IRBs/IECs, and regulatory authorities as required.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

13.1.2. Responsibilities of the Investigator and Good Clinical Practice

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.3. Informed Consent Process

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) informed consent that has been approved by an IRB or IEC associated with the study site.

The informed consent must be obtained prior to the initiation of any study-specific measures. The process of obtaining informed consent should be documented in the patient source documents. The date when the Informed Consent was obtained will be captured in the patient's case report forms (CRFs).

Karyopharm will provide to Investigators, in a separate document, proposed ICFs that are considered appropriate for this study and comply with the ICH GCP guidelines and regulatory requirements. Any changes to the ICFs suggested by the Investigator must be agreed to by Karyopharm before submission to the IRB/IEC, and a copy of the approved version(s) must be provided to the Karyopharm after IRB/IEC approval.

Females of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

- The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
  - CCI [redacted]
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study, through the 30-Day follow up visit. Re-consenting is not required during the Survival Follow Up period.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. If required by local regulations, in addition to the

primary ICF, there will be a separate form for female partners of participating male patients who are sexually active and accept risks.

13.4. Data Collection and Management

13.4.1. Data Confidentiality

The Investigator must ensure anonymity of the patients. Patients will be assigned a unique identifier by the Karyopharm. Signed ICFs and patient enrollment logs must be kept strictly confidential to enable patient identification at the site.

Any patient records or datasets that are transferred to Karyopharm will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why?
- Who will use or disclose that information?
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g., has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential patient information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

13.4.2. Data Collection

Data collection is the responsibility of the clinical study staff at the site, under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the eCRF system.

13.4.3. Site Monitoring

Before study initiation, Karyopharm personnel (or designated contract research organization [CRO]) will review the protocol with the Investigators and their staff (e.g., at a site initiation visit). During the study, the monitor will visit the site regularly to check the completeness of patient

records, accuracy of entries on the CRFs, adherence to the protocol and to GCP, progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The Investigator must also keep the original signed ICF (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Karyopharm monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

13.4.4. Data Captures

This study will utilize electronic data capture (EDC), the designated clinical site staff will enter the data required by the protocol into the eCRF. The eCRFs will be constructed using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Clinical site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the Investigator staff.

The Investigator is responsible for assuring that the data entered into the eCRF is complete and accurate, and that entry and updates are performed in a timely manner.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

13.4.5. Database Management and Quality Control

Karyopharm personnel (or designated CRO) will review the eCRF data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

At the conclusion of the study, after discrepancies and missing values have been completed and the data have been verified to be complete and accurate, the database will be declared locked.

For EDC studies, after database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

13.5. Structure of Committees

13.5.1. Data Safety Monitoring Board

An independent DSMB will be established and will review the safety of study treatment and any SAEs that occur during the study. Details on how the DSMB will review safety and response data are provided in the DSMB Charter.

The DSMB will be composed of at least two oncologists (at least one of whom specializes in melanoma) and a statistician. Following their initial meeting, the DSMB will meet approximately every 6 months to review clinical data and provide recommendations to the Sponsor on whether the study should continue. The DSMB may also meet more frequently, if needed.

13.6. Dissemination of Clinical Study Data

Results from the study (including demographics, baseline characteristics, primary and secondary endpoints) will be posted in a publicly accessible database (such as ClinicalTrials.gov or EudraCT) in accordance with applicable laws, regulations, and/or guidelines.

In addition, upon study completion and finalization of the clinical study report, the results of this study may be submitted for publication in a peer-reviewed journal or presented at a scientific/biomedical conference.

13.7. Source Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Karyopharm-sponsored study, each site will permit authorized representatives of Karyopharm and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

The Investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the clinical study unless Karyopharm provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

13.8. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

13.9. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

14. REFERENCES

Abdul Razak AR, Mau-Soerensen M, Gabrail NY, Gerecitano JF, Shields AF, Unger TJ, et al. First-in-class, first-in-human phase I study of selinexor, a selective inhibitor of nuclear export, in patients with advanced solid tumors. J Clin Oncol. 2016 Dec 1;34(34):4142.

Agarwala SS. Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: cytotoxic T-lymphocyte antigen-4 blockade in advanced melanoma. Melanoma Res. 2010 Feb 1;20(1):1-0.

Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer. 2019 Aug 1;145(3):639-48.

Arance A, de la Cruz Merino L, Petrella TM, Jamal R, Ny L, Carneiro A, et al. Lenvatinib plus pembrolizumab for patients with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: Updated findings of LEAP-004. ASCO Annual Meeting 2021.

Azmi AS, Bao B, Kauffman M, Shacham S, Mohammad RM. Specific inhibitors of nuclear export (SINE) for cancer therapy: from bench to bedside. Cancer Res. 2013 April; 73(8): AM2013-3445.

Bajwa R, Cheema A, Khan T, Amirpour A, Paul A, Chaughtai S, et al. Adverse effects of immune checkpoint inhibitors (programmed death-1 inhibitors and cytotoxic T-lymphocyte-associated protein-4 inhibitors): results of a retrospective study. research Clin Med Res. 2019 Apr;11(4):225.

Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36):6199.

Breit MN, Kisseberth WC, Bear MD, Landesman Y, Kashyap T, McCauley D, et al. Biologic activity of the novel orally bioavailable selective inhibitor of nuclear export (SINE) KPT-335 against canine melanoma cell lines. BMC Vet Res. 2014 Jul 15; 10:160

Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. Cancer. 2017 Jun 1;123(S11):2143-53.

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med.2011 Jun 30;364(26):2507-16.

Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. Cancer Biol Ther. 2019 Nov 2;20(11):1366-79.

Elloul S, Chang H, Klebanov B, Kashyap T, Werman M, Lee M, et al. Selinexor, a selective inhibitor of nuclear export (SINE) compound, shows synergistic anti-tumor activity when combined with PD-1 blockade in a mouse model of colon cancer. Cancer Res. 2016 Jul 76 (14): Abstract 2219.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan 1;45(2):228-47.

Etchin J, Le BT, Kentsis A, Stone RM, McCauley D, Kauffman M, et al. Novel Inhibitors of CRM1/XPO1 Nuclear Exporter Exhibit Striking Activity Against AML “primagrafts,” Including

AML Leukemia Initiating Cells, While Sparing Normal Hematopoietic Cells. Blood. 2013 Nov 122 (21): 3932.

Farren MR, Hennessey RC, Shakya R, Elnaggar O, Young G, Kendra K, et al. The exportin-1 inhibitor selinexor exerts superior antitumor activity when combined with T-cell checkpoint inhibitors. Mol Cancer Ther. 2017 Mar 1;16(3):417-27.

Fenton SE, Sosman JA, Chandra S. Resistance mechanisms in melanoma to immuneoncologic therapy with checkpoint inhibitors. Cancer Drug Resist 2019;2:744-761.

Fragomeni RA, Chung HW, Landesman Y, Senapedis W, Saint-Martin JR, Tsao H, et al. CRM1 and BRAF inhibition synergize and induce tumor regression in BRAF-mutant melanoma. Mol Cancer Ther. 2013 Jul 1;12(7):1171-9.

Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist. 2011 Jan;16(1):5.

Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019 Apr 1;30(4):582-8.

Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, et al. Nivolumab versus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018; 19: 1480-92.

Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015 Oct 1;33(28):3193.

Jenkins RW, Fisher DE. Treatment of Advanced Melanoma in 2020 and Beyond. J Invest Dermatol. 2021 Jan;141(1)23-31.

Jiang X, Wang J, Deng X, Xiong F, Ge J, Xiang B, et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Mol Cancer. 2019 Dec;18(1):1-7.

Kluger HM, Tawbi HA, Ascierto ML, Bowden M, Callahan MK, Cha E, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. J Immunother Cancer. 2020; 8:e000398.

Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008 Feb 1;26(4):527-34.

Lala M, Li TR, de Alwis DP, Sinha V, Mayawala K, Yamamoto N, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020 May 1;131:68-75.

Lapalombella R, Sun Q, Williams K, Tangeman L, Jha S, Zhong Y, et al. Selective inhibitors of nuclear export show that CRM1/XPO1 is a target in chronic lymphocytic leukemia. Blood. 2012 Nov 29;120(23):4621-34.

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015 Jul 2;373(1):23-34.

Lipson EJ, Tawbi HA, Schendorf D, Ascierto PA, Matamala L, Castillo Gutierrez E, et al. Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047). 2021 ASCO Annual Meeting. Abstr. 9503.

NCCN. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 2007 Jul 1;19(7):813-24.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec 1;5(6):649-56.

Pathria G, Wagner C, Wagner SN. Inhibition of CRM1-mediated nucleocytoplasmic transport: triggering human melanoma cell apoptosis by perturbing multiple cellular pathways. J Invest Dermatol. 2012 Dec 1;132(12):2780-90.

Peggs KS, Quezada SA, Allison JP. Cell intrinsic mechanisms of T-cell inhibition and application to cancer therapy. Immunol Rev. 2008 Aug;224(1):141-65.

Rebecca VW, Somasundaram R, Herlyn M. Pre-clinical modeling of cutaneous melanoma. Nat Commun. 2020 Jun 5;11(1):1-9.

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32.

Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015 Jun 10;33(17):1889.

Schreuer M, Jansen Y, Planken S, Chevolet I, Seremet T, Kruse V, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAFV600-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol. 2017 Apr 1;18(4):464-72.

Senapedis WT, Baloglu E, Landesman Y. Clinical translation of nuclear export inhibitors in cancer. Semin Cancer Biol. 2014 Aug 1 (27): 74-86.

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar 1;18(3):e143-52.

Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020 Mar 5.

Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014 Apr 1;32(10):1020.

Trott J, Anderson K, Kim J, Graef A, Shacham S, Landesman Y, et al. Abstract LB-086: Combination therapy of immune checkpoint and nuclear exporter inhibitors in a renal cell carcinoma mouse model. Cancer Res 2016;76(14 Suppl):Abstract LB-08.

Tyler PM, Servos MM, de Vries RC, Klebanov B, Kashyap T, Sacham S, et al. Clinical dosing regimen of selinexor maintains normal immune homeostasis and T-cell effector function in mice: implications for combination with immunotherapy. Mol Cancer Ther. 2017 Mar 1;16(3):428-39.

US National Library of Medicine. ClinicalTrials.gov [Internet]. NCT02419495: Selinexor With Multiple Standard Chemotherapy or Immunotherapy Regimens in Treating Patients With Advanced Malignancies. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02419495

US National Library of Medicine. ClinicalTrials.gov [Internet]. NCT03455764: MCS110 With BRAF/MEK Inhibition in Patients With Melanoma. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03455764

US National Library of Medicine. ClinicalTrials.gov [Internet]. NCT03272464: INCB039110 in Combination With Dabrafenib and Trametinib in Patients With BRAF-mutant Melanoma and Other Solid Tumors. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03272464

US National Library of Medicine. ClinicalTrials.gov [Internet]. NCT04256707 Relative Bioavailability/Bioequivalence of Different Formulations of Selinexor, the Impact of Hepatic Impairment on Selinexor Pharmacokinetics, Tolerability and Antitumor Activity of Selinexor Combination Treatment (SPRINT). 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04256707

US National Library of Medicine. ClinicalTrials.gov [Internet]. NCT02025985: Study of KPT-330 (Selinexor) in Female Patients With Advanced Gynaecologic Malignancies (SIGN)2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02025985

Wang AY, Liu H. The past, present, and future of CRM1/XPO1 inhibitors. Stem Cell Investig. 2019;6:6.

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013 Jul 11;369:122-33.

Wu K, Wang W, Ye Y, Huang J, Zhou Y, Zhang Y, et al. Integration of protein interaction and gene co-expression information for identification of melanoma candidate genes. Melanoma Res. 2019 Apr 1;29(2):126-33.

Yang J, Bill MA, Young GS, La Perle K, Landesman Y, Shacham S, et al. Novel small molecule XPO1/CRM1 inhibitors induce nuclear accumulation of TP53, phosphorylated MAPK and apoptosis in human melanoma cells. PloS one. 2014 Jul 24;9(7):e102983.

Yang J, Dong M, Shui Y, Zhang Y, Zhang Z, Mi Y, et al. A pooled analysis of the prognostic value of PD-L1 in melanoma: evidence from 1062 patients. Cancer Cell Int. 2020 Dec;20:1-1.

APPENDIX 1. RECIST VERSION 1.1

(Modified from Eisenhauer 2009)

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non target) must have reduction in the short axis to <10mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD)

Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD)

At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions will also constitute progressive disease.

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since the treatment started.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Evaluation of Best Overall Response – Patient with Target (± non-target) disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR-Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE

Target lesions	Non-Target lesions	New Lesions	Overall response
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR: complete response; NE: non-evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

Evaluation of Best Overall Response – Patient with Non-Target Disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR-Non-PD	No	Non-CR/Non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR: complete response; NE: non-evaluable; PD: progressive disease; PR: partial response.

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

Method of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

CT, MRI

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease

is mandatory to differentiate between response or stable disease (an effusion may be an adverse drug reaction of the treatment) and PD.

APPENDIX 2. iRECIST

(Modified from Seymour 2017)

A systematic modification of RECIST 1.1 was undertaken by the RECIST Working Group to address observations of the patterns of response of tumors to immune-modulating agents, which resemble tumor flare and have been termed pseudoprogression. Some patients who experience these increases in tumor measurement after immunotherapy go on to have late, but deep and durable responses. Therefore, a data-driven method was developed for consistently measuring tumor response to immune-based therapeutics.

RECIST 1.1 is still used to define measurability and for management of bone lesions, cystic lesions, and lesions with previous local treatment. The method of tumor measurement (CT/MRI preferred) is also unchanged. The main modification is the concept of resetting the dimensions against which following assessments are measured if RECIST 1.1 progression is followed by tumor shrinkage.

The assessment of timepoint response is unchanged from RECIST 1.1; that is, the method of assessment of target and non-target lesions, lymph nodes, lesions that become too small to measure, lesions that split or coalesce, and the definitions of CR, PR, SD, and PD. The RECIST 1.1 definitions are used to determine "immune" response: immune complete response (iCR), immune partial response (iPR), immune stable disease (iSD), immune unconfirmed progressive disease (iUPD), and immune confirmed progressive disease (iCPD).

The difference primarily lies in the ability to assign responses of iCR, iPR, and iSD after iUPD has been documented, as long as progression is not confirmed at the next assessment, resulting in iCPD. If iUPD is not confirmed at the following assessment (per RECIST 1.1 – that is, increase in size or number of lesions), the response for that timepoint is defined by the RECIST 1.1 guidelines for response. If tumor shrinkage occurs (compared with baseline) meeting the criteria of iCR, iPR, or iSD, then iUPD must occur again (compared with nadir values) and be confirmed (by further growth) for iCPD to be assigned. If there is no change in tumor number or size from the iUPD, the timepoint response would again be iUPD. The assessment of iUPD can be made multiple times, with iCR, iPR, or iSD occurring afterward as long as iCPD is not confirmed at the next assessment.

Immune best overall response (iBOR) is determined as with RECIST 1.1 if there is no iUPD. In the case of iUPD, a subsequent iBOR of iSD, iPR, or iCR is still possible if the overall RECIST 1.1 criteria are met, provided that the criteria for iCPD (that is, disease progression at the assessment following iUPD) are not met. The duration of iCR and iPR is from the timepoint when criteria for iCR or iPR are first met; the duration of iSD is calculated from baseline.

For immune progression-free survival (iPFS), the event date should be the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment. The date of an iUPD that is disregarded due to iSD, iPR, or iCR at the next visit should not be used as the progression event date. Table 13 illustrates comparisons between RECIST 1.1 and iRECIST, and Table 14 provides guidance for assigning timepoint response without or with previous iUPD.

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	**iRECIST**
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the eCRF (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Result in iUPD, but iCPD is assigned on the basis of this category ONLY if at the next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD.
Confirmation of progression	Not required	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST.
Abbreviations: iCPD = confirmed progression; iCR = complete response; iPR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; iSD = stable disease; iUPD = unconfirmed progression.

Assignment of Timepoint Response Using iRECIST

	Timepoint Response with No Previous iUPD in Any Category	Timepoint Response with Previous iUPD in Any Category[a]
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR/iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD)
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD.
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new target lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified
Target, non-target, and new lesions defined according to RECIST 1.1; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.		
"i" indicates immune responses assigned using iRECIST. Abbreviations: iCPD = confirmed progression; iCR = complete response; iPR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; iSD = stable disease; iUPD = unconfirmed progression.		

	Timepoint Response with No Previous iUPD in Any Category	Timepoint Response with Previous iUPD in Any Category[a]
a Previously identified in assessment immediately before this timepoint.		

APPENDIX 3. STRONG AND MODERATE CYP3A INHIBITORS AND INDUCERS

Type	Example Medications
Strong CYP3A inducers	Apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampin, rifapentine, St John's Wort extract
Moderate CYP3A inducers	Asunaprevir, beclabuvir, bosentan, cenobamate, dabrafenib, daclatasvir, efavirenz, elagolix, etravirine, lersivirine lesinurad, lopinavir, lorlatinib, modafinil, nafcillin, rifabutin, ritonavir, semagacestat, talviraline, telotristat ethyl thioridazine, tipranavir
Strong CYP3A inhibitors	Aquinavir, boceprevir, ceritinib, cobicistat, conivaptan, clarithromycin, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice DS, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, mifepristone, nefazodone, nelfinavir, posaconazole, ribociclib, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir (GS-9350), troleandomycin, VIEKIRA pak, voriconazole
Moderate CYP3A inhibitors	amprenavir, aprepitant, atazanavir, atazanavir/-ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, darunavir /ritonavir, diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, fluconazole, grapefruit juice, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (Schisandra sphenanthera), netupitant, nilotinib, ravuconazole, tofisopam, verapamil, voxelotor

Note: This is based on Metabolism and Transport Drug Interaction Database (https://www.druginteractioninfo.org/) and is not an exhaustive list. For an updated FDA list, see the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#cypEnzymes

APPENDIX 4. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS CRITERIA

ECOG PERFORMANCE STATUS SCALE	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982