



CLINICAL STUDY PROTOCOL

KCP-330-027

Open-Label, Phase 1/2 Study Evaluating the Relative Bioavailability/Bioequivalence of Different Formulations of Selinexor, the Impact of Hepatic Impairment on Selinexor Pharmacokinetics, and the Tolerability and Antitumor Activity of Selinexor Combination Treatment (SPRINT)

Study Number:	KCP-330-027
Study Phase:	Phase 1/2
Investigational Product:	Selinexor (KPT-330)
EudraCT Number	2021-000617-16
Indication:	Non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and other solid tumors
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. +1 (617) 658-0600
Protocol Date and Version:	23 April 2021, Version 6.0
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CONDUCT In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.	
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PROTOCOL APPROVAL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study KCP-330-027 dated 23 April 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	Date
Karyopharm Therapeutics Inc.	

PPD	Date
Karyopharm Therapeutics Inc.	

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study KCP-330-027 dated 23 April 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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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
AUC _{0-inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC _{0-t}	area under the concentration-time curve from time zero to time of last concentration measured
BA/BE	bioavailability/bioequivalence
BOR	best overall response
BSA	body surface area
BUN	blood urea nitrogen
C	Cycle
CAPEOX	capecitabine and oxaliplatin
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
C _{max}	maximum plasma concentration
CPI	checkpoint inhibitor
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A
D	Day
DCR	disease control rate
DDR	DNA damage repair
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram

Abbreviation	Definition
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EOMT	end of monotherapy treatment
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FOLFIRI	folinic acid, 5-fluorouracil, and irinotecan
FOLFOX	folinic acid, 5-fluorouracil, and oxaliplatin
FOLFOXIRI	folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
hCG	human chorionic gonadotropin
HI	hepatic impairment
HPLC-MS/MS	high-performance liquid chromatography with tandem mass spectrometry
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IEC	Institutional Ethics Committee
CCI	
IRB	Institutional Review Board
iRECIST	Immunotherapeutic Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
KRAS	Kirsten rat sarcoma (gene homolog)
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Moderate Hepatic Impairment
MM	multiple myeloma

Abbreviation	Definition
MRI	magnetic resonance imaging
mPFS	median progression-free survival
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network®
NCI	National Cancer Institute
NRAS	Neuroblastoma - rat sarcoma (gene homolog)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDn	Pharmacodynamics
PDnRO	Pharmacodynamics (XPO1) receptor occupancy
Pem	Pembrolizumab
PFS	progression-free survival
PHI	protected health information
PK	Pharmacokinetics
PLT	platelet count
PR	partial response
PO	Orally
QW	once weekly
REB	research ethics board
RECIST	Response Evaluation Criteria in Solid Tumors
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
SAP	statistical analysis plan
SHI	Severe Hepatic Impairment
SINE	selective inhibitor of nuclear export
SOA	schedule of assessments
t _{1/2}	terminal half-life
T _{max}	time to maximum plasma concentration

Abbreviation	Definition
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
V_d/F	apparent volume of distribution
WBC	white blood cell
XPO1	exportin 1

1. PROTOCOL SUMMARY

1.1. Synopsis

Sponsor: Karyopharm Therapeutics Inc.	Investigational Product: Selinexor (KPT-330)	Study Phase: Phase 1/2
Title of Study: Open-Label, Phase 1/2 Study Evaluating the Relative Bioavailability/Bioequivalence of Different Formulations of Selinexor, the Impact of Hepatic Impairment on Selinexor Pharmacokinetics, and the Tolerability and Antitumor Activity of Selinexor Combination Treatment (SPRINT)		
Protocol Number: KCP-330-027		
Study Location: Israel and EU; US and Canada (Arm A only)		
Study Rationale: The study has 2 parts: monotherapy and combination therapy (see schema below). - In the Monotherapy Part, patients will first receive single agent selinexor and then those with normal hepatic function can switch to combination therapy after completing the planned doses of monotherapy and the required PK sample collection. Patients with impaired hepatic function will remain on single-agent treatment. - In the Combination Therapy Part, all patients will receive a combination therapy as described below:		
<pre> graph TD Start[Screen, enroll, and assign patients] --> Monotherapy Start --> CombinationTherapy[Combination Therapy] Monotherapy --> NormalHepaticFunction[Normal Hepatic Function CRC: KRAS WT 1-3 lines^a (no ICI), KRAS Mut 1-2 lines^a (no ICI) NSCLC: 1-2 prior lines (1 ICI)^a] Monotherapy --> ImpairedHepaticFunction[Impaired Hepatic Function Any solid tumor At least 1 prior line^a] NormalHepaticFunction --> S20100[S20-100: Selinexor 5 x 20 mg (Week 1) then 1 x 100 mg (Week 2)] NormalHepaticFunction --> S10020[S100-20: Selinexor 1 x 100 mg (Week 1) then 5 x 20 mg (Week 2)] ImpairedHepaticFunction --> MHI[Moderate Hepatic Impairment (MHI): Selinexor 2 x 20 mg weekly] ImpairedHepaticFunction --> SHI[Severe Hepatic Impairment (SHI): Selinexor 2 x 20 mg weekly] S20100 --> ContinueCombinationTherapy[Continue to Combination Therapy] S10020 --> ContinueCombinationTherapy MHI --> ContinueCombinationTherapy SHI --> ContinueCombinationTherapy CombinationTherapy --> ArmA[Arm A NSCLC 1-2 prior lines^a (1 ICI)] CombinationTherapy --> ArmB[Arm B CRC KRAS WT 1-3 lines^a (no ICI), KRAS Mut 1-2 lines^a (no ICI)] CombinationTherapy --> ArmC[Arm C CRC Regardless of KRAS status 1-2 prior lines^a] ArmA --> ArmATreatment[Selinexor 60 mg weekly + docetaxel 75 mg/m² once every 3 weeks] ArmB --> ArmBTreatment[Selinexor 80 mg weekly + pembrolizumab 200 mg once every 3 weeks] ArmC --> Cohort1[Cohort 1: Selinexor 40 mg on Days 1, 3, 15 and 18 in a 28-day cycle + FOLFIRI] ArmC --> Cohort2[Cohort 2: Selinexor 80 mg on Days 1 and 15 in a 28-day cycle + FOLFIRI] ContinueCombinationTherapy --> AllArmsContinue[For All Arms, Patients Continue Therapy Until PD] AllArmsContinue --> ArmATreatment AllArmsContinue --> ArmBTreatment AllArmsContinue --> Cohort1 AllArmsContinue --> Cohort2 </pre>		
^a Lines of systemic therapy ICI = immune checkpoint inhibitor; CRC = colorectal cancer; KRAS = Kirsten rat sarcoma; NSCLC = non-small cell lung cancer; PD = progressive disease, WT = wild type; Mut = mutant		

Monotherapy Part:

Patients with normal hepatic function:

A new tablet formulation of selinexor (100 mg tablets) has been developed to allow for single-tablet dosing. In the Monotherapy Part of this study, the relative bioavailability/bioequivalence of this new formulation compared to the currently available 20 mg tablet will be established in patients with normal hepatic function.

After completing the planned doses for the relative bioavailability/bioequivalence study, these patients can continue in the study and switch to treatment with combination therapy, if they meet the combination therapy reassessment criteria.

Patients with hepatic impairment:

Patients with any type of advanced or metastatic solid tumor who have moderate or severe hepatic impairment can be enrolled into this part of the study. Although no clinically significant drug-drug interactions have been reported to date in more than 3,200 patients treated with selinexor alone or in combination, the elimination of selinexor is in part attributable to cytochrome P450 3A4 (CYP3A4)-mediated metabolism. The sparsely sampled pharmacokinetic (PK) data obtained from patients with moderate (n=8) and severe (n=6) hepatic impairment in previous company-sponsored studies is inadequate to assess whether impaired hepatic function could lead to increased selinexor exposures. Therefore, the Moderate Hepatic Impairment (MHI) treatment arm and the Severe Hepatic Impairment (SHI) treatment arm in this study will include patients with moderate and severe hepatic impairment, respectively, to characterize the relationship between hepatic function and selinexor PK. The duration of the PK evaluation will be 3 days.

Patients in the MHI and SHI arms will remain in the study on monotherapy only, at the discretion of the Investigator, until PD, or intolerance.

Combination Therapy Part:

The objective of the Combination Therapy Part is to independently evaluate the safety and tolerability and to explore the preliminary anti-tumor activity of 3 combination therapies in the following 3 arms:

- Arm A: the combination of selinexor with docetaxel in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have received 1-2 prior lines of systemic therapy that included 1 line of therapy with an anti-PD1/L1 monoclonal antibody (mAb).
- Arm B: the combination of selinexor with pembrolizumab, a humanized IgG4 anti PD-1 mAb, in patients with advanced or metastatic colorectal cancer (CRC) who have received 1-3 prior systemic treatments for Kirsten rat sarcoma (KRAS) wild-type (WT) CRC or 1-2 prior treatments for KRAS mutant CRC, but all may not have received prior therapy with an anti-PD1/L1 mAb.
- Arm C: the combination of selinexor with FOLFIRI in patients with advanced or metastatic CRC who have received 1-2 prior systemic treatments regardless of KRAS status. This combination will have 2 dose regimens (Cohort C1 and Cohort C2). Approximately 6 patients will be treated in each of these 2 dose cohorts (first C1 is enrolled, then C2). Based on safety and preliminary anti-tumor activity from these 2 dose cohorts, an optimal dose regimen will be selected for further expansion with up to additional 14 patients.

Note: KRAS status documentation is required for patients in all treatment arms.

In patients with NSCLC, the combination of selinexor with docetaxel is proposed for the following reasons: (1) docetaxel is a commonly used chemotherapy for patients with NSCLC whose disease progressed on prior immune checkpoint inhibitors and chemotherapy; (2) preclinical data demonstrates that (a) XPO1 is overexpressed in lung cancer cells, particularly those arising in the setting of exposure to nicotine-derived nitrosamine ketone (a tobacco carcinogen); (b) selinexor and other SINE compounds

are active in in NSCLC cell lines and xenografts and (c) KRAS-driven NSCLC also depends on XPO1, which clears nuclear I κ B α and supports NF- κ B activity. KRAS-mutant models are selectively sensitive to selinexor.; (3) preclinical data combining selinexor with taxane-based therapy suggests synergy (combinations with docetaxel in prostate cancer and breast cancer mouse models, and combinations with paclitaxel in breast and ovarian cancer mouse models); (4) preliminary clinical data from an ongoing Investigator-sponsored study ([NCT03095612](#)) have shown promising anti-tumor activity of this combination in patients with KRAS mutant NSCLC who were treated with at least 1 prior systemic regimen that contained an immune checkpoint inhibitor (ICI); (5) data from the multi-arm Investigator-sponsored study [NCT02419495](#) demonstrating the maximum tolerated dose (MTD) of selinexor with cisplatin and paclitaxel and in a weekly paclitaxel study in breast cancer; and (6) the data from the current study that has been enrolling patients in Israel using the combination of selinexor and docetaxel in patients with NSCLC who have received a checkpoint inhibitor and chemotherapy. As of 12 Apr 2021, 13 patients with advanced, metastatic NSCLC with progressive disease after 1 to 2 lines of prior lines of systemic therapy including 1 checkpoint inhibitor have enrolled with 12 evaluable for response with at least one on study imaging scan. Ten patients are still on therapy for 2 to 13 months. There are 2 patients (16.7%) with PR, -67.2% and -36.3% reduction in disease, on treatment over 12 months and 6 months, respectively. Five patients (41.6%) have SD for 2-6 months. Two patients were discontinued due to PD; 1 for radiological PD and 1 for clinical PD with stable imaging. One patient with stable imaging died during cycle 5 due to comorbid medical issues unrelated study treatment (This patient had a history of congestive heart failure and died due to this – considered unrelated to study drug). There were no deaths due to study related toxicity and enrollment is ongoing. Overall, the treatment is well tolerated and adverse events (AEs) are reversible and manageable with supportive care and dose modifications. This amendment will open enrollment to additional patients in the US to further characterize safety and efficacy in NSCLC patients.

The emerging anti-tumor activity signal from this study warrants further evaluation of the efficacy of the combination of selinexor with docetaxel in patients with NSCLC whose disease has progressed on prior immuno-oncology therapy. **This is the only arm that will be opened in the US and Canada.**

In patients with CRC, the combination of selinexor with pembrolizumab is proposed based on non-clinical and clinical evidence of synergy effect of this combination. Results from several nonclinical studies show that selinexor can upregulate immune function and sensitize tumors to PD-1/ programmed death-ligand 1 (PD-L1) blockade: (1) the combination of selinexor and PD-1 or PD-L1 blockade has been assessed in *in vivo* studies and demonstrated synergistic anti-tumor activity in an aggressive murine colon cancer model as well as other solid tumor models; (2) a combination of selinexor and anti-PD-1 or anti-PD-L1 monoclonal antibody shows significant immunomodulatory activity, inducing changes in the frequency and phenotype of immune cell populations, including increased frequency of NK cells, induced frequency of differentiated TH1 cells, and increased frequency of activated T-cells; (3) selinexor induces PD-1 and PD-L1 gene expression, sensitizing tumor cells to immunotherapy and synergizes with anti-PD-1 to inhibit tumor cell proliferation and to induce apoptosis *in vitro* ([Farren 2017](#); [Elloul 2016](#); [Trott 2016](#)); (4) in clinical studies, single-agent selinexor has demonstrated activity against CRC with KRAS mutation or WT ([Abdul Razak 2016](#)); and (5) the safety and anti-tumor activity of combining selinexor with a PD-1/PD-L1 inhibitor has been established in an ongoing Phase 1b Investigator sponsored study ([NCT02419495](#)). Preliminary clinical data of selinexor in combination with pembrolizumab or nivolumab demonstrated an acceptable tolerability profile.

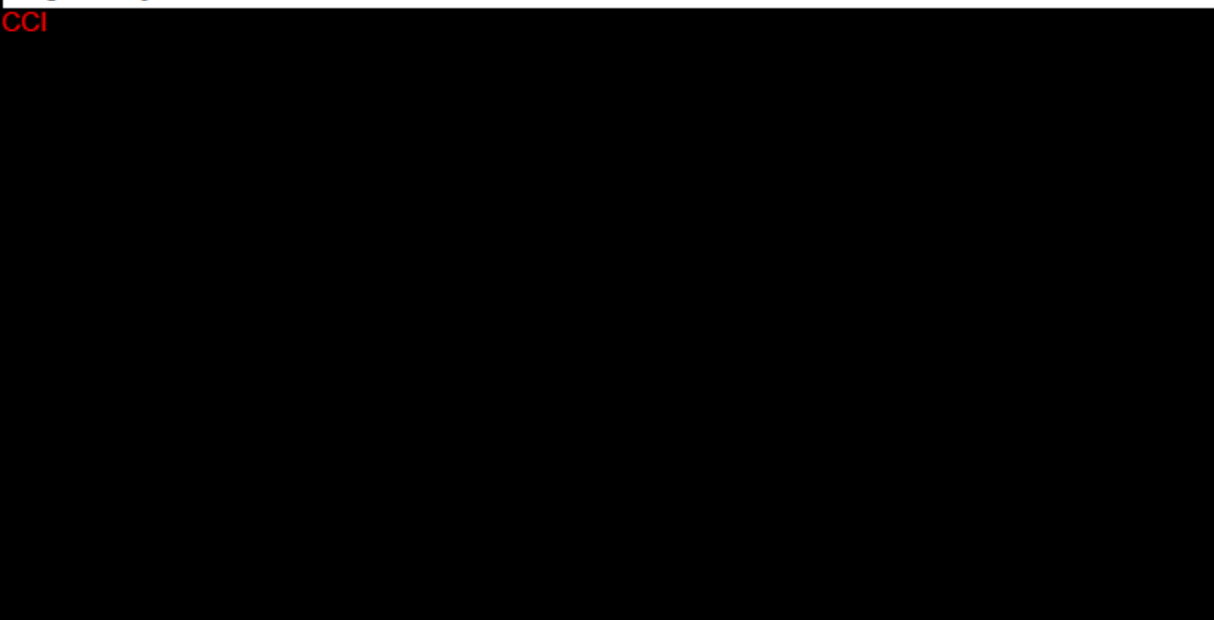
As of 31 March 2021, there were 24 patients out of 30 patients who had at least one post baseline efficacy evaluation based on imaging. The median age was 57.5 years, 19 (63.3%) were male, and 16 (53.3%) had RAS mutations. Median number of prior antineoplastic regimens was 2. All patients entered the study with documented progressive disease. In this group, 11 patients had stable disease as their best overall response (BOR), and 8 of these 11 patients with stable disease (73%) had RAS mutant tumors. Notably none of the RAS mutated tumors were MSI-H. Additionally, 16 patients had PD as their BOR with 8 of these 16 (50%) having wild type tumors. The mPFS in CRC RAS mut was 12.9 weeks,

95% CI (8.3, NA) vs RAS WT 5.9 weeks, 95% CI: (5.6, NA) ($p = 0.26$ (patients with mutation status 'Unknown' are excluded); HR 0.538, [95% CI 0.196, 1.474.]). The increased PFS and disease stabilization observed among patients with RAS mutated CRC, whose tumors were notably also MSS, and treated with selinexor and pembrolizumab as contrasted with patients with RAS wild-type tumors indicates that this combination may be an effective treatment for patients with RAS mutant CRC who would otherwise have few options and be ineligible for checkpoint inhibitors. These results support the clinical evaluation of the combination of selinexor with a PD-1/PD-L1 inhibitor in patients with CRC.

In patients with CRC, the combination of selinexor with FOLFIRI will also be explored. Selinexor is an oral selective XPO1 inhibitor, and consequently restores the highly effective tumor suppressing pathways that lead to selective elimination of genomically damaged (i.e., neoplastic) cells by apoptosis, together with its ability to restore tumor cell sensitivity to chemotherapeutic or targeted agents such as irinotecan, oxaliplatin or olaparib makes it an ideal candidate for combination to augment the anti-tumor effects of standard chemotherapeutic agents or selective targeted therapy. In CRC (WiDR) and gastric (AGS) mouse xenograft studies, selective inhibitor of nuclear export (SINE) compounds showed synergy with irinotecan ([Subhash 2018](#)). In addition, selinexor showed *in vitro* synergy with fluorouracil (5-FU) in fibrosarcoma cell line HT1080 ([Burke 2017](#)). The combination of selinexor and FOLFIRI was tested in IST-11 ([NCT02419495](#)) in 3 patients with solid tumor malignancies and no patients met DLT criteria. Since non-clinical data has shown promising synergy, there is need for testing this combination specifically in CRC to evaluate safety, tolerability and preliminary efficacy of this combination and to establish the optimal dose.

Objectives and Endpoints:

Objectives	Endpoints
<i>Monotherapy Part</i>	
Primary	
- To determine the relative bioavailability of the 100 mg (Tablet B) and 20 mg (Tablet A) tablets of selinexor at 100 mg once weekly (QW) dose in patients with normal hepatic function - To assess the PK of selinexor after a single dose of 40 mg (2×20 mg) among patients with moderate and severe hepatic impairment relative to 100 mg (5×20 mg) among patients with normal hepatic function	The following plasma PK parameters for selinexor for the 2 formulations and different hepatic function: - area under the concentration-time curve (AUC) from time 0 to time of last concentration measured (AUC_{0-t}) and from time 0 extrapolated to infinity (AUC_{0-inf}) - maximum plasma concentration (C_{max})
Secondary	
To assess the additional PK of the new tablet formulation (Tablet B) and the reference (current) tablet formulation (Tablet A) in patients with normal hepatic function and of Tablet A formulation only in patients with moderate and severe hepatic impairment	The following PK parameters for selinexor for the 2 formulations in plasma: - time to maximum observed concentration (T_{max}) - terminal elimination rate constant (λ_z) - terminal half-life ($t_{1/2}$) - apparent clearance (CL/F) - apparent volume of distribution (V_d/F)

To explore changes in the protein binding of selinexor and the subsequent effects on its PK, in patients with varying degrees of hepatic function	The following PK parameters for selinexor (Tablet A formulation) in plasma: - fraction unbound (f_u) - maximum free-drug concentration ($C_{max,u}$) - area under the free-drug concentration-time curve from time zero extrapolated to infinity (AUC_u) - apparent free-drug clearance (CL_u/F) - apparent free-drug volume of distribution (V_u/F)
- To assess the tolerability of single agent selinexor at 100 mg once weekly in patients with advanced or metastatic NSCLC and CRC - To assess the tolerability of single agent selinexor in patients with any type of advanced or metastatic solid cancer indication and moderate or severe hepatic impairment	Based on AE reports, physical examination results (including vital signs), and clinical laboratory results by means of the occurrence, nature and severity of AEs
Exploratory	
CCI 	
<i>Combination Therapy Part: Arm A and Arm B</i>	
Primary	
To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	Objective response rate (ORR): per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab
Secondary	

To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	Progression-free survival (PFS), duration of response (DOR), disease control rate (DCR): per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab and OS
To assess the safety and tolerability of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	Based on AE reports, physical examination results (including vital signs), and clinical laboratory results by means of the occurrence, nature and severity of AEs
Exploratory	
CCI	
Combination Therapy Part: Arm C	
Primary	
To assess the safety and tolerability of QW vs BIW selinexor in combination with FOLFIRI in patients with CRC	Based on, physical examination results, clinical laboratory results by means of the occurrence, nature and severity of AEs
Secondary	
To assess the preliminary anti-tumor activity of selinexor in combination with FOLFIRI in patients with CRC	ORR, DCR, DOR, PFS per RECIST 1.1, and OS
Exploratory	
CCI	
Overall Study Design: This is a 2-part, multi-arm, open-label study in patients with solid tumors. <u>Monotherapy Part</u> The relative bioavailability (BA) and bioequivalence (BE) of two different formulations of selinexor will be evaluated using a 2-sequence crossover design (S20-100 and S100-20 treatment arms) in patients with normal hepatic function (including only patients with NSCLC or CRC). The impact of hepatic function on selinexor PK will also be evaluated in the Monotherapy Part using 2 additional parallel study arms of patients with any advanced or metastatic solid tumors and with moderate or severe hepatic impairment (MHI and SHI treatment arms, respectively). Patients with normal hepatic function in the bioavailability/bioequivalence (BA/BE) arms will continue into the Combination Therapy Part after completing all planned doses and PK sampling in the Monotherapy Part, if they meet the Combination Therapy Part reassessment criteria. Patients that do not	

meet the reassessment criteria will be allowed to continue treatment with monotherapy as per the discretion of the Investigator. Patients with MHI or SHI will not switch to combination therapy and will continue with monotherapy treatment, at the discretion of the Investigator, until disease progression or intolerance.

For the Monotherapy Part, patients will be allocated to 1 of the following test formulation treatment arms for QW dosing:

Arm	Planned N	Hepatic Function	Cycle Duration	Week 1 ^a	Week 2 ^a
S20-100	10	Normal	14 days	5 × 20 mg tablet (Tablet A) ^b	1 × 100 mg tablet (Tablet B)
S100-20	10	Normal	14 days	1 × 100 mg tablet (Tablet B)	5 × 20 mg tablet (Tablet A) ^b
MHI	8	Moderate impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)
SHI	6	Severe impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)

MHI = moderate hepatic impairment, SHI = severe hepatic impairment

^a If dosing and PK/PDn receptor occupancy (PDnRO) sampling must be repeated due to insufficient PK samples, the repeat dose will be administered after 7 days (5 days minimum, 21 days maximum) and will be considered the same “study day” as the previous dose. The Sponsor must be notified of any event leading to the collection of insufficient PK samples within 48 hours.

^b Indicates the portions of the Monotherapy Part from which PK data will be obtained for the evaluation of selinexor PK relative to hepatic function.

Approximately 20 patients (CRC or NSCLC) with normal hepatic function will be enrolled for the BA/BE portion (S20-100 and S100-20 arms) of the Monotherapy Part. Randomization with a 1:1 ratio will not include stratification factors.

For the assessment of hepatic impairment, 8 patients in the MHI arm and 6 patients in SHI arm will be enrolled.

For Week 1 (for all patients) and Week 2 (for patients in the S20-100 and S100-20 arms), following an overnight fast of at least 10 hours, patients will be fed a standard low-fat meal 30 minutes prior to administration of selinexor. Patients should finish the meal within 30 minutes; and, the selinexor dose should be administered 30 minutes after the start of the meal. The start time of fasting and eating must be recorded. Water intake can be allowed *ad libitum* except for 1 hour before and after drug administration. Blood sampling for selinexor PK (plasma) analyses will be collected pre-dose (≤10 minutes before taking selinexor), 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 1.5 hours (±5 min), 2 hours (±10 min), 3 hours (±10 min), 4 hours (±10 min), 5 hours (±10 min), 6 hours (±10 min), 8 hours (±20 min), 10 hours (±20 min; optional timepoint), 24 hours (±1 hour), 30 hours (±1 hour), and 48 hours (±2 hour) post selinexor dose. Blood samples for the assessment of protein binding will be collected at 3- and 8- hours post-dose from patients administered Tablet A in the S20-100 and S100-20 arms (Day 1 and Day 8, respectively) and all patients in the MHI and SHI arms. Blood samples for PDn XPO1 receptor occupancy (PDnRO) analyses will be collected on Day 1 (pre-dose [≤10 minutes before taking selinexor], 2 hours [±10 min], 4 hours [±10 min], 8 hours [±20 min], 24 hours [±1 hour], 30 hours [±1 hour], and 48 hours [±2 hour] post selinexor dose) and Day 8 (predose [≤10 minutes before taking selinexor]. Additional PDnRO samples will be collected on Day 8 (4 hours [±10 min] and 8 hours [±20 min] post selinexor dose)

from patients in the S20-100 and S100-20 arms. PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor. The exact actual time of dosing, as well as the exact time of each sample collection, must be recorded.

If insufficient PK samples are collected in Week 1 (for all patients) or Week 2 (for patients in the S20-100 and S100-20 arms), selinexor administration and PK/PDnRO blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum). For the MHI and SHI arms, dosing can go up to 4 weeks if both doses need to be repeated. When dosing/sampling is repeated, all timepoints need to be collected, including those already obtained, or the patient will need to be replaced.

Safety will be evaluated through reporting of treatment-emergent adverse events (TEAEs), physical examinations, and clinical laboratory testing. Patients will receive best supportive care to manage the main adverse drug reactions of selinexor, which are nausea, anorexia, and fatigue. Dose reductions may be made, as appropriate, by the Investigator in discussion with the Sponsor's Medical Monitor.

Computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at Screening.

Patients from the S20-100 or S100-20 arms who complete the Monotherapy Part will be allowed to continue into the Combination Therapy Part provided that they do not meet any of the combination therapy assessment/reassessment exclusion criteria. If a patient experiences significant toxicity related to selinexor and cannot start the combination therapy immediately following monotherapy, dose interruption and weekly retesting is allowed for up to 21 days after the End of Monotherapy Treatment Visit. Patients requiring >21 days to recover from toxicities related to selinexor should be discussed with the Sponsor's Medical Monitor for documented approval to continue to the Combination Therapy Part.

Patients with any solid tumor in the MHI and SHI arms may continue therapy (selinexor 40 mg QW) following the 3-day PK period with the option to escalate to selinexor 60 mg QW after completion of at least one 21-day cycle at 40 mg QW, and subsequently to selinexor 80 mg QW after completion of at least one 21-day cycle at 60 mg QW based on patient's tolerability and PK data and after documented approval following the discussion and agreement between the Sponsor and Investigator is received.

Combination Therapy Part

The safety and preliminary antitumor activity of selinexor in patients with advanced or metastatic NSCLC and CRC will be evaluated, in combination with docetaxel for patients with NSCLC (Arm A, the initial cohort including 20 patients and an additional cohort of 20 patients to a total of 40), pembrolizumab (Arm B, n=up to 40) or FOLFIRI (Arm C, n=up to 20) for patients with CRC.

Arm A has demonstrated activity using the combination of selinexor and docetaxel in 2-3L NSCLC and following 1 line of treatment following the use of anti-PD-1/L1 mAb therapy as well as 1 line of platinum-doublet chemotherapy. Activity is seen in RAS mutated NSCLC and further data will be collected by opening this arm to 20 additional patients including patients in the US.

Arm B completed the previously planned enrollment in Israel under protocol version 5. Given the preliminary signal of activity seen in patients with RAS mutant CRC treated in Arm B with the combination of selinexor and pembrolizumab, this amendment increases enrollment in Arm B for patients with RAS mutant CRC to 40 patients in Israel only to further evaluate this early signal.

Patients enrolled in the Combination Therapy Part will receive treatment until progressive disease (PD) or intolerable toxicity occur.

Safety will be assessed through the continuous reporting of AEs, regularly scheduled clinical laboratory tests (hematologic and chemistry), and physical examinations.

Tumor assessment will be performed with either CT or MRI (CT with contrast preferred; for each patient, the imaging method should remain the same throughout the study), based on RECIST v1.1 criteria for all arms other than Arm B which will use iRECIST criteria.

Number of Patients (Planned): In the Monotherapy period, approximately 20 NSCLC or CRC patients with normal hepatic function were enrolled in the BA/BE arm, and 8 and 6 patients with moderate or

severe hepatic impairment were enrolled in the MHI and SHI arms, respectively. The monotherapy Arm B completed the previously planned enrollment in Israel under protocol version 5.

In the combination therapy period, up to 40 NSCLC patients (in 2 cohorts of 20 patients each) will be enrolled in Arm A (with up to 20 patients enrolled in the US and Canada), up to 40 CRC patients total including additional patients with RAS mutant CRC, will be enrolled in Arm B in Israel only, and up to 26 CRC patients will be enrolled in Arm C in Israel and the EU.

Some patients with normal hepatic function were rolled over from the BA/BE arm to the combination therapy arms.

Key Inclusion Criteria:

Common inclusion criteria for all patients:

1. Are ≥ 18 years of age at the time of informed consent.
2. Have histologically confirmed solid tumor (any type of advanced or metastatic solid tumor for the Hepatic Impairment Arm of the Monotherapy Part), advanced or metastatic NSCLC or CRC and evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST v1.1), or iRECIST criteria as applicable).
3. Willing to provide written informed consent in accordance with federal, local, and institutional guidelines and comply with all requirements of the study.
4. Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use highly effective (dual methods of) contraception throughout the study and for 4 months following the last dose of study drug (childbearing potential excludes: Age > 50 years and naturally amenorrhoeic for > 1 year, or previous bilateral salpingo-oophorectomy or hysterectomy); and male patients must use an effective barrier method of contraception throughout the study and for 4 months following the last dose of study drug if sexually active. Male patients must agree not to donate sperm during the study treatment period.

For the Monotherapy Part only (BA/BE and HI arms):

5. Have received at least 1 line of systemic anticancer treatment unless there is no first-line standard of care therapy or standard of care therapy is contraindicated (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy). Patients must have failed prior standard curative therapy for their disease, must be intolerant to or be ineligible for any potentially curative approved treatment, irrespective of line of therapy.
6. Must have either normal hepatic function, or moderate or severe hepatic impairment (as defined by the NCI organ dysfunction working group (NCI-ODWG) criteria:
 - a. S20-100 and S100-20 arms: normal hepatic function (total bilirubin and AST $\leq$ ULN). Note: Patients with mild hepatic dysfunction (total bilirubin > 1 to $1.5 \times$ ULN OR AST $>$ ULN) may be included if liver function tests are stable for the past 3 months and enrollment is approved in writing by the Sponsor's Medical Monitor.
 - b. MHI arm: ≥ 1 week of documented moderate hepatic impairment (total bilirubin $> 1.5-3 \times$ ULN, any level of AST).
 - c. SHI arm: ≥ 1 week of documented severe hepatic impairment (total bilirubin $> 3-10 \times$ ULN, any level of AST).

For Combination Therapy Part only:

7. Previous treatment lines (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy):
 - a. Arm A: For patients with NSCLC, have received 1-2 prior line(s) of systemic anti-cancer treatment with 1 regimen including an anti-PD-1/L1 mAb.
 - b. Arm B: For patients with RAS mutant CRC, 1-2 prior lines of systemic treatments, and

no prior anti-PD-1/L1 mAb.

- KRAS WT: have 1-3 prior lines of systemic treatments (enrollment closed for WT with protocol version 5).
- KRAS mutant (at least 50% of patients): 1-2 prior lines of systemic treatments.

- c. Arm C: For patients with CRC participating in the combination arm with FOLFIRI, 1-2 prior lines of systemic therapy are allowed.
- d. Arms B and C: For patients with CRC who are not candidates for curative resection of metastatic lesions.

8. Must have hepatic function as follows:

- a. Arm A (combination with docetaxel): Patients with NSCLC who are to receive docetaxel and have bilirubin $\leq$ ULN, and AST and/or ALT $\leq$ 1.5 x ULN
- b. Arms B and C: total bilirubin $\leq$ 1.5 x ULN and AST $\leq$ 2.5 x ULN, ALT $\leq$ 2.5 x ULN; for Arm B, unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be $\leq$ 4 x ULN.

Key Exclusion Criteria:

Common exclusion criteria for all patients:

1. Have inadequate hematopoietic function defined as (without transfusion or growth factor support within 7 days prior to first dose):
 - a. Absolute neutrophil count (ANC) $< 1.5 \times 10^9/L$; platelet count (PLT) $< 100 \times 10^9/L$; or hemoglobin (Hb) < 10 g/dL (Note: This does not apply to the MHI and SHI arms).
2. Have inadequate renal function defined as a calculated creatinine clearance (CrCl) of < 20 mL/min using the formula of Cockcroft and Gault.
3. Have any other medical condition especially any gastrointestinal (GI) dysfunctions or GI disease that could interfere with the absorption of selinexor (e.g., inability to swallow or retain oral medications, malabsorption syndrome, a history of GI surgery which may result in intestinal blind loop, significant gastroparesis, unresolved nausea, vomiting, or diarrhea [National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1]).
4. Ongoing infection requiring parenteral antibiotics, antivirals, or antifungals on Day 1 dosing.
5. Prior exposure to a SINE compound or selinexor.
6. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:
 - a. Not recovered from major surgery ≤ 21 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 CTCAE Grade > 1 . Patients with any of the following will not be excluded: immune checkpoint-related endocrinopathies that are well controlled with hormonal supplements, patients with electrolyte abnormalities that are well-managed with supplementation, patients with Grade 2 lymphopenia, or patients with alopecia of any grade. 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. Serious active psychiatric or active medical condition that could interfere with participation in the study or in the opinion of the Investigator would make study involvement unreasonably hazardous.
8. In the opinion of the Investigator, patients who are below their ideal body weight and would be unduly impacted by changes in their weight.
9. Known allergy to selinexor (all patients), docetaxel (NSCLC Arm A only), pembrolizumab (CRC Arm B only), OR 5-FU, leucovorin, or irinotecan (CRC Arm C only),
10. Female patients who are pregnant or breastfeeding.

For Monotherapy Part only (BA/BE and HI arms):

11. Have an Eastern Cooperative Oncology Group (ECOG) performance status of:
 - a. ≥ 3 for patients to be enrolled into the S20-100 or S100-20 arms of the study.
 - b. ≥ 4 for patients to be enrolled into the MHI and SHI arms of the study.
12. For MHI and SHI arms: ANC $< 1 \times 10^9/L$; PLT $< 75 \times 10^9/L$; or Hb < 8 g/dL.
13. Received strong cytochrome P450 3A (CYP3A) inhibitors ≤ 7 days prior to Day 1 dosing OR strong CYP3A inducers ≤ 14 days prior to Day 1 dosing.
14. Inability or unwillingness to undergo a series of PK sampling.

For Combination Therapy Part only:

15. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 3 for Arms A and B, and ECOG PS ≥ 2 for Arm C.
16. Arm B, patients with CRC who are to receive pembrolizumab:
 - a. Had a diagnosis of immunodeficiency or are receiving systemic steroid therapy (> 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy.
 - b. Patients with controlled diabetes mellitus and patients with endocrinopathies on stable hormone replacement therapy, are eligible for the trial.
 - c. Have active autoimmune disease requiring systemic treatment during the past 2 years. Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.
Note: The Investigator needs to evaluate the patient's medical history to confirm that they are eligible to receive the combination with pembrolizumab per these criteria.
 - d. For patients with CRC who have received live-attenuated vaccine against an infectious disease (e.g., nasal spray influenza vaccine) ≤ 14 days prior to the intended C1D1 of the Combination Therapy.
17. Arm C: Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: for patients who are initially enrolled onto the BA/BE arm in the monotherapy part and plan to switch to combination therapy after completing the planned dosing and PK sample collection, dose interruption between the Monotherapy Part and the Combination Therapy Part is allowed for recovery from AEs. Patients requiring > 21 days to recover from toxicities related to selinexor should be discussed with the Sponsor's Medical Monitor for documented approval to continue to the Combination Therapy Part if inclusion/exclusion criteria are met. Experiencing PD during the Monotherapy Part does not constitute exclusion from the Combination Therapy Part.

Study Treatment:

Monotherapy Part:

Following an overnight fast of at least 10 hours during Week 1 (all patients) and Week 2 (S20-100 and

S100-20 arms only) patients will be administered a single oral dose of selinexor 30 minutes after the start of a standard, low-fat meal. The meal is to be consumed within 30 minutes or less. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for 1 hour before and after drug administration. Patients in the S20-100 and S100-20 arms should receive standardized meals scheduled at the same time on Day 1 and Day 8 of the Monotherapy Part. In order to avoid contact with skin, tablets must be swallowed whole (not chewed) and should not be crushed prior to use.

For patients assigned to the S20-100 or S100-20 arms, selinexor will be provided as 100 mg QW doses in the following 2 formulations:

- 5 × 20 mg tablets (Tablet A)
- 1 × 100 mg tablet (Tablet B)

For patients assigned to MHI or SHI arms, selinexor will be provided as a single agent, 40 mg dose (2 × 20 mg tablets [Tablet A]). Patients in the MHI and SHI arms may continue to receive selinexor monotherapy 40 mg QW throughout the study. These patients will not receive Combination Therapy. Intra-patient dose escalation may be allowed after a patient's tolerability and pharmacokinetics data is evaluated. Selinexor dose may be escalated to 60 mg QW after completion of at least one 21-day cycle at 40 mg QW, and subsequently to 80 mg QW after completion of at least one 21-day cycle at 60 mg QW based on review of the patient's tolerability and PK data and after documented approval from the Sponsor is received.

Dose interruption and reduction are allowed for management of TEAEs, and patients receiving a reduced dose may remain on study; however, patients receiving a reduced dose will not be eligible for PK/PDnRO blood sampling and may be replaced, if needed.

Combination Therapy Part

Selinexor can be taken with or without food throughout the Combination Therapy Part. Selinexor 20 mg tablets will be used during the Combination Therapy Part.

The NSCLC cohort (Arm A) will receive selinexor 60 mg orally (PO) QW and docetaxel 75 mg/m² IV once every 3 weeks.

The CRC Arm B will receive selinexor 80 mg PO QW and pembrolizumab 200 mg IV every 3 weeks.

The CRC Arm C will receive two different dose regimens: Cohort 1, selinexor 40 mg (PO) on Days 1, 3, 15, and 17 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² bolus then 5-FU 2400 mg/m² continuous over 46-48 hours; IV on Day 1 and 15 of a 28-day cycle); Cohort 2, selinexor 80 mg (PO) on Days 1 and 15 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² bolus; 5-FU 2400 mg/m² continuous over 46 - 48 hours; IV on Day 1 and 15 of a 28-day cycle).

Dose reductions for docetaxel and FOLFIRI (Arms A and C) for cycle 1 are allowed for prior toxicities per their respective labels. Note: Docetaxel dosing must maintain a 3-week schedule.

Duration of Treatment:

Monotherapy Part

The Monotherapy Part for the S20-100 and S100-20 arms is expected to last approximately 2 weeks. Patients assigned to the MHI and SHI arms may continue to receive single-agent selinexor also after Day 14 until they experience PD as per RECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria.

Combination Therapy Part

For patients with NSCLC, treatment in the Combination Therapy Part will continue until patients experience PD as per RECIST 1.1 (as assessed by the Investigator), or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment.

For patients with CRC receiving pembrolizumab, treatment in the Combination Therapy Part will

continue until patients experience PD as per iRECIST (as assessed by the Investigator) or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment. 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. Since some patients treated with immunotherapy may benefit from continued treatment despite meeting the radiological criteria for initial PD, if a patient has no clinical deterioration, initial PD or mixed response will be confirmed by repeat evaluation at the next tumor assessment.

These CRC patients who have unconfirmed apparent progression may continue to receive treatment until progression is confirmed at the next imaging assessment. However, in the judgement of their Investigator, the following must apply. The patient must:

- Be clinically stable and have no intolerable AEs
- Be likely to benefit from additional study treatment

For patients with CRC receiving FOLFIRI, treatment in the Combination Therapy Part will continue until patients experience PD as per RECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment.

Duration of Follow-up:

Follow-up will continue for 1 year after the 30-day Safety Visit. For patients who discontinued due to radiological PD, follow-up will be limited to survival follow-up.

Overview of Statistical Methods:

Sample size estimation:

Approximately 20 patients with either NSCLC or CRC with normal hepatic function will be enrolled and randomized with a 1:1 ratio to the S100-20 and S20-100 arms to evaluate the bioavailability of the new 100-mg tablet formulation (Tablet B) relative to the current 5 × 20 mg tablet formulation (Tablet A). Evaluation of these data will also serve as a pilot bioequivalence study (BE of Tablet B with Tablet A as the reference) to inform the feasibility and design of a future BE study. Moreover, these 20 patients with normal hepatic function will serve as the reference group for the evaluation of patients with hepatic impairment in the MHI and SHI arms, and can roll over into the combination therapy arms.

The sample size for the hepatic impairment arms is 6 for the severe (SHI) and 8 for the moderate (MHI) hepatic impairment arms.

Combination Arm A will enroll approximately 40 patients (in 2 cohorts with up to 20 patients enrolled in the US and Canada), Arm B will enroll approximately 40 patients in Israel and Arm C will enroll up to 26 patients in Israel and the EU to assess the tolerability, safety, and anti-tumor activity.

Statistical methodology for the Monotherapy Part BA/BE and hepatic impairment analyses:

Bioequivalence analyses will be performed on the PK population following FDA's guidance "Statistical Approaches to Establishing Bioequivalence." Standard noncompartmental PK parameters will be calculated based on plasma concentration data for selinexor from individual patients.

For the analyses of the hepatic impairment arms, descriptive demographic statistics will be provided for each hepatic function group. Regression modeling will be performed for comparison among hepatic function groups and association between hepatic function groups and PK parameters. Pharmacokinetic parameters will be the dependent variable and age, gender, race, and baseline body weight may be included as covariates. Estimates of the mean difference between hepatic function groups and corresponding 95% confidence intervals (CIs) will be calculated.

Statistical methods for Arm A, B, C1, C2 for efficacy analysis.

- ORR will be estimated for each arm separately, by calculating the percentage of patients in that arm who have a response of PR or CR, as assessed by RECIST 1.1 [Arms A, C], and iRECIST [Arm B].

- PFS will be analyzed for each arm separately by Kaplan-Meier descriptive statistics calculated as the time from the first dosing date until disease progression or death due to any reason.
- DCR will be calculated as the proportion of patients in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD), as assessed by RECIST1.1 [Arms A, C], and iRECIST [Arm B].
- DOR will be analyzed by Kaplan-Meier descriptive statistics for patients who have achieved overall response PR or better, with DOR calculated as the time from the date of first PR or better assessment until disease progression.

Detailed analysis plan will be described in SAP.

Statistical methods for the Combination Therapy Part safety analysis:

All safety analyses will be performed using the Safety Population. 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 NCI CTCAE, v.5.0. Investigators will provide their assessment on causality (i.e., whether the AE is related or not related to selinexor). Treatment-emergent AEs, serious adverse events (SAEs), AEs of at least Grade 3 in severity, AEs related to selinexor, and AEs leading to withdrawal of treatment will be summarized 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.

1.2. Schedules of Assessments

Table 1: Monotherapy Part – Patients with Normal Hepatic Function (S20-100, S100-20)

Activity/Assessment	Screening (≤21 days of D1)	D1 ±1 day	D2 ±1 day	D3 ±1 day	D8 (D15) ±1 day	D9 (D16) ±1 day	D10 (D17) ±1 day	EOMT (D15/D21) ^a ±1 day
Procedures								
Informed consent signed	X							
Demographics	X							
Inclusion/Exclusion criteria	X	X						
Medical history ^b	X	X ^b						
Randomization		X						
Physical examination ^c	X	(X)						X
Vital signs ^d	X	X			X			X
Weight ^e	X	X			X			X
Height	X							
ECG	X	As clinically indicated						
ECOG PS ^f	X	X						X
Nutritional consultation ^g	X	Throughout, as needed						
Supportive care		Ondansetron 8 mg 30 min before each dose of selinexor and every 8 hours (3 times per day) for 3 days post selinexor						
Concomitant medications review		Throughout						
Adverse events ^h		Throughout						
Laboratory								
Serum chemistry and hematology ⁱ	X	X			X			X
Pregnancy test ^j	X	X						X
Anti-tumor Activity								
Tumor assessment by CT/MRI scans ^k	X							X ^k
Drug Administration								
Selinexor ^l		X			X ^m			
Biobank								
In-patient stay (optional) ⁿ		X	X	X	X	X	X	
PK sampling		X ^o	X	X	X ^o	X	X	
PK (Protein Binding) ^p		(X)			(X)			
PDnRO blood sampling ^q		X	X	X	X			
CCI								

Abbreviations: BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = Electrocardiogram; EOMT = end of monotherapy treatment; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; PDn = pharmacodynamics; PDnRO = pharmacodynamic Receptor Occupancy; PS MP = post-selinexor Monotherapy Part; QW = once weekly; RA = Reassessment Visit; RECIST = Response Evaluation Criteria in Solid Tumors; SV = safety visit.

- ^a The EOMT visit, the Combination Therapy Reassessment visit, and the C1D1 treatment visit may be conducted on the same day, as long as it is at least 7 days after the last dose of selinexor. See [Table 2](#) for additional tests required for eligibility assessment for the Combination Therapy Part. The EOMT visit can be as early as D15, unless additional PK sample collection is required and then the Monotherapy Part will continue for a third week, having the EOMT at D21 $\pm$ 1.
- ^b Medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of Screening, any medical conditions that require medication. All prior cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history will be obtained, and smoking history will be documented. Results from prior testing of KRAS status is required for patients with CRC. To be collected for patients with NSCLC and other tumor types, if available.
- ^c Full physical examination will be performed prior to receiving first dose of study drug (C1D1) and at the EOMT Visit. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate.
- ^d Vital signs include systolic and diastolic blood pressure (BP), pulse measurements, and body temperature ($^{\circ}$ C or $^{\circ}$ F).
- ^e Indoor clothing and without shoes.
- ^f ECOG performance status criteria are provided in [Appendix 2](#).
- ^g Patients must be given documented nutritional consultation per local practice to discuss any food recommendation and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening part of the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consult, in person or by telephone. Nutritional consultation is to be provided throughout, as needed.
- ^h Adverse event must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) where possible. All AEs will begin to be recorded post-dosing and any AEs which were experienced prior to dosing will be added to the patient's medical history. SAEs will be reported once the ICF is signed. Adverse event monitoring should be continued for at least 30 days following the last dose of study drug (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study drug by the Investigator). See [Section 10.1](#) for additional details.
- ⁱ Serum chemistry and hematology must be conducted $\leq$ 3 days before the first dose. If the results are within required levels, hematology and serum chemistry do not need to be repeated on D1. See [Table 12](#) for a list of lab tests.
- ^j Female patients of childbearing potential must have a negative serum hCG pregnancy test $\leq$ 3 days before C1D1.
- ^k The same method of assessment (CT or MRI of chest, abdomen and pelvis [other regions as clinically indicated for the assessment of disease]) should be used throughout the study for each target lesion. CT or MRI of the chest, abdomen, and pelvis performed more than 21 days prior to D1 may be allowed to be used for the baseline scan following discussion with the Sponsor's Medical Monitor. CT with contrast is preferred. Every effort should be made to obtain the latest historic scans available (preferably CT) and to use them to perform lesion identification, characterization and measurement.
- ^l Selinexor will be provided in 2 formulations for the Monotherapy Part: as 20 mg tablets (Tablet A), and as 100 mg tablets (Tablet B). All patients will be dosed in the clinic for the D1 and D8 doses. All in-clinic doses must be at least 7 days apart (5 days minimum, 21 days maximum).
- ^m If a dose reduction is required on D8, the patient should not continue in the Monotherapy Part and may proceed to the EOMT visit and undergo eligibility assessment to proceed to the Combination Therapy as early as D15.

- ⁿ Patients may remain in hospital on Day 1 and Day 8 (and testing should be repeated on Day 15). In addition, patients who live far from the hospital may also stay in the hospital or near the hospital overnight from Day 2 to Day 3, and Day 9 to Day 10 (if needed on Day 16 to Day 17).
- ^o Patients should fast ≥ 10 hours before the in-clinic dosing. A standard low-fat meal will be given 30 minutes prior to in-clinic dosing. A meal record should be completed for the standard low-fat meal (Section 7.3.2). Blood samples for the determination of plasma concentrations of selinexor will be collected pre-dose (≤ 10 minutes prior), 15 min (± 5 min), 30 min (± 5 min), 1 hour (± 5 min), 1.5 hours (± 5 min), 2 hours (± 10 min), 3 hours (± 10 min), 4 hours (± 10 min), 5 hours (± 10 min), 6 hours (± 10 min), 8 hours (± 20 min), 10 hours (± 20 min; optional timepoint), 24 hours (± 1 hour), 30 hours (± 1 hour), and 48 hours (± 2 hour) post dose.
- ^p When patients in the S20-100 or S100-20 arms receive Tablet A (5×20 mg) or Tablet B (1×100 mg) during the 2 crossover parts (Day 1 and Day 8, respectively), additional blood samples will be collected at 3 hours (± 10 min) and 8 hours (± 20 min) post dose for the purpose of conducting protein binding analyses.
- ^q Blood samples for the determination of XPO1 receptor occupancy of selinexor (PDnRO) will be collected on Day 1 (pre-dose [≤ 10 minutes before taking selinexor], 2 hours [± 10 min], 4 hours [± 10 min], 8 hours [± 20 min], 24 hours [± 1 hour], 30 hours [± 1 hour], and 48 hours [± 2 hour] post selinexor dose) and on Day 8 (pre-dose [≤ 10 minutes before taking selinexor], 4 hours [± 10 min] and 8 hours [± 20 min post selinexor dose]). PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor.

CCI

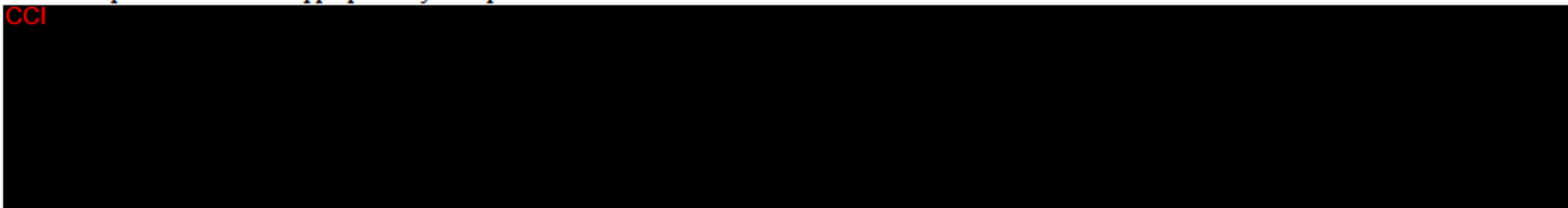


Table 2: Monotherapy Part – Patients with Hepatic Impairment (MHI and SHI Arms)

Activity/ Assessment	Screening ≤21 days prior to C1D1	Cycle 1 (21 d)					Cycle 2 (21 d)		Cycles ≥3 (21 d)			EOT ^a ≤6 days after last dose	30-day SV ^b (±4)	Response and Survival FU ^c (±14)
		D1	D2	D3	D8 (±1)	D15 (±1)	D1 (±2)	D8, D15 (±2)	D1 (±3)	D8 (±3)	D15 (±3)			
Procedures														
Informed consent signed	X ^d													
Demographics	X													
Inclusion/Exclusion criteria	X	X												
Medical history ^e	X	X												
Hepatic function assessment ^f	X	X			X	X	X		X			X		
Physical examination ^g	X	(X)					(X)		(X)			X	(X)	
Vital signs ^h	X	X			X	X	X		X			X	X	
Weight ⁱ	X	X					X		X			X		
Height	X													
ECG ^a	X	As clinically indicated												
ECOG PS ^j	X	X					X		X			X		
Nutritional consultation ^k	X	Throughout, as needed												
Supportive care – during PK	Ondansetron 8 mg per day - For the PK part													
Supportive care – upon completion of PK	Ondansetron 8 mg per day + olanzapine 5 mg or equivalent (every night)													
Concomitant medication review	Throughout													
Adverse events ^l	Throughout													
Telephone contact														X
Antineoplastic therapy												X	X	X ^c
Laboratory														
Serum chemistry, hematology, coagulation test ^m	X	X			X	X	X ⁿ		X ⁿ			X ⁿ		
Pregnancy test ^o	X	X					X		X			X		

Activity/ Assessment	Screening ≤21 days prior to C1D1	Cycle 1 (21 d)					Cycle 2 (21 d)		Cycles ≥3 (21 d)			EOT ^a ≤6 days after last dose	30-day SV ^b (±4)	Response and Survival FU ^c (±14)
		D1	D2	D3	D8 (±1)	D15 (±1)	D1 (±2)	D8, D15 (±2)	D1 (±3)	D8 (±3)	D15 (±3)			
Anti-tumor Activity														
CT/MRI scan ^p	X										X ^p			X ^c
Drug Administration														
Selinexor (weekly)		X			X	X	X	X	X	X	X			
Biobank														
In-patient stay (optional) ^a		X	X	X										
PK sampling ^r		X	X	X										
PK (Protein Binding) ^s		X												
PDnRO blood sampling ^t		X	X	X	X									

Abbreviations: C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = Electrocardiogram; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetic; PDnRO = pharmacodynamic Receptor Occupancy; RECIST = Response Evaluation Criteria in Solid Tumors; SV = safety visit; QW = once weekly.

- ^a EOT visit is ≤6 days after the last dose of study drug or the date at which the decision was made to discontinue treatment. In the case of dose interruption, the EOT visit could be as long as 28 days after the last dose of study drug.
- ^b If the EOT visit is delayed due to a dose interruption before discontinuation, the 30-Day Safety Visit may be performed together with the EOT visit, if both visits fall within 26-34 days following study drug discontinuation.
- ^c Response and survival follow-up every 3 months up to 1 year, after the 30-day Safety Visit. For patients who discontinued treatment without PD, if possible, conduct tumor assessments and physical examination at Investigator's discretion or per standard of care until PD or the start of new anti-neoplastic therapy. For patients who had PD at discontinuation or for patients without PD for whom the above assessments are not possible, a telephone call will be made to the patient or the patient's contact every 3 months for 1 year to inquire about survival, disease status, general health, and subsequent antineoplastic therapies.
- ^d The time window for ICF is up to 2 months prior to C1D1.
- ^e Medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of Screening, any medical conditions that require medication. All prior cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history will be obtained, and smoking history will be documented. Results from prior testing of KRAS status is required for patients with CRC. To be collected for patients with NSCLC and other tumor types, if available.
- ^f Hepatic function will be assessed per NCI criteria, provided in Section 9.2.3.
- ^g Full physical examinations will be performed on or prior to receiving the first dose of study drug (C1D1) and at the EOT Visit. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate.
- ^h Vital signs include systolic and diastolic blood pressure (BP), pulse measurements, body temperature (°C or °F).
- ⁱ Indoor clothing and without shoes.
- ^j ECOG performance status criteria are provided in Appendix 2.

- ^k Patients must be given documented nutritional consultation per local practice to discuss any food recommendation and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening part of the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consult, in person or by telephone. Nutritional consultation is to be provided throughout, as needed.
- ^l Adverse events must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) where possible. All AEs will begin to be recorded post-dosing and any AEs which were experienced prior to dosing will be added to the patient's medical history. SAEs will be reported once the ICF is signed. Adverse event monitoring should be continued for at least 30 days following the last dose of study drug (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study drug by the Investigator). See Section 10.1 for additional details.
- ^m Serum chemistry and hematology tests at C1D1 do not need to be repeated if the previous lab tests were done within ≤ 3 days before C1D1 and results are within range. See Table 12 for a list of lab tests.
- ⁿ For Cycle 2 and beyond, labs done other than on D1 will be as needed at the discretion of the Investigator.
- ^o Female patients of childbearing potential must have a negative serum hCG pregnancy test ≤ 3 days before C1D1.
- ^p To ensure comparability, the same method of assessment (CT or MRI of chest, abdomen, and pelvis [and other regions as clinically indicated for the assessment of disease]) should be used throughout the trial for each marker lesion. The scans must be obtained and reviewed prior to the start of the next cycle of therapy per RECIST 1.1 criteria. CT or MRI of the chest, abdomen, and pelvis performed more than 21 days prior to D1 may be allowed to be used for the baseline scan following discussion with the Sponsor's Medical Monitor. In addition to the baseline scans, every effort should be made to obtain the latest historic scans available (preferably CT) and to use them to perform lesion identification, characterization and measurement. After screening, tumor assessments are to be done on any day of the last week (between D15 and D21) of Cycles 3, 6 and 9. Then, tumor assessments are to be done every 3 months, on any day of the last week of every 4 cycles (i.e., C14, C18, C22, etc.).
- ^q Patients may remain in hospital on Day 1. In addition, patients who live far from the hospital may also stay in the hospital or near the hospital overnight from Day 2 to Day 3.
- ^r Blood samples for the determination of plasma concentrations of selinexor will be collected during the first week starting at D1 pre-dose (≤ 10 minutes prior) and at 15 min (± 5 min), 30 min (± 5 min), 1 hour (± 5 min), 1.5 hours (± 5 min), 2 hours (± 10 min), 3 hours (± 10 min), 4 hours (± 10 min), 5 hours (± 10 min), 6 hours (± 10 min), 8 hours (± 20 min), 10 hours (± 20 min; optional timepoint), 24 hours (± 1 hour), 30 hours (± 1 hour), and 48 hours (± 2 hour) post dose.
- ^s Additional blood sample will be collected at 3 hours (± 10 min) and 8 hours (± 20 min) post D1 dose from all patients in the MHI and SHI arms for the purpose of conducting protein binding analyses.
- ^t Blood samples for the determination of XPO1 receptor occupancy of selinexor (PDnRO) will be collected on Day 1 (pre-dose [≤ 10 minutes before taking selinexor], 2 hours [± 10 min], 4 hours [± 10 min], 8 hours [± 20 min], 24 hours [± 1 hour], 30 hours [± 1 hour], and 48 hours [± 2 hour] post selinexor dose) and on Day 8 (pre-dose [≤ 10 minutes before taking selinexor]). PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor.
- ^u ECG should be done at Screening, once a month for 3 months, and every 3 months thereafter, or as clinically indicated.

Table 3: Combination Therapy Part – Docetaxel [Arm A] and Pembrolizumab [Arm B] (21-day Cycle)

Activity/ Assessment	Screening (<21 days of C1D1)/ RA ^a ≤28 D PS-MP	C1D1 ^b ±1 D	≥C2 D1 ±3 D	≥C3 D1 ±3 D	EOT ^c Up to 6 days after discontinuation decision	30-D SV ^d ±4 D	Response and Survival FU ^e ±14 D
Procedures							
Informed consent signed	X						
Combination Therapy Reassessment Criteria (RA) ^f	X						
Eligibility confirmation by Sponsor ^g	X	(X)					
Demographics	X						
Inclusion/Exclusion criteria	X	X					
Medical history ^h	X	X					
Physical examination ⁱ	X	(X)	(X)	(X)	X	X	
Vital signs ^j	X	X	X	X	X	X	
Weight ^k	X	X	X	X	X		
Height	X						
ECOG PS ^l	X	X	X	X	X		
ECG	X	As clinically indicated					
Nutritional consultation ^m	X	Throughout, as needed					
Supportive care		Ondansetron 8 mg or 5-HT3 equivalent + olanzapine 5 mg or equivalent (every morning) or NK1 antagonist					
Concomitant medications review	X	Throughout					
Adverse events ⁿ	X	Throughout					
Telephone contact							X ^e
Anti-neoplastic therapy after EoT					X	X	X ^e
Laboratory							
Serum chemistry and hematology ^o	X	X	X	X	X		
Pregnancy test ^p	X	X	X	X	X		
Anti-tumor Activity							
Tumor assessment by CT/MRI scans ^q X	X ^r			X ^s (C3, C6, etc.)			X ^e
For patients with CRC only: CEA ^q	X			X			X ^e
Drug Administration							
Selinexor (weekly) ^t		X	X	X			

Activity/ Assessment	Screening (<21 days of C1D1)/ RA ^a ≤28 D PS-MP	C1D1 ^b ±1 D	≥C2 D1 ±3 D	≥C3 D1 ±3 D	EOT ^c Up to 6 days after discontinuation decision	30-D SV ^d ±4 D	Response and Survival FU ^e ±14 D
Docetaxel or pembrolizumab (every 3 weeks) ^h -		X	X	X			
Biobank							
CCI							

Abbreviations: BSA = body surface area; C = cycle; CEA = carcinoembryonic antigen; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; PDn = pharmacodynamics; PS MP = post-selinexor Monotherapy Part; QW = once weekly; RA = Reassessment Visit; RECIST = Response Evaluation Criteria in Solid Tumors; iRECIST = Immunotherapeutic Response Evaluation Criteria in Solid Tumors; SV = safety visit

^a The Reassessment Visit is intended for evaluation of patient's eligibility to proceed to Combination Therapy (reassessment procedures) for patients that participated in the Monotherapy Phase. It may be conducted at the same time as the EOMT visit. Patients who meet any of the Combination Therapy Reassessment Criteria may be re-evaluated once weekly for up to 28 days after the last dose of selinexor in the Monotherapy Part.

^b C1D1 of the Combination Therapy Part must be at least 7 days post last Monotherapy Part dose.

^c EOT window is ≤6 days after the decision was made to discontinue treatment.

^d 30-day Safety Visit is planned for 30 days after last dose of study drug (±4 days). If the EOT visit is delayed due to a dose interruption before discontinuation, the 30-day Safety Visit may be performed together with the EOT visit, if both visits fall within 26-34 days following study drug interruption.

^e Response and Survival follow-up every 3 months up to 1 year, after the 30-Day Safety Visit. For patients who discontinued treatment without PD, if possible, conduct tumor assessments and physical examination at Investigator's discretion or per standard of care until PD or the start of new anti-neoplastic therapy or until 1-year follow-up is completed. For patients who had PD at discontinuation or for patients without PD for whom the above assessments are not possible, a telephone call will be made to the patient or the patient's contact every 3 months for 1 year to inquire about survival, disease status, general health, and subsequent antineoplastic therapies.

^f If not done at EOMT.

^g Applies only to patients requiring more than 21 days to recover from selinexor-related toxicities in the Monotherapy Part. After Reassessment Criteria evaluation and before C1D1.

^h Medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of Screening, any medical conditions that require medication. All prior cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history will be obtained, and smoking history will be documented. Results from prior testing of KRAS status is required for patients with CRC. To be collected for patients with NSCLC and other tumor types, if available.

ⁱ Full physical examinations will be performed prior to first dose of study drug (C1D1) of the Combination Therapy Part and at the EOT Visit. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate.

^j Vital signs include systolic and diastolic blood pressure (BP), pulse measurements, and body temperature (°C or °F).

^k Indoor clothing and without shoes.

^l ECOG performance status criteria are provided in [Appendix 2](#).

^m Patients must be given documented nutritional consultation per local practice to discuss any food recommendation and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening part of the study and prior to administration of study drug on

C1D1. The Investigator or any study staff can provide the nutritional consult, in person or by telephone. Nutritional consultation is to be provided throughout, as needed.

- ⁿ Adverse event must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) where possible. All AEs will begin to be recorded post-dosing and any AEs which were experienced prior to dosing will be added to the patient's medical history. SAEs will be reported once the ICF is signed. Adverse event monitoring should be continued for at least 30 days following the last dose of study drug (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study drug by the Investigator). See Section 10.1 for additional details.
- ^o Serum chemistry and hematology tests at C1D1 do not need to be repeated if the previous lab tests were done within ≤ 3 days before C1D1 and results are within range. See Table 12 for a list of lab tests.
- ^p Female patients of childbearing potential must have a negative serum hCG pregnancy test ≤ 3 days before C1D1.
- ^q To ensure comparability, the same method of assessment (CT or MRI of chest, abdomen, and pelvis [and other regions as clinically indicated for the assessment of disease]) should be used throughout the trial for each marker lesion. The scans must be obtained and reviewed prior to the start of the next cycle of therapy, per RECIST 1.1 for Arm A and iRECIST for Arm B. CT with contrast is preferred. For patients with CRC, CEA should be measured at the same time points as the CT/MRI imaging. Every effort should be made to obtain the latest historic scans available (preferably CT) and to use them to perform lesion identification, characterization and measurement.
- ^r Patients enrolled directly into combination therapy should have their baseline scan done within 21 days prior to C1D1. If the patient's scan for the Monotherapy Part Screening tumor assessment was performed ≤ 42 days prior to Combination Therapy Part C1D1, it may be used as the baseline scan for this Part and should not be repeated. Scanning at Reassessment Visits is only required for patients whose Screening scan was performed > 21 days prior to Combination Therapy Part C1D1 (e.g., due to dose interruptions).
- ^s Tumor assessments to be done on any day of the last week (between D15 and D21) of Cycles 3, 6, 9, 12, 15, and 18. After one year, tumor assessment frequency can be reduced to once every 3 months, on any day of the last week of every 4 cycles (i.e. Cycles 22, 26, 30 etc.), at the Investigator's discretion.
- ^t Selinexor will be taken on Days 1, 8, and 15 of each cycle.
- ^u Docetaxel, for patients with NSCLC, will be taken on Day 1 of each cycle; pembrolizumab, for patients with CRC, will be taken on Day 1 of each cycle.

CCI

Table 4: Combination Therapy Part – FOLFIRI [Arm C] (28-day Cycle)

Activity/ Assessment	Screening (<21 D of C1D1) / RA ^a ≤ 28 D PS-MP	C1 D1 ^b ±1 D	C1 D15 ±1 D	C2 D1 ±2 D	C2 D15 ±2 D	C3-4 D1 ±3D	C3-4 D15 ±3D	EOT ^c up to 6 days after discontinuation decision	30-D SV ^d ±4 D	Response and Survival FU ^e ±14 D
Procedures										
Informed consent signed	X									
Combination Therapy Reassessment Criteria ^f	X									
Eligibility confirmation by Sponsor ^g	X	(X)								
Demographics	X									
Inclusion/Exclusion criteria	X	X								
Medical history ^h	X	X								
Physical examination ⁱ	X	(X)		(X)		(X)		X	(X)	
Vital signs ^j	X	X		X		X		X	X	
Weight ^k	X	X		X		X		X		
Height	X									
ECOG PS ^l	X	X		X		X		X		
ECG	X	As clinically indicated								
Nutritional consultation ^m	X	Throughout, as needed								
Supportive care		Ondansetron 8 mg 1 hour before each dose of selinexor and every 8 hours (3 times per day) for 3 days post selinexor + olanzapine 5 mg or equivalent (every night) + NK1 antagonist 125 mg orally on D1, 80 mg orally on D2 and D3								
Concomitant medications review		Throughout								X ^e
Adverse events ⁿ	X	Throughout								X ^e
Telephone contact										X ^e
Anti-neoplastic therapy								X	X	X ^e
Laboratory										
Serum chemistry and hematology ^o	X	X		X		X		X		
Pregnancy test ^p	X	X		X		X		X		
Anti-tumor Activity										
Tumor assessment by CT/MRI scans ^q	X ^r	X ^r		X		X ^s (C4)		X		X ^e
For CRC patients: CEA ^q	X	X		X		X		X		X
Drug Administration										
Selinexor 40 mg ^t + FOLFIRI ^m (Cohort 1)		X (D1, D3)	X (D15, D17)	X (D1, D3)	X (D15, D17)	X (D1, D3)	X (D15, D17)			

Activity/ Assessment	Screening (<21 D of C1D1) / RA ^a ≤ 28 D PS-MP	C1 D1 ^b ±1 D	C1 D15 ±1 D	C2 D1 ±2 D	C2 D15 ±2 D	C3-4 D1 ±3D	C3-4 D15 ±3D	EOT ^c up to 6 days after discontinuation decision	30-D SV ^d ±4 D	Response and Survival FU ^e ±14 D
Selinexor 80 mg [†] + FOLFIRI [†] (Cohort 2)		X (D1)	X (D15)	X (D1)	X (D15)	X (D1)	X (D15)			
Biobank										
CCI										

- Abbreviations: BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; PDn = pharmacodynamics; PS MP = Post-selinexor Monotherapy Part; QW = once weekly; RA = Reassessment Visit; RECIST = Response Evaluation Criteria in Solid Tumors; SV = safety visit; w/o = without
- ^a The Reassessment Visit is intended for evaluation of patient's eligibility to proceed to Combination Therapy (reassessment procedures) for patients that participated in the Monotherapy Phase. It may be conducted at the same time as the EOMT visit. Patients who meet any of the Combination Therapy Reassessment Criteria may be re-evaluated once weekly for up to 28 days after the last dose of selinexor in the Monotherapy Part.
- ^b C1D1 of the Combination Therapy Part must be at least 7 days post last Monotherapy Part dose.
- ^c EOT window is up to 6 days after the decision was made to discontinue treatment.
- ^d 30-Day Safety Visit is planned for 30 days after last dose of study drug (±4 days). If the EOT visit is delayed due to a dose interruption before discontinuation, the 30-Day Safety Visit may be performed together with the EOT visit, if both visits fall within 26-34 days following study drug interruption.
- ^e Response and Survival follow-up every 3 months up to 1 year, after the 30-Day Safety Visit. For patients who discontinued treatment without PD, if possible, conduct tumor assessments and physical examination at Investigator's discretion or per standard of care until PD or the start of new anti-neoplastic therapy or until 1-year follow-up is completed. For patients who had PD at discontinuation or for patients without PD for whom the above assessments are not possible, a telephone call will be made to the patient or the patient's contact every 3 months for 1 year to inquire about survival, disease status, general health, and subsequent antineoplastic therapies.
- ^f If not done at EOMT.
- ^g Applies only to patients requiring more than 21 days to recover from selinexor-related toxicities in the Monotherapy Part. After Reassessment Criteria evaluation and before C1D1.
- ^h Medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of Screening, any medical conditions that require medication. All prior cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history will be obtained, and smoking history will be documented. Results from prior testing of Note: KRAS status documentation is required for patients in all treatment arms.
- ⁱ To be collected for patients with NSCLC and other tumor types, if available.
- ^j Full physical examinations will be performed prior to first dose of study drug (C1D1) of the Combination Therapy Part and at the EOT Visit. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate.
- ^k Vital signs include systolic and diastolic blood pressure (BP), pulse measurements, and body temperature (°C or °F).
- ^l Indoor clothing and without shoes.
- ^m ECOG performance status criteria are provided in [Appendix 2](#).
- ⁿ Patients must be given documented nutritional consultation per local practice to discuss any food recommendation and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening part of the study and prior to administration of study drug on

C1D1. The Investigator or any study staff can provide the nutritional consult, in person or by telephone. Nutritional consultation is to be provided throughout, as needed.

- ⁿ Adverse event must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0) where possible. All AEs will begin to be recorded post-dosing and any AEs which were experienced prior to dosing will be added to the patient's medical history. SAEs will be reported once the ICF is signed. Adverse event monitoring should be continued for at least 30 days following the last dose of study drug (i.e., through 30 days following last dose or until resolution or through the end of the study for events considered related to study drug by the Investigator). See Section 10.1 for additional details.
- ^o Serum chemistry and hematology tests at C1D1 do not need to be repeated if the previous lab tests were done within ≤ 3 days before C1D1 and results are within range. See Table 12 for a list of lab tests.
- ^p Female patients of childbearing potential must have a negative serum hCG pregnancy test ≤ 3 days before C1D1.
- ^q To ensure comparability, the same method of assessment (CT or MRI of chest, abdomen, and pelvis [and other regions as clinically indicated for the assessment of disease]) should be used throughout the trial for each marker lesion. The scans must be obtained and reviewed prior to the start of the next cycle of therapy, per RECIST 1.1. CT with contrast is preferred. CEA should be measured at the same time points as the CT/MRI imaging. Every effort should be made to obtain the latest historic scans available (preferably CT) and to use them to perform lesion identification, characterization, and measurement.
- ^r If the patient's scan for the Monotherapy Part Screening tumor assessment was performed ≤ 42 days prior to Combination Therapy Part C1D1, it may be used as the baseline scan for this Part and should not be repeated. Scanning at Reassessment Visits is only required for patients whose Screening scan was performed >42 days prior to Combination Therapy Part C1D1 (e.g., due to dose interruptions).
- ^s Tumor assessments to be done on any day of the last week of even-numbered cycles, that is, any day between D21 and D28 of Cycles 2, 4, 6, 8 and 10 then tumor assessments to be done on any day of the last week of every 4 cycles (i.e., C14, C18, C22, etc.).
- ^t In-home dosing of selinexor only occurs during non-clinic days.
- ^u FOLFIRI for patients with CRC: irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² push; 5-FU 2400 mg/m² continuous over 46 hours; IV on Day 1 and 15 of a 28-day cycle); Cohort 2, selinexor 80 mg (PO) on Days 1 and 15 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² push; 5-FU 2400 mg/m² continuous over 46 hours; IV on Day 1 and 15 of a 28-day cycle.

CCI

2. INTRODUCTION

Selinexor (KPT-330) is an oral, first-in-class, slowly reversible, potent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1), a protein that transports tumor suppressor proteins out of the nucleus, leading to their functional inactivation. Selinexor has demonstrated clinical activity across a broad range of tumor types, including lung cancer, colorectal cancer, and other cancers with Kirsten rat sarcoma (KRAS) mutations.

2.1. Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the world, with an estimated incidence of 2.1 million new cases in 2018 and approximately 1.76 million deaths in the same year (Bray 2018). More than 80% of lung cancers are classified as non-small cell lung cancer (NSCLC) and the most common histological forms of NSCLC are adenocarcinoma and squamous cell carcinoma.

For the majority of NSCLC patients, the recommended first-line therapy is an anti-programmed cell death protein 1 (PD-1) agent usually with chemotherapy, or chemotherapy alone. If a patient's disease relapses or is refractory to an anti-PD-1/programmed death-ligand 1 (PD-L1) agent, one of the most feasible and most common treatment options for second-line therapy is docetaxel (NCCN 2020, Planchard 2018). Preliminary results in an ongoing Phase 1 study have shown that selinexor plus docetaxel can induce durable objective responses in patients with heavily pretreated KRAS-mutant NSCLC (NCT03095612). This study aims to evaluate the combination of selinexor with docetaxel more broadly for NSCLC patients who have been treated with ICI therapy.

Currently, initial systemic treatment of advanced or metastatic NSCLC depends on the presence or absence of various driver mutations. For example, if NSCLC patients have mutations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) fusion protein, their disease may be treated initially by one of a number of tyrosine kinase inhibitors (NCCN 2020; Planchard 2018). However, these mutations are found in a small proportion of NSCLC patients, only 15% and 5% respectively (Kawaguchi 2016; Soda 2007). For patients without a driver mutation, the recommended first-line therapy is an anti-programmed cell death protein 1 (PD-1) agent, such as pembrolizumab, as monotherapy if the programmed death-ligand 1 (PD-L1) expression is $\geq 50\%$; or chemotherapy with or without pembrolizumab or bevacizumab in patients with lower or unknown PD-L1 expression (NCCN 2020; Planchard 2018). If a patient's disease has relapsed or is refractory to an anti-PD-1/PD-L1 agent, the options for second-line therapy include single-agent chemotherapy agents, docetaxel and pemetrexed (NCCN 2020; Planchard 2018). However, among the two FDA-approved cytotoxic agents for second-line treatment, docetaxel is more feasible in this indication, as pemetrexed is increasingly used as a component of first-line or maintenance therapy. Preliminary results in an ongoing Phase 1 study have shown that selinexor plus docetaxel can induce durable objective responses in patients with heavily pretreated KRAS-mutant NSCLC (NCT03095612). This study aims to evaluate the combination of selinexor with docetaxel for NSCLC patients who have been treated with ICI therapy.

For NSCLC patients without a driver mutation, the recommended first-line therapy is an anti-PD-1 agent, such as pembrolizumab, as monotherapy if PD-L1 expression is $\geq 50\%$; or chemotherapy with or without pembrolizumab or bevacizumab in patients with lower or unknown PD-L1

expression (NCCN 2020; Planchard 2018). For patients whose disease has relapsed or is refractory to an anti-PD-1/PD-L1 agent, there is no standard treatment. Docetaxel has been the most commonly used chemotherapy in this setting.

2.2. Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated incidence of 1.8 million new cases and is the fourth leading cause of cancer-related deaths, with an estimated 850,000 deaths in 2018 (Bray 2018). Approximately 25% of patients with CRC will have metastatic disease at the time of diagnosis and a further 25% will develop metastatic disease after curative resection of localized CRC. Over the last two decades, the development of treatment options has significantly improved the prognosis for metastatic CRC patients. Traditionally, systemic chemotherapy in this setting has been based on fluoropyrimidine regimens. By the introduction of cytotoxic agents, such as irinotecan and oxaliplatin, the response rate, time to progression, and overall survival have improved from 15-20%, 5-6 and 10-12 months to 30-40%, 8 and 20-24 months, respectively (Tournigand 2004; Colucci 2005). More recent studies have shown that survival outcomes can further be improved by adding biologic agents (e.g., an angiogenesis inhibitor [bevacizumab], an anti-EGFR antibody [cetuximab or panitumumab], and the multitargeted tyrosine kinase inhibitor [regorafenib]) to combination chemotherapy regimens in first- and second-line therapy or by using these agents as monotherapy in more advanced treatment situations.

First-line treatment of patients with unresectable advanced or metastatic colorectal cancer is typically folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX); capecitabine and oxaliplatin (CAPEOX); folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI); or folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) regimens with or without bevacizumab (NCCN 2020; Van Cutsem 2014). Cetuximab or panitumumab may be added to FOLFOX, FOLFIRI, or FOLFOXIRI for tumors with normal KRAS/neuroblastoma-RAS (NRAS) genes (NCCN 2020). Agents for second-line therapy include FOLFIRI (for patients with first-line oxaliplatin-based therapy), FOLFOX/CAPOX (for patients with first-line irinotecan-based therapy), or single-agent irinotecan with or without immunotherapy, and immunotherapy alone.

Approximately 3.5% to 6.5% of stage IV CRCs are characterized as microsatellite instability-high (MSI-H), which is the biologic footprint of deficiency in deoxyribonucleic acid (DNA) deficient mismatch repair (dMMR). Another option for treatment at progression for patients who have MSI-H/dMMR tumors is immunotherapy. Three options are available. Monotherapy with an immune ICI that targets the programmed death receptor-1 (i.e., nivolumab or pembrolizumab) is one option. In clinical trials, objective response rates with these two PD-1 inhibitors are 30% to 50%, and some responses are durable. Both drugs have been FDA approved for this indication in the United States, and the choice of one agent over the other is empiric. Patients who experience disease progression on either of these drugs should not be offered the other. Another option is the combination of nivolumab with ipilimumab, a monoclonal antibody directed against a different immune checkpoint, cytotoxic T-lymphocyte antigen 4. Although there are no randomized trials directly comparing dual therapy with monotherapy with either nivolumab or pembrolizumab alone, indirect comparisons from the CheckMate 142 trial suggest that combined immunotherapy provides improved efficacy over anti-PD-1 monotherapy and has a favorable risk: benefit ratio. The combination has received FDA approval in the US for patients with MSI-H or dMMR mCRC

that has progressed despite other treatments. Cancer immunotherapy has not been established as an effective therapy for the majority of CRCs (NCCN 2020).

If the cancer progresses again, the recommended treatment for third-line and beyond includes a treatment not received as second-line treatment, regorafenib, or participation in a clinical trial (NCCN 2020).

Selinexor has shown single agent activity against heavily pretreated CRC with an ORR of 3% and a disease control rate (DCR) of 47% in KRAS-mutant CRC (Abdul Razak 2016).

Results from several nonclinical studies have shown that selinexor can upregulate cancer immune function and sensitize tumors to PD-1/PD-L1 blockade: (1) The combination of selinexor and PD-1 or PD-L1 blockade has been assessed in *in vivo* studies and demonstrated considerable synergistic anti-tumor activity in an aggressive murine colon cancer model as well as other solid tumor models; (2) A combination of selinexor and anti-PD-1 or anti-PD-L1 monoclonal antibody shows significant immunomodulatory activity, inducing changes in the frequency and phenotype of immune cell populations including increased frequency of NK cells, induced frequency of differentiated TH1 cells, and increased frequency of activated T-cells. (3) Selinexor induces PD-1 and PD-L1 gene expression, sensitizing tumor cells to immunotherapy and synergizes with anti-PD-1 to inhibit tumor cell proliferation and to induce apoptosis *in vitro* (Farren 2017; Elloul 2016; Trott 2016). These results support the clinical evaluation of the combination of selinexor with a PD-1/PD-L1 inhibitor in patients with CRC.

This study aims to explore a novel immunotherapy combination approach for patients with CRC that is KRAS wild type (WT) who have received 2-3 prior treatments, and for patients with CRC that is KRAS mutant who have received 2 prior treatments (no more than 2).

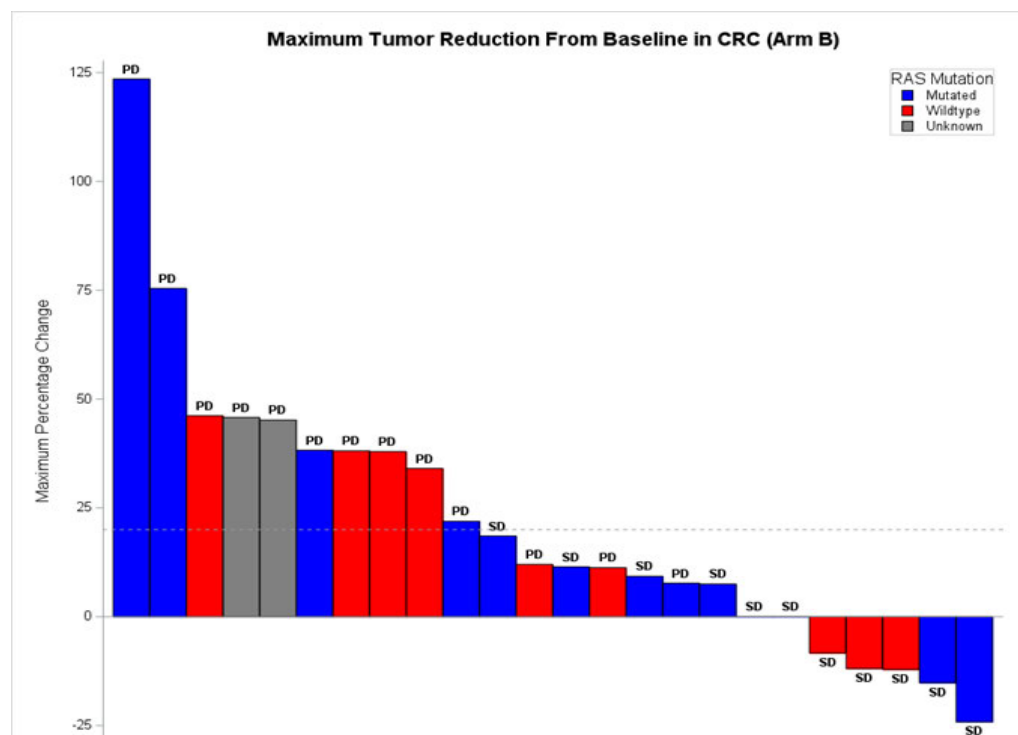
As of 31 March 2021, 30 patients have been enrolled in Arm B. Of these 30 patients, 24 are evaluable with at least 1 post baseline efficacy evaluation based on imaging. The median age is 57.5 years, 19 (63.3%) are male, and 16 (53.3%) have RAS mutations. The median number of prior antineoplastic regimens was 2. In this group, 11 patients had stable disease (SD) as their best overall response (BOR), and 8 of these 11 patients with SD (73%) had RAS mutant tumors. Notably none of the RAS mutated tumors were MSI-H. Disease stabilization was achieved in various RAS mutant tumors including NRAS mutant, KRAS^{G12V} and KRAS^{G12D}. The median progression-free survival (mPFS) in patients with RAS mutated CRC was 12.9 weeks, with 95% CI (8.3, NA) versus RAS WT 5.9 weeks, 95% CI: (5.6, NA) ($p = 0.26$) (patients with mutation status 'Unknown' were excluded); (HR 0.538, [95% CI 0.196, 1.474]). At least 1 TEAE and 1 TRAE were observed in at least 96.7% and 86.7% of patients, respectively. Most patients discontinued treatment due to PD. Among patients with treatment-related AEs, 20% had a dose modification of selinexor and 20% had a dose interruption of selinexor. One patient withdrew consent in cycle 1 for Grade 1 AEs (nausea, vomiting, headache) prior to on-study assessment; one patient withdrew consent after cycle 3 with stable disease (+9% increase) and Grade 2 fatigue and nausea and Grade 1 loss of appetite and headache. The most common AEs observed included nausea (76.7%), fatigue and vomiting (43.3% each), decreased appetite and diarrhea (36.7% each), weight decrease (26.7%) and constipation (23%). Most AEs were Grade 1 or 2. The most common Grade 3 AE was fatigue in 13.3% of patients. Side effects were generally reversible and manageable with supportive care, dose holds and dose modifications. There were no deaths from drug-related toxicity. The increased PFS and disease stabilization observed among patients with RAS mutated CRC, whose tumors were notably also microsatellite stable, and treated with

selinexor and pembrolizumab as contrasted with patients with RAS wild-type tumors indicates that this combination may be an effective treatment for patients with RAS mutant CRC who would otherwise have few options and be ineligible for checkpoint inhibitors and warrants further exploration and increasing enrollment to better characterize the efficacy signal.

Figure 1: Tumor Reduction in CRC Patients (Study KCP-330-027) (A)



Figure 2: Tumor Reduction in CRC Patients (Study KCP-330-027) (B)



2.3. Cancers with KRAS Mutation

The KRAS mutation occurs in approximately 25% of NSCLC adenocarcinomas and 35%-45% of CRC. The presence of oncogenic KRAS alterations has been proposed to portend poor response to conventional treatment and poor clinical outcomes. Pharmacologic attempts at inhibiting KRAS directly have proven not so successful to date. Recently, two KRAS inhibitors specifically targeting G12C mutation, AMG510 and MRTX849, entered early clinical development and have demonstrated encouraging anti-tumor activity in patients with KRAS^{G12C} tumors (Canon 2019; Hallin 2020). RAS^{G12C} is present in only approximately 13% of lung adenocarcinoma, 3% of colorectal cancer, and 2% of other solid tumors (AACR Project GENIE Consortium). AMG510 and MRTX849 demonstrated no effect on cancers with other type of KRAS mutations. Therefore, novel concepts are needed to improve treatment in KRAS mutant cancers. Preclinical data have demonstrated sensitivity of KRAS mutant NSCLC cell lines to the novel group of selective inhibitors of nuclear export (Kim 2016), which warrants the evaluation of selinexor in cancers with KRAS mutation.

In a multi-genomic, data-driven approach obtained by analysis of 106 cell lines, it was identified that the nuclear transport machinery is an obligatory function required for cell survival. By application of selinexor, tumor cell growth was halted, and apoptotic cell death was induced at bioavailable concentrations (0.5 – 10 μ M). Specificity to the nuclear export machinery (XPO1 cargo transport) was identified via temporary modification of target expression. Accumulation of I κ B in the nucleus was also identified, which resulted in dysregulation of crucial survival pathways via NF κ B as the responsible mechanism of cell death induction. Resistance mechanisms through

over-activation of follistatin-like 5/Hippo pathway by co-occurring mutations in follistatin-like 5 were elucidated. Compared to KRAS mutant cell lines, treatment of KRAS wild-type cell lines resulted in significantly lower induction of cancer cell death.

Therapeutic activity of selinexor has been observed in cancers with KRAS mutation and clinical activity of selinexor in KRAS mutant NSCLC and CRC has been observed in other studies ([Abdul Razak 2016](#)).

2.4. Selinexor

2.4.1. Mechanism of Action

Selinexor (KPT-330) is an orally bioavailable SINE that specifically blocks XPO1, leading to the nuclear accumulation and re-activation of TSPs and other growth modulators. Selinexor reduces the expression of DNA damage repair proteins and therefore potentiate DNA damage-based therapies and increase cancer cell death ([Kashyap 2018](#)).

Selinexor restores most of the known TSPs to the nucleus where they can carry out their normal regulatory and anti-tumor functions. Through the restoration of TSP function, selinexor is selectively cytotoxic for cells with genomic damage; i.e., for tumor cells, both *in vitro* and *in vivo*. All cell types exposed to SINE *in vitro* undergo G1 ± G2 cell cycle arrest, followed by a ‘genomic fidelity’ review. Cells with damaged genomes are induced to undergo apoptosis. Normal cells with an intact genome remain in transient, reversible cell cycle arrest until the export block is relieved. Tumors of hematopoietic lineage are particularly susceptible to induction of apoptosis by XPO1 inhibition; normal hematopoietic cells including stem cells and their functions are largely spared.

The nuclear export of eIF4E, a protein that binds to the mRNAs of many oncogenic and growth-promoting mediators, requires XPO1 for transport to cytoplasmic ribosomes. Selinexor blocks the XPO1-mediated nuclear export of eIF4E, preventing the translation of eIF4E-bound mRNAs on ribosomes with a reduction in levels of the cognate oncogenic and growth-promoting proteins. Therefore, selinexor is associated with reductions in the levels of several oncoproteins.

Multiple studies have demonstrated that selinexor had synergistic effects with gemcitabine, ([Kazim 2015](#); [Burke 2017](#)), and cisplatin ([Sun 2014](#); [Chen 2017](#); [Martignetti 2014](#); [Corno 2018](#)) and enhanced anti-lymphoma effects with dexamethasone ([Muqbil 2016](#)). The synergy with chemotherapy is in part due to sustained re-activation of TSPs following chemotherapy as well as to the inhibition of DNA damage repair by selinexor.

The safety and anti-tumor activity of combining selinexor with a PD-1/PD-L1 inhibitor have been explored in an ongoing Phase 1b study. Preliminary clinical data of selinexor in combination with pembrolizumab demonstrated an acceptable tolerability profile. In addition, 4 out of 6 evaluable patients with metastatic melanoma who were treated with this combination and were evaluable for efficacy had a clinical response. A dose level of 60 mg selinexor twice weekly plus pembrolizumab 2.0 mg/kg every 3 weeks is currently being investigated in a dose expansion to enroll 15 patients with NSCLC and 15 patients with metastatic melanoma.

In an Investigator-sponsored Phase 1/2 study ([NCT03095612](#)) of advanced KRAS mutant NSCLC, 7 patients have been treated with selinexor at 60 or 80 mg QW in combination with docetaxel 75 mg/m² every 3 weeks. All 7 patients have received more than 1 prior line of systemic therapy, including at least one line of treatment with a PD-1 or PD-L1 inhibitor. Five patients had post-

treatment restaging. Best responses in these 5 patients include 2 partial response (PR; 1 in the 60 mg cohort with 30% target lesion decrease and 1 in the 80 mg cohort with 35% target lesion decrease), 2 stable disease (SD; both in the 60 mg cohort, one of whom had 29% target lesion decrease), and 1 progressive disease (80 mg cohort). The emerging anti-tumor activity signal from this study warrants further evaluation of the efficacy of the combination of selinexor with docetaxel in patients with NSCLC whose disease has progressed on prior immuno-oncology therapy.

In a Phase 1 dose escalation study, 59 patients with CRC were treated with single agent selinexor; 52 were evaluable for efficacy. One patient with KRAS-mutant CRC achieved PR, and 44% of patients with the KRAS mutation and 21% of patients with wild-type RAS had SD, suggesting that selinexor has activity against CRC regardless of RAS mutational status ([Abdul Razak 2016](#)).

2.4.2. Pharmacology and Toxicology

Selinexor has shown potent pro-apoptotic activity with a median inhibitory concentration, 50% (half maximal inhibitory concentration) (IC_{50}) of 90 nM across a panel of 46 tumor cell lines representing a broad spectrum of tumor types. As noted above, selinexor had little effect on normal lymphocytes or other non-transformed cells, which correlated with the low incidence in animals of the typical adverse drug reactions seen with most anti-cancer therapies, such as significant myelosuppression, alopecia, mucositis and other gastrointestinal (GI) dysfunction. Selinexor and related SINE compounds have shown substantial efficacy, with dosing regimens that match those currently under investigation in humans, in a variety of mouse models of hematological and solid tumors. These include diffuse large B-cell lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, acute myeloid leukemia, multiple myeloma, T-cell acute lymphocytic leukemia, neuroblastoma, melanoma and prostate, breast, lung and ovarian cancers.

The preclinical properties of selinexor were assessed in three species: mouse (CD1), rat (Sprague-Dawley), and monkey (cynomolgus). No accumulation was observed in any of the multi-dose toxicology studies with a every other day dosing regimen for selinexor. Overall, systemic exposure was generally dose-proportional in all toxicokinetic (TK) studies that involved multiple dose levels. Oral bioavailability (F%) of selinexor was remarkably consistent among the three species with average values of 66.5%, 61.2%, and 67.5% in mice, rats, and monkeys, respectively.

Nonclinical toxicology studies indicated that the major adverse drug reactions (dose-limiting toxicities [DLTs]) across all species are reduced appetite with anorexia-induced weight loss partially consistent with satiety induction. High calorie foods and glucocorticoids can mitigate weight loss in animals taking SINE XPO1 inhibitors, and similar results are observed in patients receiving selinexor.

Macroscopic and microscopic changes in reproductive organs were noted during rat and monkey toxicology studies; most resolved or partially resolved during the recovery period. The long-term effects of these changes on reproductive potential are unknown. Secondary developmental effects due to reduced maternal body weights were also noted during a study on rat embryo/fetal development.

Please see the KPT-330 (selinexor) Investigator's Brochure for additional information.

2.4.3. Pharmacokinetics

Selinexor has exhibited linear and time independent pharmacokinetic (PK) over a dose range of 3 to 85 mg/m². 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 half-life ($t_{1/2}$) 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. There are no known clinically significant drug-drug interactions.

2.4.4. Nonclinical Studies

The nuclear export protein exportin 1 (XPO1) is responsible for the unidirectional export of ~220 different cargo proteins from the nucleus to the cytoplasm ([Lee 2019](#)). Selinexor is a first-in-class, oral selective inhibitor of nuclear export (SINE).

In the Cancer Genome Atlas data set, XPO1 expression is upregulated in CRC vs normal tissue, and high expression of XPO1 correlated with poor prognosis. Consistently, expression of XPO1 in 4 CRC PDX models was elevated compared with normal colon epithelial cells ([Inoue 2021](#)). In 40 CRC samples from patients, XPO1 overexpression was observed in 52.5% of CRC and significantly apparent with strong intensity in tumor cells compared to the normal adjacent epithelium ($P < 0.001$). XPO1 overexpression was significantly associated with advanced tumor stages ($P = 0.049$) and had tendency towards moderate/poorly differentiated tumors ([Aladhraei 2019](#)).

In PDX-derived cultures, increasing selinexor concentration correlated with increased p53 protein levels in the nucleus and decreasing in XPO1 levels. In addition, levels of the DNA damage repair proteins RAD51 and RAD50 were also reduced ([Inoue 2021](#)).

In other preclinical CRC models, XPO1 inhibition by SINE compounds or other XPO1 inhibitors resulted in inhibition of cell proliferation, nuclear localization of APC, reduced levels of β -catenin, nuclear localization of nrf2 and enhancement of radiation response ([Neufeld 2000](#); [Neufeld 2009](#); [Velichkova 2005](#); [Ki 2008](#); [Cheng 2018](#)).

In an in vitro screening of 278 cancer cell lines, XPO1 inhibition by KPT-207 (similar analog to selinexor), resulted in increased cytotoxicity of KRAS-mutant compared to RAS wild-type cells (KPTI internal information).

Preclinical data have demonstrated sensitivity of KRAS-mutant melanoma ([Yang 2014](#)) and non-small-cell lung carcinoma (NSCLC) cell lines to SINE molecules ([Kim 2016](#)) including BRAF mutated melanoma ([Salas Fragomeni 2013](#)). In a multi-genomic, data-driven approach obtained by analysis of 106 cell lines, it was identified that the nuclear transport machinery is an obligatory function required for cell survival. By application of selinexor, tumor cell growth was halted, and apoptotic cell death was induced at bioavailable concentrations (0.5 – 10 μ M).

Inhibition of XPO1 led to nuclear retention of I κ B α , which resulted in dysregulation of crucial

survival pathways via NFκB as the responsible mechanism of cell death induction and selective lethality in RAS mutant tumors ([Kim 2016](#)).

In *in vitro* studies, selinexor was active against different tumor types including lung, colon, melanoma, neuroblastoma, sarcoma, breast, cervical, gastric, prostate, pancreatic and renal cancers, with half maximal inhibitory concentrations below 1 μM in 94% of the cell lines.

In *in vivo* studies, tumor reduction and increased survival were observed at doses of selinexor 15 through 60 mg/m² (5 through 20 mg/kg) in mouse models of hematological and solid tumors. In addition, marked synergy was observed when selinexor was combined with a variety of chemotherapies and targeted therapies (including docetaxel and PD-1 inhibitors).

The major side effects across all animal models studied were reduced appetite with anorexia induced weight loss or reduction in weight gain. Cachexia (loss of muscle mass) was not observed. Similar effects are observed in humans, where high caloric foods and appetite stimulants, including glucocorticoids, are known to improve appetite and mitigate weight loss.

A quantitative whole-body autoradiography study conducted in rats previous demonstrated that [14C]-selinexor derived radioactivity was highest in the small intestine, kidney (all sections), stomach, and liver. Given that the elimination of selinexor is in part attributable to CYP3A4-mediated metabolism, impaired hepatic function could lead to increased selinexor exposures through reduced CYP3A4 activity. Only sparse PK samples are available from patients with moderate or severe hepatic impairment enrolled in previous studies (6 and 3 patients, respectively). Therefore, the information is too limited to adequately characterize the impact of hepatic function on selinexor exposures.

Nonclinical data supports the use of selinexor due to the overexpression of XPO1 noted in the setting of exposure of NSCLC cell lines to nicotine-derived nitrosamine ketones. Among the mutations that were generated included p53, p73, p21, p27, RAS, FOXO, STAT3, topoisomerase II, and PAR-4. These mutations were noted to also demonstrate XPO1 overexpression leading to dysregulated tumor suppressor proteins that were unable to prevent uncontrolled cell growth. Studies of selinexor and other SINE agents demonstrated tumor cell apoptosis in KRAS mutated NSCLC cell lines and xenografts. Additionally, synergism with chemotherapy and radiation therapy was demonstrated in the presence of molecular alterations including EGFR, p53, RAS, and PIK3A ([Gupta 2017](#), [Kim 2016](#)).

When selinexor was used in preclinical models of prostate cancer cell lines, enhanced DNA damage and slower rates of DNA repair were demonstrated in combination with docetaxel, especially in docetaxel-resistant cell lines ([Gravina 2017](#)). Selinexor was also noted to decrease the expression of DNA damage repair (DDR) proteins. This did not induce significant DNA damage in tested cell lines. Inhibition of DDR protein expression resulted in enhanced cancer cell death when cells were pretreated with DNA damaging agents. Selinexor demonstrated synergistic cytotoxic effects when cells were also exposed to cisplatin or docetaxel ([Kashyap 2018](#)).

Additional information is available in the selinexor Investigator Brochure.

2.4.5. Clinical Studies

The efficacy of selinexor monotherapy has been observed in several solid tumor types.

- In the early Phase 1 monotherapy study in solid tumors (KCP-330-002), objective response was observed in heavily-pretreated patients with KRAS-mutant CRC, melanoma, etc. Selinexor has shown single agent activity against heavily pretreated CRC with an ORR of 3% and a disease control rate (DCR) of 47% in KRAS-mutant CRC ([Abdul Razak 2016](#)). In another Phase 1 study in heavily pretreated Asian patients with advanced malignancies, the ORR of selinexor monotherapy was 12.2%. In the subset of patients with CRC, the rate of stable disease was 17% with the longest responses among patients with RAS mutated CRC ([Ho et al](#), not yet published). The preclinical and clinical data using selinexor as both a monotherapy and in combination with the anti-PD-1 mAb pembrolizumab demonstrated a treatment for patients with CRC that is otherwise minimally responsive to standard therapies due to the present of RAS mutations.
- KCP-330-004 (KING), an open-label, multicenter, Phase 2 study of selinexor monotherapy in recurrent glioblastoma ([Lassman 2019](#)). In this study selinexor 80 mg QW was evaluated in 30 patients with heavily pretreated GBM who have received a median of 2 prior therapies (range 1-7). Single agent selinexor at 80 mg QW demonstrated anti-tumor activity with 6mPFS of 19% (95% CI: 9-41), 6 cycle PFS 30% (95% CI: 17 – 54), ORR 10% (including a patient with durable PR who has been on treatment for > 3 years and a patient with CR who was on treatment for > 1 year), and mDOR of 10.8 months.
- KCP-330-005 (SIGN), an open-label, Phase 2 study of selinexor monotherapy in patients with recurrent gynecological malignancies ([Vergote 2020](#)). Selinexor single agent was evaluated in a cohort of patients with ovarian cancer who have received a median of 6 (range 1 -11) prior line of therapies. The disease control rate (PR and SD>12 weeks) and PR rate were 40% and 14%, respectively. In the endometrial cancer cohort in a patient population who have received a median of 2 (range: 1 -5) prior line of therapies, DCR and PR rate was 45% and 15%, respectively.
- KCP-330-020 (SEAL), a Phase 2/3, randomized, double blind, study of selinexor versus placebo in advanced unresectable dedifferentiated liposarcoma (DDLs). Based on unblinded Phase 2 data, mPFS for monotherapy selinexor (60 mg twice weekly) and placebo per RECIST v1.1 are 5.5 vs. 2.7 months with HR of 0.67 (95% CI: 0.33, 1.37). The improvement of PFS is promising and supports continuation of the Phase 3 portion of selinexor in DDLs ([Gounder 2018](#)). The Phase 3 portion of the study demonstrated a mPFS for selinexor (60 mg twice weekly) and placebo per RECIST v1.1 are 2.83 vs. 2.07 months with HR of 0.7 (95% CI: 0.5, 0.9) ([Gounder 2020](#)).

Selinexor was approved in July 2019 in combination with dexamethasone for the treatment of adult patients with relapsed refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

On 18 December 2020, the FDA approved XPOVIO® (selinexor), the Company's first-in-class, oral Selective Inhibitor of Nuclear Export (SINE) medicine, in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy. XPOVIO was previously approved under the FDA's Accelerated Approval

Program for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

Selinexor also received approval in June 2020 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

2.4.5.1. Investigator-sponsored Trials in Solid Tumors

Studies in solid tumors include the Investigator Sponsored Trial “Selinexor With Multiple Standard Chemotherapy or Immunotherapy Regimens in Treating Patients With Advanced Malignancies” (NCT02419495). In Arm E, Selinexor combined with carboplatin and paclitaxel, the DLT of selinexor was noted to be 60 mg weekly. This is the dose that was chosen for the combination with docetaxel.

Selinexor (60 mg-80 mg QW) in combination with docetaxel 75 mg/m² (IV) every 3 weeks has been evaluated in an ongoing Investigator-sponsored Phase 1/2 study in previously treated advanced NSCLC patients with KRAS mutation (NCT03095612). Two dose levels (DL) of selinexor were explored in dose escalation: DL1 selinexor 60 mg and DL2 selinexor 80 mg. There were 2 DLTs observed in 4 patients treated with DL2, including Grade 3 nausea and vomiting, resulting in a delay in initiating cycle 2 therapy for more than 21 days. There was 1 DLT observed in 6 patients treated with DL1 due to Grade 4 neutropenia lasting more than 7 days. DL1 was chosen as the RP2D and an expansion cohort is ongoing. As of 12 April 2021, there were 25 patients who had at least one post-baseline efficacy evaluation. Partial responses (PR) were noted in 3 patients (4%), including 1 patient with KRAS^{G12C}, 1 patient with KRAS^{G12R}, and 1 patient with KRAS^{G12V}. Preliminary clinical data of selinexor in combination with docetaxel demonstrated an acceptable tolerability profile. The most common reasons for discontinuation were due to PD and there were no deaths related to study treatment.

3. STUDY RATIONALE

Study KCP-330-027 has 2 parts: monotherapy and combination therapy.

3.1. Monotherapy Part

3.1.1. Patients with Normal Liver Function

A new tablet formulation of selinexor (100 mg tablets) has been developed to allow for single-tablet dosing. In the Monotherapy Part of this study, the relative bioavailability and bioequivalence of this new formulation compared to the currently available 20 mg tablet was established in patients with normal liver function.

After completing the planned doses for the relative bioavailability/bioequivalence study, these patients could switch to treatment with combination therapy, provided that they met the combination therapy reassessment criteria. Enrollment into this treatment arm for was closed in Israel.

3.1.2. Patients with Hepatic Impairment

Although no clinically significant drug-drug interactions have been reported to date in >3,200 patients treated with selinexor alone or in combination, the elimination of selinexor is in part attributable to cytochrome P450 3A (CYP3A4)-mediated metabolism. The sparsely sampled PK data obtained from patients with moderate (n=8) and severe (n=6) hepatic impairment in previous company-sponsored studies is inadequate to assess whether impaired hepatic function could lead to increased selinexor exposures. Therefore, the Moderate Hepatic Impairment (MHI) treatment arm and the Severe Hepatic Impairment (SHI) treatment arm in this study will include patients with moderate and severe hepatic impairment to characterize the relationship between hepatic function and selinexor PK.

Patients with any type of advanced or metastatic solid tumor who have moderate or severe hepatic impairment can be enrolled into this part of the study. Patients in the MHI and SHI arms will remain in the study on monotherapy only until PD or intolerance.

3.2. Combination Therapy Part

The main goal of the Combination Therapy Part is to independently evaluate the safety, tolerability and to explore the preliminary anti-tumor activity of 3 combination therapies in 3 arms:

- Arm A: the combination of selinexor with docetaxel in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have received 1-2 prior lines of systemic therapy that included 1 line of therapy with an anti-PD1/L1 monoclonal antibody (mAb).
- Arm B: the combination of selinexor with pembrolizumab, a humanized IgG4 anti PD-1 mAb, in patients with advanced or metastatic colorectal cancer (CRC) who have received 1-3 prior systemic treatments for KRAS wild-type (WT) CRC or 1-2 prior treatments for KRAS mutant CRC but have not received prior therapy with an anti-PD1/L1 mAb.
- Arm C: the combination of selinexor with FOLFIRI in patients with advanced or metastatic CRC who have received 1-2 prior systemic treatments regardless of KRAS status. This combination will have 2 dose regimens (Cohort C1 and Cohort C2). Approximately 6 patients will be treated in each of these 2 dose cohorts (first C1 is enrolled, then C2). Based on safety and preliminary anti-tumor activity from these 2 dose cohorts, an optimal dose regimen will be selected for further expansion with up to additional 14 patients.

In patients with NSCLC, the combination of selinexor with docetaxel is proposed for the following reasons: (1) docetaxel is a commonly used chemotherapy for patients with NSCLC whose disease progressed on prior immuno-oncology therapy, (2) preclinical data supports the use of selinexor in tumors that have been affected by nicotine-derived nitrosamine ketone exposure, resulting in overexpression of XPO1, including RAS mutated NSCLC; (3) preclinical data combining selinexor with taxane-based therapy suggests synergy (combinations with docetaxel in prostate cancer and breast cancer mouse models, and combinations with paclitaxel in breast and ovarian cancer mouse models), (4) preliminary clinical data from an ongoing Investigator-sponsored study ([NCT03095612](#)) have shown promising anti-tumor activity of this combination in patients with KRAS mutant NSCLC who were treated with at least 1 prior

regimen that contained an ICI; (5) data from the multi-arm Investigator-sponsored study [NCT02419495](#) demonstrating the MTD of selinexor with cisplatin and paclitaxel and in a weekly paclitaxel study in breast cancer; and (6) the data from the current study that has been enrolling patients in Israel using the combination of selinexor and docetaxel in patients with NSCLC who have received a checkpoint inhibitor and chemotherapy. As of 12 Apr 2021, 13 patients with advanced, metastatic NSCLC with progressive disease after 1 to 2 lines of prior lines of systemic therapy including 1 checkpoint inhibitor have enrolled with 12 evaluable for response with at least one on study imaging scan. Ten patients are still on therapy for 2 to 13 months. There are 2 patients (16.7%) with PR, -67.2% and -36.3% reduction in disease, on treatment over 12 months and 6 months, respectively. Five patients (41.6%) have SD for 2-6 months. Two patients were discontinued due to PD; 1 for radiological PD and 1 for clinical PD with stable imaging. One patient with stable imaging died during cycle 5 due to comorbid medical issues unrelated study treatment (This patient had a history of congestive heart failure and died due to this – considered unrelated to study drug). The emerging anti-tumor activity signal from these studies warrants further evaluation of the efficacy of the combination of selinexor with docetaxel in patients with NSCLC who have experienced failure of or progressed on prior immuno-oncology therapy.

In patients with CRC, the combination of selinexor with pembrolizumab is proposed based on non-clinical and clinical evidence of synergy effect of this combination. Results from several nonclinical studies show that selinexor can upregulate immune function and sensitize tumors to PD-1/PD-L1 blockade: (1) the combination of selinexor and PD-1 or PD-L1 blockade has been assessed in *in vivo* studies and demonstrated synergistic anti-tumor activity in an aggressive murine colon cancer model as well as other solid tumor models; (2) a combination of selinexor and anti-PD-1 or anti-PD-L1 monoclonal antibody shows significant immunomodulatory activity, inducing changes in the frequency and phenotype of immune cell populations, including increased frequency of NK cells, induced frequency of differentiated TH1 cells, and increased frequency of activated T-cells; (3) selinexor induces PD-1 and PD-L1 gene expression, sensitizing tumor cells to immunotherapy and synergizes with anti-PD-1 to inhibit tumor cell proliferation and to induce apoptosis *in vitro* ([Farren 2017](#); [Ellou 2016](#); [Trott 2016](#)); (4) in clinical studies, single-agent selinexor has demonstrated activity against CRC with KRAS mutation or WT ([Abdul Razak 2016](#)); and (5) the safety and anti-tumor activity of combining selinexor with a PD-1/PD-L1 inhibitor have been established in an ongoing Phase 1b Investigator sponsored study ([NCT02419495](#)). Preliminary clinical data of selinexor in combination with pembrolizumab or nivolumab demonstrated an acceptable tolerability profile.

The safety and anti-tumor activity of combining selinexor (60 mg BIW) with pembrolizumab (200 mg Q3W) was also established in an ongoing Phase 1b Investigator sponsored study ([NCT02419495](#)) in patients with metastatic melanoma. In this study, of 23 patients with metastatic melanoma who were evaluable for efficacy, 18 patients were diagnosed with non-uvular type, 9 patients were naïve to prior immunotherapy (ICI) and the other 9 patients were refractory to ICI therapy. It is a heterogeneous population including heavily treated patients with up to 5 lines of ICI treatment. The ORR among patients with ICI naïve and ICI refractory non-uvular melanoma was 56% versus 33%, respectively. The longest duration of treatment has been 15.4 months for 1 patient, while the longest DOR for 1 patient with CR is almost 13 months with the patient still on study. Adverse events reported during the study included nausea (68%), vomiting (52%), and anemia (48%). Other AEs observed were consistent with those reported

previously for selinexor and pembrolizumab. No overlapping toxicities were identified ([Glitza 2020](#)).

In patients with CRC, the combination of selinexor with FOLFIRI will be explored. Selinexor is an oral selective XPO1 inhibitor, and consequently restores the highly effective tumor suppressing pathways that leads to selective elimination of genomically damaged (i.e., neoplastic) cells by apoptosis, together with its ability to restore tumor cell sensitivity to chemotherapeutic or targeted agents such as irinotecan, oxaliplatin or olaparib makes it an ideal candidate for combination to augment the anti-tumor effects of standard chemotherapeutic agents or selective targeted therapy. In CRC (WiDR) and gastric (AGS) mouse xenograft studies, SINE compounds showed synergy with irinotecan ([Subhash 2018](#)). In addition, selinexor showed *in vitro* synergy with fluorouracil (5-FU) in fibrosarcoma cell line HT1080 ([Burke 2017](#)). The combination of selinexor and FOLFIRI was tested in IST-11 ([NCT02419495](#)) in 3 patients with solid tumor malignancies and no patients met DLT criteria. Since non-clinical data has shown promising synergy, there is need for testing this combination specifically in CRC to evaluate safety, tolerability and preliminary efficacy of this combination and to establish the optimal dose.

3.3. Dose Rationale

3.3.1. Monotherapy Part (S20-100 and S100-20 Arms) and Combination Therapy Part

Based on preliminary observations from the Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activity ranging from ~6 mg/m² to ≥85 mg/m² (approximately 10 mg to 120 mg PO).

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 or twice weekly and exhibited linear PK and dose-proportional exposure (area under the concentration-time curve [AUC] and maximum plasma concentration [C_{max}]). In Study KCP-330-002 in solid tumors, the maximum tolerated dose was defined at 65 mg/m² using a twice-a-week (Days 1 and 3) dosing schedule, which is approximately equivalent to 110 mg twice-a-week for adult patients with solid tumors assuming the average adult body surface area of 1.7 m².

The 100 mg QW dose proposed for S20-100 and S100-20 of the Monotherapy Part is necessary to evaluate bioequivalence of the new 100 mg tablets with an equivalent dose of the current 20 mg tablets. This dose has been evaluated in clinical studies, including in an ongoing Phase 3, randomized, controlled, open-label study of a combination of bortezomib and dexamethasone plus or minus selinexor 100 mg QW ([NCT03110562](#)). By the time of this amendment, a total of 22 patients have been enrolled. 22 patients have completed the monotherapy period of the study and 19 patients have tolerated the 100 mg QW dose well and are currently continuing with combination treatment. No DLT has been reported.

A dose of 60 mg selinexor QW in combination with docetaxel 75 mg/m² every 3 weeks has been selected for patients with NSCLC in the Combination Therapy Part Arm A. This is consistent with the dose being used in the ongoing Investigator-sponsored Phase 1/2 NSCLC study (Texas, USA, [NCT03095612](#)), in which responses have been observed. In this IST study, selinexor 60 mg or 80 mg once weekly in combination with docetaxel 75 mg/m² every 3 weeks was evaluated in patients with heavily pretreated NSCLC with KRAS mutation. Based on available safety data, the recommended dose of selinexor is 60 mg QW with docetaxel 75 mg/m² every 3 weeks. At the time of the protocol development, five patients had post-treatment restaging and

best responses included 2 PRs, 2SD (including one patient with 29% target lesion decrease from baseline) and 1 PD. All patients had prior exposure to pembrolizumab or nivolumab. The study continues to enroll patients onto cohort of selinexor at 60 mg QW in combination with docetaxel 75 mg/m² every 3 weeks and no new safety concerns have arisen. Based on these results, Study KCP-330-027 will evaluate selinexor 60 QW with docetaxel 75 mg/m² every 3 weeks.

A dose of 80 mg selinexor QW in combination with pembrolizumab 200 mg every 3 weeks has been selected for patients with CRC in the Combination Therapy Part Arm B. A higher dose intensity of selinexor (60 mg twice weekly) in combination with pembrolizumab 2 mg/kg every 3 weeks has been evaluated and shown to be well tolerated in an ongoing Investigator-sponsored Phase 1b study in solid tumors at MD Anderson Cancer Center ([NCT02419495](#)). This study evaluates selinexor 60 mg twice weekly (cumulatively 120 mg weekly) in combination with pembrolizumab 2 mg/kg every 3 weeks, and no DLTs were observed amongst the 32 patients treated to date and enrolment into this treatment arm was concluded. An expansion cohort is ongoing. Preliminary clinical data of selinexor in combination with pembrolizumab or nivolumab demonstrated an acceptable tolerability profile. As of 28 April 2020, the 27 patients who had at least one post-baseline efficacy evaluation for pembrolizumab, the response rate was 41% (n=11) with an additional 37% (n=10) having stable disease (SD) as their best response. In the RP2D expansion cohort in melanoma (N=19) the response rate was 42% among the evaluable patients (8/19) and 45% among all patients with melanoma (9/20). Furthermore, among the 10 patients who had received prior anti-PD-1/L1 mAb and had at least one post-baseline efficacy evaluation, the response rate was 20% (n=2) with an additional 50% (n=5) having SD as their best response. Among the 17 patients who did not receive prior immune checkpoint inhibitors and had at least one post-baseline efficacy evaluation, the response rate was 53% (n=9) with an additional 29% (n=5) having SD as best response. In the selinexor plus nivolumab combination arms of the study, the 13 patients who had at least one post-baseline efficacy evaluation so far, the response rate was 15% (n=2) with an additional 77% (n=10) having SD as their best response. Furthermore, among the 4 patients who had received prior anti-PD-1/L1 mAb and had at least one post-baseline efficacy evaluation, 100% had SD as their best response. Among the 9 patients who did not receive prior immune checkpoint inhibitors and had at least one post-baseline efficacy evaluation, the response rate was 22% (n=2) with an additional 67% (n=6) having SD as their best response. These results support the clinical evaluation of the combination of selinexor with a PD-1/PD-L1 inhibitor in CRC patients. Several studies in patients with solid tumors have shown that selinexor at a dose of 80 mg QW demonstrates similar efficacy with improved tolerability profile compared to a selinexor dose of 120 mg given as 60 mg twice weekly (

[Lassman 2019](#); [Vergote 2020](#)). Moreover, a dose of 80 mg twice weekly with low dose dexamethasone is approved for the treatment of refractory myeloma, and 100 mg selinexor once weekly in combination with standard bortezomib is well tolerated in patients with relapsed myeloma ([Bahlis 2018](#)). Based on these results, study KCP-330-027 will evaluate selinexor at a dose of 80 mg QW in combination with pembrolizumab. By the time of this amendment, 5 patients with CRC have been enrolled with 2 ongoing in the monotherapy period and 3 continuing with the combination of selinexor with pembrolizumab. The 3 patients have completed at least 1 cycle of combination therapy without DLT reported.

3.3.2. Monotherapy Part (MHI and SHI Arms)

In the monotherapy period for the MHI and SHI arms, the non-compartmental analyses from Studies KCP-330-001, KCP-330-002, and KCP-330-003 with sufficient numbers of patients with normal hepatic function and mild hepatic impairment showed that the apparent clearance (CL/F) of selinexor is almost identical between the 2 groups, which suggested the potential impact from moderate or severe hepatic impairment would be minimal or none. Furthermore, results from *in vitro* phenotyping studies indicated that selinexor is metabolized by CYP3A4 and various UGTs. In addition, conjugation with GSH and racemization to the trans form are other transformation pathways for selinexor. If extrahepatic metabolism of selinexor (via GSH conjugation, glucuronidation or racemization) accounts for the majority of the metabolic clearance of selinexor, hepatic impairment is likely to have a minor effect on the PK of selinexor.

The results from 2 sets of population PK analyses confirmed that there is no clear trend in selinexor PK between normal, moderate and severe hepatic impairment patients although the number of patients with moderate (n=6) and severe (n=3) hepatic impairment in both population PK datasets is relatively small. The safety data included additional patients with impaired hepatic function from the pooled studies (Studies KCP-330-001, KCP-330-008, KCP-330-009, KCP-330-010, KCP-330-012, KCP-330-013) and showed a similar percentage of Grade 4 or serious TEAEs (SAEs) amongst those with moderately (n=14; Grade 4 and SAEs, 28.6% and 64.3%, respectively) and mildly impaired hepatic function (n=137; Grade 4 and SAEs, 36.5% and 70.8%, respectively) as compared with those with normal hepatic function (n=817; Grade 4 and SAEs, 37.0% and 61.9%, respectively).

Despite the above-described data, which suggest hepatic function has a limited impact on selinexor's safety profile and exposures, it is important to be conservative when treating vulnerable patients such as those with moderate and severe hepatic impairment. Moreover, emesis is a common AE following selinexor treatment which could adversely impact the collection of PK. Therefore, an initial lower single dose of 40 mg will be used to assess selinexor PK in the moderately and severely hepatic impaired patients. After Week 1, patients may continue on selinexor monotherapy 40 mg QW. Dosing for these patients may be escalated to selinexor 60 mg QW after one 21-day cycle at 40 mg QW, and to selinexor 80 mg QW after one 21-day cycle at 60 mg QW based on tolerability, analysis of the patient's PK data and after documented approval from the Sponsor is received.

For assessments related to the effect of hepatic impairment on selinexor PK, selinexor plasma exposures will be evaluated for patients with normal hepatic function administered selinexor 100 mg (Monotherapy Treatment Part, S20-100 and S100-20 arms) relative to patients with MHI and SHI administered selinexor 40 mg (Monotherapy Treatment Part, MHI and SHI arms). These comparisons across treatment groups with differing doses are appropriate given that selinexor has demonstrated dose-proportional PK following a wide range of repeated oral doses (3 to 85 mg/m² [~5 to 150 mg]).

4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<i>Monotherapy Part</i>	
Primary	
- To determine the relative bioavailability of the 100 mg (Tablet B) and 20 mg (Tablet A) tablets of selinexor at 100 mg once weekly (QW) dose in patients with normal hepatic function - To assess the PK of selinexor after a single dose of 40 mg (2×20 mg) among patients with moderate and severe hepatic impairment relative to 100 mg (5×20 mg) among patients with normal hepatic function	The following plasma PK parameters for selinexor for the 2 formulations and different hepatic function: - area under the concentration-time curve (AUC) from time 0 to time of last concentration measured (AUC_{0-t}) and from time 0 extrapolated to infinity (AUC_{0-inf}) - maximum plasma concentration (C_{max})
Secondary	
To assess the additional PK of the new tablet formulation (Tablet B) and the reference (current) tablet formulation (Tablet A) in patients with normal hepatic function and of Tablet A formulation only in patients with moderate and severe hepatic impairment	The following PK parameters for selinexor for the 2 formulations in plasma: - time to maximum observed concentration (T_{max}) - terminal elimination rate constant (λ_z) - terminal half-life ($t_{1/2}$) - apparent clearance (CL/F) - apparent volume of distribution (V_d/F)
To explore changes in the protein binding of selinexor and the subsequent effects on its PK, in patients with varying degrees of hepatic function	The following PK parameters for selinexor (Tablet A formulation) in plasma: - fraction unbound (f_u) - maximum free-drug concentration (C_{max_u}) - area under the free-drug concentration-time curve from time zero extrapolated to infinity (AUC_u) - apparent free-drug clearance (CL_u/F) - apparent free-drug volume of distribution (V_u/F)
- To assess the tolerability of single-agent selinexor at 100 mg once weekly in patients with advanced or metastatic NSCLC and CRC - To assess the tolerability of single-agent selinexor in patients with any type of advanced or metastatic solid cancer indication and moderate or severe hepatic impairment	Based on AE reports, physical examination results (including vital signs), and clinical laboratory results by means of the occurrence, nature and severity of AEs
Exploratory	

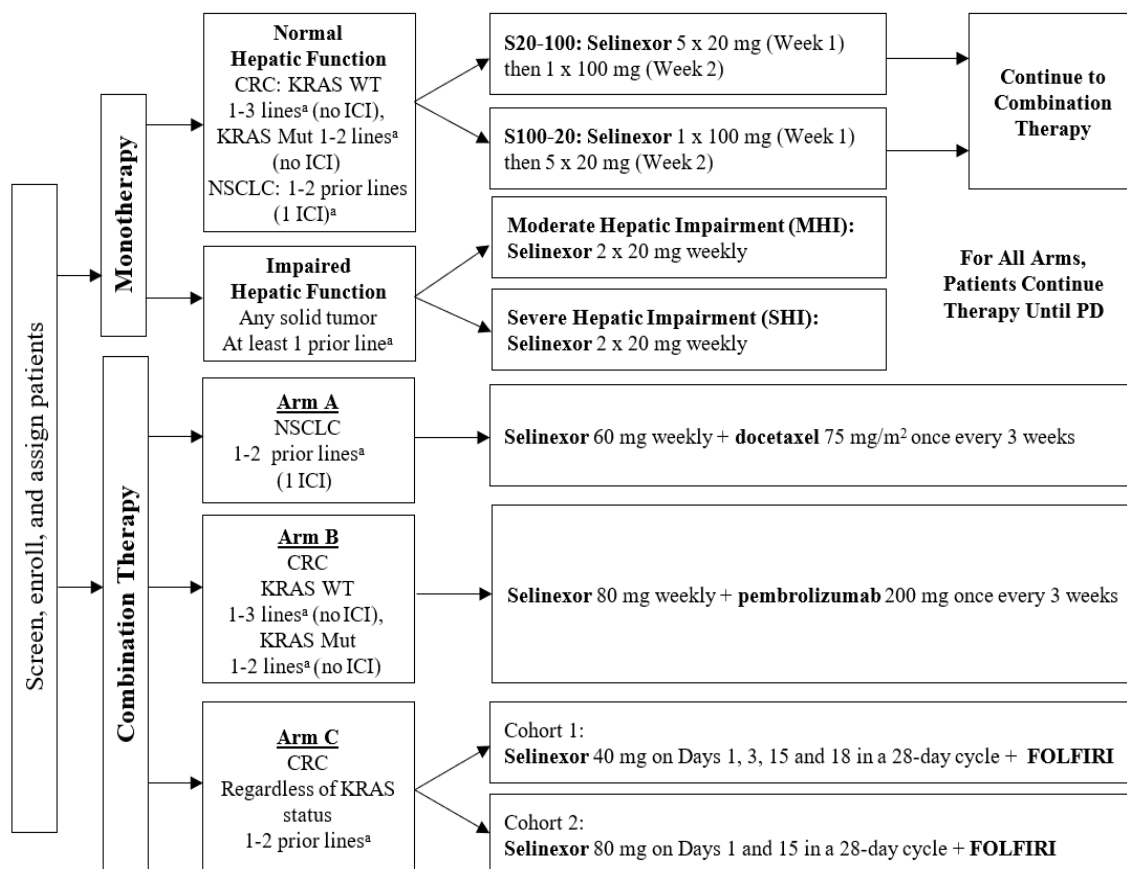
Objectives	Endpoints
CCI	
<i>Combination Therapy Part: Arm A and Arm B</i>	
Primary	
To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	ORR per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab
Secondary	
To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	PFS, DOR, DCR, per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab and OS
To assess the safety and tolerability of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	Based on AE reports, physical examination results (including vital signs), and clinical laboratory results by means of the occurrence, nature and severity of AEs
Exploratory	
CCI	

Objectives	Endpoints
<i>Combination Therapy Part: Arm C</i>	
Primary	
To assess the safety and tolerability of QW vs BIW selinexor in combination with FOLFIRI in patients with CRC	Based on, physical examination results, clinical laboratory results by means of the occurrence, nature and severity of AEs
Secondary	
To assess the preliminary anti-tumor activity of selinexor in combination with FOLFIRI in patients with CRC	ORR, DCR, DOR, PFS, per RECIST 1.1 and OS
Exploratory	
CCI	

5. STUDY DESIGN

5.1. Overall Design

This is a 2-part, multi-arm, open-label study in patients with solid tumors. The study schema is depicted in the figure below:



ICI = immune checkpoint inhibitor; CRC = colorectal cancer; KRAS = Kirsten rat sarcoma; mut = mutant; NSCLC = non-small cell lung cancer; PD = progressive disease; WT = wild type.

^a Lines of systemic therapy

5.1.1. Monotherapy Part

The relative bioavailability (BA) and bioequivalence (BE) of two different formulations of selinexor will be evaluated using a 2-sequence crossover design (S20-100 and S100-20 treatment arms) in patients with normal hepatic function (including only patients with NSCLC or CRC). The impact of hepatic function on selinexor PK will also be evaluated in the Monotherapy Part using 2 additional parallel study arms of patients with any advanced or metastatic solid tumors and with moderate or severe hepatic impairment (MHI and SHI treatment arms, respectively).

Patients with NSCLC or CRC will be enrolled into the bioavailability/bioequivalence (BA/BE) and with solid tumors in the HI arms; patients in the HI arms are required to have at least 1 prior line of systemic anticancer treatment. Patients with normal hepatic function in the BA/BE arms will continue into the Combination Therapy Part after completing all planned doses and PK

sampling in the Monotherapy Part, provided that they meet the Combination Therapy Part reassessment criteria. Patients that do not meet the reassessment criteria will be allowed to continue treatment with monotherapy as per discretion of the Investigator. Patients with MHI or SHI will not switch to combination therapy and will continue with monotherapy treatment, at the discretion of the Investigator, until disease progression or intolerance.

For the Monotherapy Part, patients will be allocated to 1 of the following test formulation treatment arms for QW dosing.

Table 5: Formulation of Selinexor Used during Each Week of the Monotherapy Part by Treatment Arm

Arm	Planned N	Hepatic Function	Cycle Duration	Week 1 ^a	Week 2 ^a
S20-100	10	Normal	14 days	5 × 20 mg tablet (Tablet A) ^b	1 × 100 mg tablet (Tablet B)
S100-20	10	Normal	14 days	1 × 100 mg tablet (Tablet B)	5 × 20 mg 10 tablet (Tablet A) ^b
MHI	8	Moderate impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)
SHI	6	Severe impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)

MHI = moderate hepatic impairment; SHI = severe hepatic impairment.

^a If dosing and PK/PDn receptor occupancy (PDnRO) sampling must be repeated due to insufficient PK samples for reasons outlined in Section 9.3, the repeat dose will be administered after 7 days (5 days minimum, 21 days maximum) and will be considered the same “study day” as the previous dose (Section 7.5.3.1) The Sponsor must be notified of any event leading to the collection of insufficient PK samples within 48 hours.

^b Indicates the portions of the Monotherapy Part from which PK data will be obtained for the evaluation of selinexor PK relative to hepatic function.

Approximately 20 patients with normal hepatic function will be enrolled for the BA/BE portion (S20-100 and S100-20 arms) of the Monotherapy Part. Randomization with a 1:1 ratio will not include stratification factors.

For the assessment of hepatic impairment, 8 patients in the MHI arm and 6 patients in SHI arm will be enrolled.

For Week 1 (for all patients) and Week 2 (for patients in the S20-100 and S100-20 arms) following an overnight fast of at least 10 hours, patients will be fed a standard low-fat meal 30 minutes prior to administration of selinexor. Patients should finish the meal within 30 minutes; and, the selinexor dose should be administered 30 minutes after the start of the meal. The start time of fasting and eating must be recorded. Water intake can be allowed ad libitum except for 1 hour before and after drug administration. Blood sampling for selinexor PK (plasma) analyses will be collected pre-dose (≤10 minutes before taking selinexor), 15 min (±5 min), 30 min (±5 min), 1 hour (±5 min), 1.5 hours (±5 min), 2 hours (±10 min), 3 hours (±10 min), 4 hours (±10 min), 5 hours (±10 min), 6 hours (±10 min), 8 hours (±20 min), 10 hours

(± 20 min; optional timepoint), 24 hours (± 1 hour), 30 hours (± 1 hour), and 48 hours (± 2 hour) post selinexor dose. Blood samples for the assessment of protein binding will be collected at 3- and 8-hours post-dose from patients administered Tablet A or Tablet B in the S20-100 and S100-20 arms (Day 1 and Day 8, respectively) and all patients in the MHI and SHI arms. Blood samples for PDn XPO1 receptor occupancy (PDnRO) analyses will be collected on Day 1 (pre-dose [≤ 10 minutes before taking selinexor], 2 hours [± 10 min], 4 hours [± 10 min], 8 hours [± 20 min], 24 hours [± 1 hour], 30 hours [± 1 hour], and 48 hours [± 2 hour] post selinexor dose) and Day 8 (predose [≤ 10 minutes before taking selinexor]). Additional PDnRO samples will be collected on Day 8 (4 hours [± 10 min] and 8 hours [± 20 min] post selinexor dose) from patients in the S20-100 and S100-20 arms. PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor. The exact actual time of dosing and each sample is collected must be recorded.

If insufficient PK samples are collected in Week 1 (for all patients) or Week 2 (for patients in the S20-100 and S100-20 arms), selinexor administration and PK/PDn blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum). For the MHI and SHI arms, dosing can go up to 4 weeks if both doses need to be repeated. When dosing/sampling is repeated, all timepoints need to be collected, including those already obtained, or the patient will need to be replaced. Details for situations where PK sampling of a formulation may be repeated are provided in Section 10.3 .

Safety will be evaluated through reporting of treatment-emergent adverse events (TEAEs), physical examinations, and clinical laboratory testing. Patients will receive best supportive care to manage the main adverse drug reactions of selinexor, which are nausea, anorexia, and fatigue (Section 7.9). Dose reductions may be made (Section 7.5), as appropriate, by the Investigator in discussion with the Sponsor's Medical Monitor.

Computed tomography (CT) or magnetic resonance imaging (MRI) will be performed at Screening.

Patients from the S20-100 or S100-20 arms who complete the Monotherapy Part will be allowed to continue into the Combination Therapy Part provided that they do not meet any of the combination therapy assessment/reassessment exclusion criteria. If a patient experiences significant toxicity related to selinexor and cannot start the combination therapy immediately following monotherapy, dose interruption and weekly retesting is allowed for up to 21 days after the End of Monotherapy Treatment Visit. Patients requiring >21 days to recover from toxicities related to selinexor should be discussed with the Sponsor's Medical Monitor for documented approval to continue to the Combination Therapy Part.

Patients with any solid tumor in the MHI and SHI arms may continue therapy (selinexor 40 mg QW) following the 3-day PK period with the option to escalate to selinexor 60 mg QW after completion of at least one 21-day cycle at 40 mg QW, and subsequently to selinexor 80 mg QW after completion of at least one 21-day cycle at 60 mg QW based on patient's tolerability and PK data and after documented approval following the discussion and agreement between the Sponsor and Investigator is received.

5.1.2. Combination Therapy Part

The safety and preliminary antitumor activity of selinexor in patients with advanced or metastatic NSCLC and CRC will be evaluated in combination with docetaxel for patients with NSCLC (Arm A in 2 cohorts of 20 patients each [n=40]; including up to 20 patients in the US and Canada), pembrolizumab (Arm B [n=40]) for patients with CRC in Israel only, or FOLFIRI (Arm C [n=up to 26]) for patients with CRC in Israel or the EU ([Table 6](#)).

Patients can complete screening assessments up to 21 days prior to the start of selinexor dosing. Laboratory tests will be completed ≤ 3 days before dosing ([Section 9.4.5](#)).

Patients enrolled in the Combination Therapy Part will receive treatment until progressive disease (PD) or intolerable toxicity occur.

Safety will be assessed through the continuous reporting of AEs, regularly scheduled clinical laboratory tests (hematologic and chemistry), and physical examinations.

Tumor assessment will be performed with either CT or MRI (CT with contrast preferred; for each patient, the imaging method should remain the same throughout the study), based on RECIST v1.1 criteria for the selinexor + docetaxel and selinexor + FOLFIRI arms (Arms A and C), and based on iRECIST for the selinexor + pembrolizumab arm (Arm B) .

Table 6: Dosing Schedules in the Combination Therapy Part

Arm	Planned N	Tumor Type	Number Prior Therapies	Cycle Duration	Selinexor Dose	Docetaxel Dose	Pembrolizumab Dose	FOLFIRI Dose
A	40	NSCLC	1-2	21 days	60 mg weekly	75 mg/m ² once every 3 weeks	-	-
B	40	CRC	2-3	21 days	80 mg weekly	-	200 mg once every 3 weeks	-
C1	10	CRC	1-2	28 days	40 mg on Days 1, 3, 15 and 17	-	-	Irinotecan 180 mg/m ² ; leucovorin 400 mg/m ² ; 5-FU 400 mg/m ² bolus; then 5-FU 2400 mg/m ² continuous over 46-48 hours (IV) on Day 1 and 15 of a 28-day cycle
C2	10	CRC	1-2	28 days	80 mg on Days 1 and 15	-	-	Irinotecan 180 mg/m ² ; 5-FU 2400 mg/m ² ; leucovorin 400 mg/m ² ; 5-FU 400 mg/m ² bolus; then 5-FU 2400 mg/m ² continuous over 46-48 hours; IV on Day 1 and 15 of a 28-day cycle

C1 = Cohort 1; C2 = Cohort 2.

6. STUDY POPULATION

6.1. Inclusion/Exclusion Criteria

Common inclusion criteria for all patients:

1. Are ≥ 18 years of age at the time of informed consent.
2. Have histologically confirmed solid tumor (any type of advanced or metastatic solid tumor for the Hepatic Impairment Arm of the Monotherapy Part), advanced or metastatic NSCLC or CRC and evidence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST v1.1 or iRECIST criteria, as applicable).
3. Willing to provide written informed consent in accordance with federal, local, and institutional guidelines and comply with all requirements of the study.
4. Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use highly effective (dual methods of) contraception throughout the study and for 4 months following the last dose of study drug (childbearing potential excludes: Age > 50 years and naturally amenorrhoeic for > 1 year, or previous bilateral salpingo-oophorectomy or hysterectomy); and male patients must use an effective barrier method of contraception throughout the study and for 4 months following the last dose of study drug if sexually active. Male patients must agree not to donate sperm during the study treatment period.

For the Monotherapy Part only (BA/BE and HI arms):

5. Have received at least 1 line of systemic anticancer treatment unless there is no first-line standard of care therapy or standard of care therapy is contraindicated (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy). Patients must have failed prior standard curative therapy for their disease, must be intolerant to or be ineligible for any potentially curative approved treatment, irrespective of line of therapy.
6. Must have either normal hepatic function, or moderate or severe hepatic impairment (as defined by the NCI organ dysfunction working group (NCI-ODWG) criteria:
 - a. S20-100 and S100-20 arms: normal hepatic function (total bilirubin and AST $\leq$ ULN).
Note: Patients with mild hepatic dysfunction (total bilirubin > 1 to $1.5 \times$ ULN OR AST $>$ ULN) may be included if liver function tests are stable for the past 3 months and enrollment is approved in writing by the Sponsor's Medical Monitor.
 - b. MHI arm: ≥ 1 week of documented moderate hepatic impairment (total bilirubin > 1.5 – $3 \times$ ULN, any level of AST).
 - c. SHI arm: ≥ 1 week of documented severe hepatic impairment (total bilirubin > 3 – $10 \times$ ULN, any level of AST).

For Combination Therapy Part only:

7. Previous treatment lines (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy):

- a. Arm A: For patients with NSCLC, have received 1-2 prior line(s) of systemic anti-cancer treatment with 1 regimen including an anti-PD-1/L1 mAb (Section 9.2.2).
 - b. Arm B: For patients with RAS mutant CRC, 1-2 prior lines of systemic treatments, and no prior anti-PD-1/L1 mAb.
 - KRAS WT: have 1-3 prior lines of systemic treatments (enrollment closed to WT with protocol version 5)
 - KRAS mutant (at least 50% of patients): 1-2 prior lines of systemic treatments.
 - c. Arm C: For patients with CRC participating in the combination arm with FOLFIRI, 1-2 prior lines of systemic therapy are allowed.
 - d. Arms B and C: For patients with CRC who are not candidates for curative resection of metastatic lesions.
8. Must have hepatic function as follows:
- a. Arm A (combination with docetaxel): Patients with NSCLC who are to receive docetaxel and have bilirubin $\leq$ ULN, and AST and/or ALT $\leq$ 1.5 x ULN
 - b. Arms B and C: total bilirubin $\leq$ 1.5 x ULN and AST $\leq$ 2.5 x ULN, ALT $\leq$ 2.5 x ULN; for Arm B, unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be $\leq$ 4 x ULN.

Key Exclusion Criteria:

Common exclusion criteria for all patients:

1. Have inadequate hematopoietic function defined as (without transfusion or growth factor support within 7 days prior to first dose):
 - a. For S20-100 or S100-20 arms: absolute neutrophil count (ANC) $< 1.5 \times 10^9/L$; platelet count (PLT) $< 100 \times 10^9/L$; or hemoglobin (Hb) < 10 g/dL. (Note: This does not apply to the MHI and SHI arms.)
 - b. For Arms A-C: ANC $< 1.5 \times 10^9/L$; PLT $< 100 \times 10^9/L$; or Hb < 10 g/dL
2. Have inadequate renal function defined as a calculated creatinine clearance (CrCl) of:
 - a. all patients: < 20 mL/min using the formula of Cockcroft and Gault.
3. Have any other medical condition especially any gastrointestinal (GI) dysfunctions or GI disease that could interfere with the absorption of selinexor (e.g., inability to swallow or retain oral medications, malabsorption syndrome, a history of GI surgery which may result in intestinal blind loop, significant gastroparesis, unresolved nausea, vomiting, or diarrhea [National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1]).
4. Ongoing infection requiring parenteral antibiotics, antivirals, or antifungals:
 - a. All patients: on Day 1 dosing.
5. Prior exposure to a SINE compound or selinexor.
6. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:

- a. Not recovered from major surgery ≤ 21 days for Arms A, B, and C 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 CTCAE Grade >1 . Patients with any of the following will not be excluded: immune checkpoint-related endocrinopathies that are well controlled with hormonal supplements, patients with electrolyte abnormalities that are well-managed with supplementation, patients with Grade 2 lymphopenia, or patients with alopecia of any grade. 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. Serious active psychiatric or active medical condition that could interfere with participation in the study or in the opinion of the Investigator would make study involvement unreasonably hazardous for Arms A-C.
 8. Known allergy to selinexor (all patients), docetaxel (NSCLC Arm A only), pembrolizumab (CRC Arm B only), 5-FU, leucovorin, or irinotecan (CRC Arm C only),
 9. Female patients who are pregnant or breastfeeding.

For Monotherapy Part only (BA/BE and HI arms):

10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of:
 - a. ≥ 3 for patients to be enrolled into the S20-100 or S100-20 arms of the study.
 - b. ≥ 4 for patients to be enrolled into the MHI and SHI arms of the study.
11. For MHI and SHI arms: ANC $<1 \times 10^9/L$; PLT $<75 \times 10^9/L$; or Hb <8 g/dL.
12. Received strong cytochrome P450 3A (CYP3A) inhibitors ≤ 7 days prior to Day 1 dosing OR strong CYP3A inducers ≤ 14 days prior to Day 1 dosing.
13. Inability or unwillingness to undergo a series of PK sampling.

For Combination Therapy Part only:

14. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 3 for Arms A and B, and ECOG PS ≥ 2 for Arms C.
15. Arm B: patients with CRC who are to receive pembrolizumab:
 - a. Had a diagnosis of immunodeficiency or are receiving systemic steroid therapy (>10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy.
 - b. Patients with controlled diabetes mellitus and patients with endocrinopathies on stable hormone replacement therapy, are eligible for the trial.

- c. Have active autoimmune disease requiring systemic treatment during the past 2 years. Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.

Note: The Investigator needs to evaluate the patient's medical history to confirm that they are eligible to receive the combination with pembrolizumab per these criteria.

- d. For patients with CRC who have received live-attenuated vaccine against an infectious disease (e.g., nasal spray influenza vaccine) ≤ 14 days prior to the intended C1D1 of the Combination Therapy.

16. Arm C: Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: for patients who are initially enrolled onto the BA/BE arm in the monotherapy part and plan to switch to combination therapy after completing the planned dosing and PK sample collection, dose interruption between the Monotherapy Part and the Combination Therapy Part is allowed for recovery from AEs. Patients requiring >21 days to recover from toxicities related to selinexor should be discussed with the Sponsor's Medical Monitor for documented approval to continue to the Combination Therapy Part if inclusion/exclusion criteria are met. Experiencing PD during the Monotherapy Part does not constitute exclusion from the Combination Therapy Part.

6.2. Combination Therapy Reassessment Criteria

Prior to initiating combination therapy, patients in the S20-100 and S100-20 arms will be reassessed. Patients will be excluded if they meet any of the following combination therapy reassessment criteria:

1. Have an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 3 for Arms A and B and ECOG PS ≥ 2 for Arm C.
2. Arm B patients with CRC who are to receive pembrolizumab:
 - a. Had a diagnosis of immunodeficiency or are receiving systemic steroid therapy (>10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy.
 - b. Patients with controlled diabetes mellitus and patients with endocrinopathies on stable hormone replacement therapy, are eligible for the trial.
 - c. Have active autoimmune disease requiring systemic treatment during the past 2 years. Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.

Note: The Investigator needs to evaluate the patient's medical history to confirm that they are eligible to receive the combination with pembrolizumab per these criteria.

- d. For patients with CRC who have received live-attenuated vaccine against an infectious disease (e.g., nasal spray influenza vaccine) ≤ 14 days prior to the

intended C1D1 of the Combination Therapy.

3. Arm C: Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: Dose interruption between the Monotherapy Part and the Combination Therapy Part is allowed for recovery from AEs. Patients requiring >21 days to recover from toxicities related to selinexor should be discussed with the Sponsor's Medical Monitor for documented approval to continue to the Combination Therapy Part. Experiencing PD during the Monotherapy Part does not constitute exclusion from the Combination Therapy Part.

6.3. 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, reason for screen failure, and any serious adverse event (SAE).

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

7. STUDY TREATMENT

7.1. Study Treatments Administered

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

7.1.1. Selinexor Formulations

Selinexor will be provided in 2 formulations for the Monotherapy Part: as 20 mg tablets (Tablet A) and 100 mg tablets (Tablet B).

- Tablet A is provided as film-coated, immediate-release 20 mg tablets for oral administration in 12-tablet blister pack wallets.
- Tablet B is provided as film-coated, immediate-release 100 mg tablets for oral administration in 50-count bottles.

Refer to the Pharmacy Manual for additional information on selinexor.

7.1.2. Docetaxel (NSCLC Cohort), FOLFIRI (CRC Cohort), and Pembrolizumab (CRC Cohort) in Combination Therapy Part

Refer to the Pharmacy manual for procurement of combination therapy.

7.2. Study Drug Labeling and Storage

7.2.1. Labeling

All labels (selinexor, docetaxel, irinotecan, leucovorin, 5-FU, and pembrolizumab) will include conditions for storage, lot number, and other information required by the Food and Drug Administration (FDA), International Council for Harmonization (ICH), and/or Annex 13, and all local regulations for investigational medications.

Medication labels for each blister pack or bottle of selinexor will be in the local language and comply with the legal and regulatory requirements of each country. They will include storage conditions for the drug. Additional information about selinexor labeling is in the Pharmacy Manual.

7.2.2. Storage

Selinexor tablets should be stored at $\geq 2^{\circ}\text{C}$ and $\leq 30^{\circ}\text{C}$ ($\geq 35.6^{\circ}\text{F}$ and $\leq 86^{\circ}\text{F}$) in a locked and secured area with access restricted to the site staff pharmacist or designee(s).

Docetaxel, pembrolizumab, 5-FU, leucovorin and irinotecan (FOLFIRI) should be stored as directed in their respective prescribing information.

7.3. Study Drug Dosing and Administration

7.3.1. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the selinexor as per protocol.

Selinexor will be dispensed to the patient by authorized site personnel only. Additional dispensing instructions for selinexor will be provided in the Pharmacy Manual. Selinexor tablets should be taken PO with about 240 mL (8 ounces) of water.

For the Combination Part, docetaxel (Arm A), pembrolizumab (Arm B) and FOLFIRI (Arm C) will be administered at the site, only by authorized site personnel.

7.3.2. Dosing Information

7.3.2.1. Monotherapy Part

Following an overnight fast of at least 10 hours during Week 1 (all patients) and Week 2 (S20-100 and S100-20 arms only) patients will be administered a single oral dose of selinexor 30 minutes after the start of a standard, low-fat meal. The meal is to be consumed within 30 minutes or less. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for 1 hour before and after drug administration. Patients in the S20-100 and S100-20 arms should receive standardized meals scheduled at the same time on Day 1 and Day 8 of the Monotherapy Part. In order to avoid contact with skin, tablets must be swallowed whole (not chewed) and should not be crushed prior to use.

For patients assigned to the S20-100 or S100-20 arms, selinexor will be provided as 100 mg QW doses in the following 2 formulations:

- 5 × 20 mg tablets (Tablet A)
- 1 × 100 mg tablet (Tablet B)

For patients assigned to MHI or SHI arms, selinexor will be provided as a single agent, 40 mg dose (2 × 20 mg tablets [Tablet A]). Patients in the MHI and SHI arms may continue to receive selinexor monotherapy 40 mg QW throughout the study. These patients will not receive Combination Therapy. Intra-patient dose escalation may be allowed after a patient's tolerability and pharmacokinetics data is evaluated. Selinexor dose may be escalated to 60 mg QW after completion of at least one 21-day cycle at 40 mg QW, and subsequently to 80 mg QW after completion of at least one 21-day cycle at 60 mg QW based on review of the patient's tolerability and PK data and after documented approval from the Sponsor is received.

Dose interruption and reduction are allowed for management of TEAEs, and patients receiving a reduced dose may remain on study; however, patients receiving a reduced dose will not be eligible for PK/PDnRO blood sampling and may be replaced, if needed.

7.3.2.2. Combination Therapy Part

Selinexor can be taken with or without food throughout the Combination Therapy Part. Selinexor 20 mg tablets will be used during the Combination Therapy Part.

The NSCLC cohort (Arm A) will receive selinexor 60 mg orally (PO) QW and docetaxel 75 mg/m² IV once every 3 weeks. The CRC Arm B will receive selinexor 80 mg PO QW and pembrolizumab 200 mg IV every 3 weeks. The CRC Arm C will receive two different dose regimens: Cohort 1, selinexor 40 mg (PO) on Days 1, 3, 15, and 17 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² bolus then 5-FU 2400 mg/m² continuous over 46-48 hours; IV on Day 1 and 15 of a 28-day cycle); Cohort 2, selinexor 80 mg (PO) on Days 1 and 15 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² bolus; 5-FU 2400 mg/m² continuous over 46 – 48 hours; IV on Day 1 and 15 of a 28-day cycle).

For additional details on drug formulation, preparation, and administration of selinexor, please refer to the Pharmacy Manual and the selinexor IB.

7.3.2.2.1. Docetaxel

Docetaxel will be administered IV at the site by qualified personnel, according to the procedures provided in the docetaxel prescribing information.

7.3.2.2.2. Pembrolizumab

Pembrolizumab will be administered IV at the site by qualified personnel, according to the procedures provided in the pembrolizumab prescribing information.

7.3.2.2.3. FOLFIRI

FOLFIRI will be administered IV at the site by qualified personnel, according to the procedures provided in the irinotecan, leucovorin, and 5-FU prescribing information.

7.3.3. Dosing Schedules

7.3.3.1. Dosing Sequence and Timing: Monotherapy Part

For the S20-100 and S100-20 arms, the selinexor dose throughout the Monotherapy Part is 100 mg PO QW and will comprise approximately 14 days.

Patients will be randomly assigned to S20-100 (Tablet A [5×20 mg selinexor tablet] on Day 1 and Tablet B [1×100 mg selinexor tablet] on Day 8) or S100-20 (Tablet B on Day 1 and Tablet A on Day 8). Patients with moderate or severe hepatic impairment will be assigned to the MHI or SHI arm based on their hepatic function and receive Tablet A (2×20 mg selinexor tablet) on Day 1.

For patients in the S20-100 and S100-20 arms, all patients will fast for at least 10 hours and consume a low-fat meal before selinexor dosing as described in Section 7.3.2.1 .

For the MHI and SHI arms, a single dose of selinexor 40 mg will be administered during Week 1. Patients may continue therapy (selinexor 40 mg QW) with the option to escalate to selinexor 60 mg QW after completion of at least one 21-day cycle at 40 mg QW, and subsequently to selinexor 80 mg QW after completion of at least one 21-day cycle at 60 mg QW dose based on review of the patient's tolerability and PK data and after documented approval from the Sponsor is received (Section 7.5).

If insufficient PK samples are collected in Week 1 (for all patients) or Week 2 (for patients in the S20-100 and S100-20 arms), selinexor administration and PK/PDnRO blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum) (Section 7.5.3.1). For the MHI and SHI arms, dosing can go up to 4 weeks if both doses need to be repeated. When dosing/sampling is repeated, all timepoints need to be collected, including those already obtained, or the patient will need to be replaced. Details for situations where PK sampling of a formulation may be repeated are provided in Section 10.3 .

7.3.3.2. Dosing Sequence and Timing: Combination Therapy Part

Cycles in Arm A and Arm B of the Combination Therapy Part are 21 days, due to the once every 3-week dosing schedule of docetaxel and pembrolizumab. In Arm C, the cycles are 28 days due to the dosing schedule of FOLFIRI (Table 6).

In Arm A, patients will receive selinexor 60 mg PO QW in combination with docetaxel 75 mg/m² IV every 3 weeks in a 21-day cycle. Dose reductions for docetaxel and FOLFIRI for cycle 1 are allowed for prior toxicities per their respective labels. On Day 1 of each cycle, the day docetaxel is administered at the site, patients should take their selinexor at the site, before IV infusion of docetaxel. Docetaxel dosing must maintain every 3-week schedule. Weekly low dose is not allowed. The Day 8 and Day 15 doses of selinexor may be taken at home.

In Arm B, patients will receive selinexor 80 mg PO QW in combination with pembrolizumab 200 mg IV every 3 weeks in a 21-day cycle. On Day 1 of each cycle, the day pembrolizumab is administered at the site, patients should take their selinexor at the site, before IV infusion of pembrolizumab. The Day 8 and Day 15 doses of selinexor may be taken at home.

In Arm C, patients will receive two different dose regimens: Cohort 1, selinexor 40 mg (PO) on Days 1, 3, 15, and 17 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin

400 mg/m²; 5-FU 400 mg/m² bolus then 5-FU 2400 mg/m² continuous over 46-48 hours; IV on Day 1 and 15 of a 28-day cycle); Cohort 2, selinexor 80 mg (PO) on Days 1 and 15 in a 28-day cycle and FOLFIRI (irinotecan 180 mg/m²; leucovorin 400 mg/m²; 5-FU 400 mg/m² bolus; 5-FU 2400 mg/m² continuous over 46 - 48 hours; IV on Day 1 and 15 of a 28-day cycle).

7.4. Missed or Vomited Doses of Selinexor

7.4.1. Missed Doses of Selinexor

7.4.1.1. Monotherapy Part: In-clinic Dosing

Doses of selinexor for evaluations of bioequivalence and hepatic impairment will be taken in the clinic. The visit day may be adjusted; however, in-clinic doses must be at least 7 days apart (5 days minimum, 21 days maximum if dosing is repeated for PK sample collection).

For missed doses of selinexor taken at home during the Monotherapy Part (Patients with hepatic impairment who continued therapy or any patient who required a dose reduction after the Week 1 dose), see Section 7.4.1.2 below. For timing after dose interruptions, see Section 7.5.3.1.

7.4.1.2. Combination Therapy Part (and In-Home Dosing during the Monotherapy Part)

Missed selinexor doses should be managed as follows:

- If a dose was missed, the dose should be taken the next day. All missed and delayed doses should be documented.
- If a dose must be skipped (e.g., due to recommendation of the Investigator), the next dose will be taken as per schedule. All missed and delayed doses should be documented.

7.4.2. Vomited Doses of Selinexor

If a dose is vomited ≤ 1 hour after ingestion and an intact tablet is seen, it will be replaced immediately. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

If a dose for PK evaluation (Week 1 for all patients; Week 2 for patients in the S20-100 and S100-20 arms) is vomited ≤ 6 hours after ingestion, no further PK/PDnRO blood samples for that dose will be collected (including cases where the vomited dose [≤ 1 hour after ingestion] was replaced). Instead, selinexor administration and PK/PDnRO blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum, Section 7.5.3.1). Timepoints for PK/PDnRO blood sample collection are described in Section 9.3.

7.5. Dose Modifications

All dose modifications will be captured in the electronic case report form (eCRF). Dose modifications should be associated in the eCRF with the AE requiring the modification.

For the MHI and SHI arms: An initial lower single dose of 40 mg will be used to assess selinexor PK in the moderately and severely hepatic impaired patients. After Week 1, patients may continue selinexor monotherapy 40 mg QW. Dosing for these patients may be escalated to selinexor 60 mg

QW after one 21-day cycle at 40 mg QW, and to selinexor 80 mg QW after one 21-day cycle at 60 mg QW based on tolerability, analysis of the patient's PK data if available and after documented approval from the Sponsor is received.

7.5.1. Selinexor Dose Modification

Based on preliminary observations from Phase 1 studies in patients with advanced hematological and solid tumors, selinexor shows a reasonably wide therapeutic range, with activity ranging from ~6 mg/m² to ≥85 mg/m² (approximately 10 mg to 120 mg orally). Therefore, in order to optimize specific anti-tumor activity and tolerability, up to 2 dose reductions will be allowed as described in Table 7. The guidelines for using these dose reductions in conjunction with dose interruption and supportive care for specific AEs are given in Table 8. For some AEs, dose interruption is recommended rather than dose reduction.

Note: Patients in the Monotherapy Part requiring a dose reduction after the Week 1 dose will not be eligible for the PK analysis. Such patients are allowed to remain in the study (if medically appropriate) but will be replaced for the PK analysis.

Table 7: Prespecified Dose Modifications for AEs Related to Selinexor

Starting Dose	Dose Reductions	
	First Reduction	Second Reduction
80 mg QW	60 mg (3 X 20 mg) QW	40 mg (2 X 20 mg) QW
60 mg QW	40 mg (2 X 20 mg) QW	20 mg (1 X 20 mg) QW
40 mg QW	20 mg (1 X 20 mg) QW	Discontinue treatment

CRC = colorectal cancer, NSCLC = non-small cell lung cancer, QW = once weekly

Table 8: Suggested Supportive Care and Dose Adjustment Guidelines for AEs Related to Selinexor

Adverse Event	Occurrence	Action
<i>Hematologic Adverse Events</i>		
Thrombocytopenia		
Platelet count $50 \times 10^9/L$ to $<75 \times 10^9/L$ [Grade 2] with NO concurrent bleeding	Any	Monitor until platelet count returns to at least $75 \times 10^9/L$, with no concurrent bleeding. Interrupt one dose of selinexor. Restart selinexor at the same dose level.
Platelet count $25 \times 10^9/L$ to $<75 \times 10^9/L$ [Grade 2 or 3] with concurrent bleeding	Any	Interrupt selinexor. Restart selinexor at 1 dose level lower after bleeding has resolved (see Table 7). Consider additional supportive care and discuss with Sponsor's Medical Monitor.
Platelet count $<50 \times 10^9/L$	Any	Interrupt selinexor / all therapies.

Adverse Event	Occurrence	Action
[Grade 3/4]		Monitor until platelet count returns to at least $75 \times 10^9/L$, with no concurrent bleeding. Restart selinexor at 1 dose level lower (see Table 7). Consider additional supportive care and discuss with Sponsor's Medical Monitor.
Neutropenia		
ANC 0.5 to $1.0 \times 10^9/L$ [Grade 3] without fever	Any	Maintain selinexor dose and initiate growth factor support.
ANC $<0.5 \times 10^9/L$ [Grade 4] OR febrile neutropenia	Any	Interrupt selinexor. Initiate growth factor support. Monitor until ANC returns to $\geq 1.0 \times 10^9/L$. Restart selinexor at 1 dose level lower (see Table 7).
Anemia		
Hb <8.0 g/dL [Grade 3]	Any	Reduce selinexor by 1 dose level (see Table 7). Administer blood transfusions and/or other treatments per institutional guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	Interrupt selinexor. Administer blood transfusions and/or other treatments per institutional guidelines. Monitor until Hb returns to ≥ 8.0 g/dL. Restart selinexor at 1 dose level lower (see Table 7).
Nonhematologic Adverse Events		
Hyponatremia		
Sodium <130 mmol/L [Grade ≥ 2]	Any	Interrupt selinexor and provide appropriate supportive care. Monitor until sodium returns to ≥ 130 mmol/L. Restart selinexor a one dose level lower.
Fatigue		
Grade 2 lasting >7 days OR Grade 3	Any	Interrupt selinexor and provide appropriate supportive care. Monitor until fatigue resolves to Grade 1 or baseline. Restart selinexor at 1 dose level lower (see Table 7).
Nausea and Vomiting		
Grade 1 or 2 nausea OR Grade 1 or 2 vomiting	Any	Maintain selinexor dose and initiate additional anti-nausea medications.
Grade 3 nausea OR Grade ≥ 3 vomiting	Any	Interrupt selinexor. Initiate additional anti-nausea medications.

Adverse Event	Occurrence	Action
		Monitor until nausea or vomiting has resolved to $\leq$ Grade 2 or baseline. Restart selinexor at 1 dose level lower (see Table 7).
Diarrhea		
Grade 2	First	Maintain selinexor dose and institute supportive care.
	Second and subsequent	Reduce selinexor by 1 dose level (see Table 7). Institute supportive care.
Grade ≥ 3	Any	Interrupt selinexor and institute supportive care. Monitor until diarrhea resolves to Grade ≤ 2 . Restart selinexor at 1 dose level lower (see Table 7).
Weight Loss and Anorexia		
Weight loss of 10% to $<20\%$ [Grade 2] from baseline OR anorexia [Grade 3] associated with significant weight loss or malnutrition	Any	Interrupt selinexor and institute supportive care. Monitor until weight returns to $>90\%$ of baseline weight. Restart selinexor at 1 dose level lower (see Table 7).
Other Nonhematologic Adverse Events		
Grade 3 or 4	Any	Interrupt selinexor and institute supportive care. Monitor until resolved to $\leq$ Grade 2. Restart selinexor at 1 dose level lower (see Table 7).

ANC = absolute neutrophil count; Hb = hemoglobin.

For all Grade ≥ 3 hematologic or non-hematologic AEs that are NOT study drug related, after consultation with the Sponsor's Medical Monitor and at the discretion of the Investigator, study drug dosing may be maintained.

For all study drug-related AEs, if the above prescribed dose reductions/interruptions result in a stabilization of ≥ 4 weeks, a re-escalation may be considered after approval from the Medical Monitor.

7.5.2. Docetaxel, Pembrolizumab, or FOLFIRI

For AEs related to docetaxel (Arm A), pembrolizumab (Arm B), FOLFIRI (Arm C) during the Combination Therapy Part, refer to dose adjustment guidelines in the respective drug's prescribing information. If an AE requires interruption of either of these drugs but not selinexor, selinexor treatment may continue.

7.5.3. Cycle Timing after Interrupted Doses

7.5.3.1. Monotherapy Part

In-clinic doses (those at which PK sampling will be done) must be at least 7 days apart (5 days minimum, 21 days maximum, if dosing is repeated for PK sample collection) for relative bioavailability/bioequivalence evaluation.

If Week 1 (for all patients) or Week 2 (for patients in the S20-100 and S100-20 arms) dosing and PK sampling must be repeated after 7 days (5 days minimum, 21 days maximum) for reasons

outlined in Section 9.3, the repeat dose will be considered the same “study day” as the previous dose. For example, if the formulation assigned to D1 for a patient must be repeated due to too many missing timepoints or due to a medically necessary CYP3A inhibitor or inducer, the same formulation will be repeated at D8, but will be considered the D1 dose. In such a scenario, the next formulation would then be administered on D15, but would be considered the D8 dose.

If a dose reduction or interruption (followed by a dose reduction) is required due to an AE within the initial 2 weeks, the patient will not be eligible for the bioequivalence analyses.

During the Monotherapy Part, the selinexor dose may be interrupted for up to 21 days. Patients must receive at least 2 selinexor doses before being reassessed for the Combination Therapy Part, regardless of whether their data are included in the bioequivalence analysis.

7.5.3.2. Combination Therapy Part

Docetaxel or pembrolizumab dosing will be done on D1 of any given 21-day cycle. If one of these drugs must be interrupted but selinexor is not concurrently interrupted, the cycle continues. For example, if docetaxel must be withheld starting C4 D1, but selinexor can continue, the next possible dose of docetaxel would be given on C5 D1 (21 days later), if the patient had recovered from AEs. Otherwise, the dose of docetaxel would be delayed for a minimum of another 3 weeks, until C6 D1.

FOLFIRI dosing will be done on D1 and D15 of any given 28-day cycle. If one of the drugs in the FOLFIRI regimen must be interrupted but selinexor is not concurrently interrupted, the cycle continues. For example, if FOLFIRI must be withheld starting C4 D1, but selinexor can continue, the next possible dose of FOLFIRI would be given on C4 D15, if the patient had recovered from AEs. Otherwise, the dose of FOLFIRI would be delayed for another 15 days, until C5 D1.

In a similar manner, if selinexor is interrupted, but the combination drugs may continue, the cycle continues, and next cycle begins when the next dose of combination drugs is next scheduled.

If all drugs are interrupted, the count of the cycle is also interrupted. When either selinexor or the combination partner drug is reintroduced, the count begins at the same point of the interruption. For example, if AEs prevent dosing of either drug on C3 D1, once the AEs resolve, the next dosing day will be called C3 D1.

7.5.4. Maximum Length of Dose Interruptions – Combination Therapy Part

7.5.4.1. Interruption of All Study Drugs

If an AE requires interruption of all study drugs, the interruption may last 28 days before a patient should be discontinued from study treatment. Patients may be allowed to return to study treatment after an interruption of longer than 28 days if the Investigator and Sponsor’s Medical Monitor agree it is in the patient’s best interest to resume therapy.

7.5.4.2. Interruption of Docetaxel, Pembrolizumab, or FOLFIRI; Selinexor Continues

If an AE requires interruption of only docetaxel (Arm A), pembrolizumab (Arm B), or FOLFIRI (Arm C) but the AE does not require interruption of selinexor, then docetaxel, pembrolizumab, or FOLFIRI may remain interrupted as long as 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

docetaxel, pembrolizumab, or FOLFIRI the patient may continue treatment with single-agent selinexor, at the discretion of the Investigator.

7.5.4.3. Interruption of Selinexor; Docetaxel, Pembrolizumab or FOLFIRI Continues

If an AE requires interruption of selinexor but not docetaxel (Arm A), pembrolizumab (Arm B), or FOLFIRI (Arm C), the interruption may last as long as 2 cycles before the patient should be discontinued from study treatment. Patients may be allowed to continue study treatment with docetaxel, pembrolizumab or FOLFIRI after a 2-cycle interruption of selinexor if the Investigator and Sponsor's Medical Monitor agree that the patient is benefitting, and if resumption of selinexor may be indicated in the future.

7.5.5. Dose-limiting Toxicities

An AE are considered to be a DLT if it meets the criteria defined herein and occurs during Cycle 1 of the Combination Therapy Part.

A DLT is defined as any of the following and was considered to be at least possibly related to study drug administration:

- Miss >25% of planned dose for any study drug due to an AE during cycle 1
- A dose reduction during Cycle 1 due to a study drug-related toxicity
- Discontinuation of a patient before completing Cycle 1, due to study drug-related toxicity

Non-hematologic DLT:

- Grade 3 nausea, vomiting, dehydration, diarrhea or fatigue lasting >4 days despite optimal supportive medications.
- Any other clinically significant Grade 3 or 4 non-hematological toxicity with the following exceptions:
 - Electrolyte abnormalities including hyponatremia that are reversible and asymptomatic
 - Hair loss
 - ALT, AST or alkaline phosphatase levels in the setting of baseline Grade 2 elevations
 - Hyperglycemia

Hematologic DLT:

- Febrile neutropenia
- Grade 4 neutropenia lasting >7 days
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura

Exceptions: AEs that met the above definitions but were clearly unrelated to study drug were not considered DLTs. In addition, other events which did not meet the definition of a DLT but were of concern to the Investigator and Sponsor may have been considered DLTs.

7.6. Duration of Treatment

7.6.1. Monotherapy Part

The Monotherapy Part for the S20-100 and S100-20 arms is expected to last approximately 2 weeks. Patients assigned to the MHI and SHI arms may continue to receive single-agent selinexor also after Day 14 until they experience PD as per RECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria (Section 8).

7.6.2. Combination Therapy Part

For patients with NSCLC, treatment in the Combination Therapy Part will continue until patients experience PD as per RECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment.

For patients with CRC receiving pembrolizumab, treatment in the Combination Therapy Part will continue until patients experience PD as per iRECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment. 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. Since some patients treated with immunotherapy may benefit from continued treatment despite meeting the radiological criteria for initial PD, if a patient has no clinical deterioration, initial PD or mixed response will be confirmed by repeat evaluation at the next tumor assessment. These CRC patients who have unconfirmed apparent progression may continue to receive treatment until progression is confirmed at the next imaging assessment. However, in the judgement of their Investigator, the following must apply:

- Be clinically stable and have no intolerable AEs
- Be likely to benefit from additional study treatment

For patients with CRC receiving FOLFIRI, treatment in the Combination Therapy Part will continue until patients experience PD as per RECIST 1.1 (as assessed by the Investigator) or meet any other discontinuation criteria, unless the Investigator determines that the patient is continuing to receive benefit from the study treatment.

7.7. Sponsor-supplied Study Drug Accountability

The Investigator or designee must maintain an accurate record of receipt of shipment and dispensing of Sponsor-supplied study treatment in a drug accountability log. Accountability for Sponsor-supplied study treatment will be documented throughout the study and reconciled. Patients will be asked to return all used and unused Sponsor-supplied study treatment and packaging on a regular basis, and at the end of the study or at the time of discontinuation of selinexor. All unused Sponsor-supplied study treatment must be destroyed with accompanied documentation as directed in the Pharmacy manual.

7.8. Study Treatment Compliance

The Investigator or other study staff will either directly administer or supervise study drug given in the clinic and instruct the patient on study drug self-administration at home, as appropriate.

Compliance to oral Sponsor-supplied study drug taken at home will be assessed by the Investigator and/or study personnel at each visit and recorded in source documents after discussion with the patient and after performing Sponsor-supplied study drug accountability.

The Investigator will account for the number of Sponsor-supplied tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF and drug accountability logs along with the reasons for subsequent verification.

7.9. Supportive Care, Concomitant Medications, and Restrictions

7.9.1. Supportive Care

Supportive measures for optimal medical care should be provided to all patients in this study. In addition to the required prophylactic therapy outlined below, 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.

7.9.1.1. Ondansetron

During the Monotherapy and Combination Parts, in order to minimize nausea, all patients should receive 5-HT₃ antagonists (ondansetron 8 mg or equivalent), unless contraindicated, during breakfast (i.e., 30 minutes prior to selinexor dosing in the Monotherapy Part) and continued every 8 hours (3 times a day)-3 times daily for 3 days after dosing (Mikhael 2020, Gavriatopoulou 2020). Among patients with severe hepatic impairment, do not exceed a total daily dose of 8 mg. Alternative antiemetic agents may be used if the patient does not tolerate or has inadequate antiemetic effect with 5-HT₃ antagonists (after discussion with the Sponsor's Medical Monitor during the Monotherapy Part).

7.9.1.2. Olanzapine

During the Combination Therapy Part, in addition to 5-HT₃ antagonist, all patients should receive olanzapine 2.5-5.0 mg PO daily at night, starting on C1D1 and continuing for the first 2 months of the study treatment and continue if needed based on the experience in the early myeloma studies (Mikhael 2020, Gavriatopoulou 2020).

7.9.1.3. NK1 Antagonists

NK1 antagonists (125 mg orally on D1, 80 mg orally on D2 and D3) will be added to 5-HT₃ antagonist and olanzapine in patients receiving selinexor in combination with FOLFIRI. If the patient does not tolerate olanzapine well, or needs another antiemetic, an NK1 antagonist can be used daily together with ondansetron for the first 2 months or longer as deemed necessary.

7.9.1.4. Combination Therapy Part

All patients receiving docetaxel should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. See docetaxel prescribing information for details.

Loperamide should be administered as a prophylactic or therapeutic measure for late diarrhea, which can occur more than 24 hours after administration of irinotecan (Arm C) and can be life threatening. Atropine may be administered as well as prophylactic or therapeutic measure for early diarrhea (usually transient and infrequently severe) and in patients experiencing other cholinergic symptoms, unless it is restricted due to tachycardia, glaucoma, pyloric obstruction, worsening urinary retention, or viscid bronchial plugs.

See pembrolizumab and FOLFIRI prescribing information for instructions concerning the need of other pre-medications.

7.9.2. Concomitant Medications and Procedures

Concomitant medications include any prescription or over-the-counter preparation, including vitamins, dietary supplements, 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 clinical findings, if applicable.

7.9.2.1. Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as part of standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed.

There are no restrictions on the use of acetaminophen or acetaminophen-containing products in combination with study drug, EXCEPT on days of study drug dosing, where acetaminophen must not exceed a total daily dose of 1 gram.

7.9.2.1.1. Use of Blood Products and Anti-Coagulants

Patients may receive supportive care with erythropoietin, darbepoetin, granulocyte-colony stimulating factor or granulocyte macrophage-colony stimulating factor, pegylated growth factors, and platelet stimulatory factors, at the discretion of the Investigator and in accordance with clinical practice or institutional guidelines, prior to entry and throughout the study.

The use of blood products, transfusions, etc. will be documented in the eCRF.

7.9.2.1.2. Glucocorticoid Therapy

Glucocorticoids ≤ 20 mg oral prednisone (or equivalent) per day, are permitted at Screening and during the study for nonmalignant conditions (e.g., asthma, nausea, irritable bowel disease), as needed.

Treatment with glucocorticoids should be avoided during the Monotherapy Part.

7.9.2.1.3. Radiation Treatment

If clinically indicated, palliative radiation therapy to non-target lesions is permitted. Study treatment should be held for 2 days before the start of palliative radiation therapy and 2 days after palliative radiation therapy. Treatment shall not be discontinued solely due to palliative radiation.

7.9.2.2. Prohibited 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's Medical Monitor. Prohibited concomitant medications for each part of the study are as follows:

Monotherapy Part: Strong cytochrome P450 3A (CYP3A) inhibitors or inducers are prohibited ≤ 3 days prior to PK sampling and throughout PK sampling. During the Monotherapy Part, if patients must receive any strong CYP3A inhibitors or inducers ≤ 3 days before the planned dosing, the planned PK/PDnRO blood sampling (Section 9.3) will be postponed to the following week (after 7 days [5 days minimum, 21 days maximum]), when dosing with the same formulation will be performed. Site personnel are required to notify the Sponsor within 24 hours after prescribing medications that are strong or moderate CYP3A inhibitors or inducers to patients during weeks when their PK sampling takes place. In addition, proton-pump inhibitors should be avoided on Day 1 of PK assessments. Acetaminophen should not exceed a total daily dose of 1 gram on dosing days of each week which PK will be collected.

Combination Therapy Part: Patients in Arm A should abstain from taking any strong CYP3A inhibitors while receiving docetaxel. If CYP3A administration cannot be avoided, see docetaxel prescribing information for dose adjustment recommendations. Patients in Arm B are prohibited from receiving live-attenuated vaccines. Patients in Arm C should abstain from taking any strong CYP3A inhibitors or inducers while receiving FOLFIRI. Refer to the full prescribing information for docetaxel, pembrolizumab, irinotecan, leucovorin, and fluorouracil (Arm C) for the most current information on prohibited concurrent medications.

A list of strong and moderate CYP3A inhibitors and inducers is provided in [Appendix 3](#).

7.9.3. Nutritional Consultation

Patients must be given documented nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This may 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 consultation, in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed, per local guidance.

7.9.4. Restrictions

7.9.4.1. Diet

Except for PK sampling days, there are no dietary restrictions during this study. During PK sampling days, standardized low-fat meals will be provided by the site. Grapefruit and Seville orange juice must be avoided. After a 10-hour overnight fast, the standardized low-fat meal should be started, 30 minutes prior to dosing, and the meal should be eaten within 30 minutes or less. Selinexor should be administered 30 minutes after start of the meal, with about 8 oz (240 mL) of water.

Patients are allowed to drink water as desired except for 1 hour before and 1 hour after dosing. Grapefruit and Seville orange juice must be avoided.

Additional food/meals allowed 4 hours after the selinexor dosing.

Throughout the study, patients on study drug should maintain adequate caloric and fluid intake.

8. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

8.1. Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, for any reason, 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:

- PD as defined by RECIST 1.1 or iRECIST criteria, as applicable (see exception in Section 7.6)
- Clinical progression as determined by the Investigator in consultation with the Sponsor's Medical Monitor
- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Any other medically appropriate reason or significant protocol violation, in the opinion of the Investigator
- Patient withdraws consent to continue study treatment. For information regarding from which part of the study the patient withdraws consent should be documented and recorded in the eCRF (i.e., if a patient only withdraws consent only to study treatment but agrees to complete the safety and survival follow-up per protocol, or a patient withdraws consent to all study procedures).
- Pregnancy

Patients who discontinue study treatment for any reason (e.g., AE, PD, personal or Investigator decision) should be encouraged to continue in the study, so follow-up information on PD and survival status may be collected. If the patient is receiving clinical benefit despite PD and it is in the best interest of the patient, per the treating physician, the patient may remain on therapy.

Patients may withdraw consent and decline further participation in the study at any time. Patients who withdraw consent must be withdrawn from the study. Withdrawal of consent will be documented and recorded in the eCRF.

8.2. 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 required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and explain to the patient the importance of maintaining the assigned visit schedule and ascertain whether 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 documented telephone calls 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 be lost to follow-up, and this will be documented in the patient medical record.

8.3. 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 the Institutional Ethics Committees (IECs), Institutional Review Boards (IRBs) Investigators, and Regulatory Authorities.

The Sponsor will work with the Investigators at the sites to ensure that any patients receiving study drug at the time of early termination of the study will be informed of the alternative treatment options available for them.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the 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 (including the Combination Therapy Reassessment 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.

9.1. 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 12.3). 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.

9.2. Baseline Assessments

9.2.1. Demographics

Patient demographics (including gender, race, ethnicity, and age at the time of consent) will be collected, as allowed by local regulations.

9.2.2. Medical History

The medical history will include medical conditions or symptoms experienced during the previous 30 days as well as those ongoing at the time of Screening, any medical conditions that require medication, including the start date of all current medical history/conditions by at least the month/year.

A complete ophthalmic history and smoking history will be obtained and documented.

A detailed history of prior anti-cancer procedures/therapies for the disease under study (e.g., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, or surgery), including start and end dates, best response, PD during or after therapy, as well as discontinuations due to intolerability or toxicity. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cancer molecular profiling, including but not limited to KRAS mutation, EGFR mutation, anaplastic lymphoma kinase (ALK) fusion protein, PD-L1 expression level, dMMR and microsatellite stability status) will also be collected. Data from standard-of-care procedures will be part of the patient's medical history and may be used for study purposes.

For the purpose of previous lines of systemic therapy documentation please use the following definitions:

Definitive chemoradiotherapy followed by adjuvant therapy (such as adjuvant durvalumab for the treatment of NSCLC) would be counted as one line of systemic therapy.

Treatment with chemotherapy combined with an anti-PD-1/L1 mAb followed by maintenance anti-PD-1/L1 mAb would be considered one line of systemic therapy.

Adjuvant therapy, neoadjuvant therapy, or maintenance therapy alone will not be counted as one line of systemic therapy. Adjuvant/neoadjuvant chemotherapy should be documented even if not considered a line of therapy.

9.2.3. Hepatic Impairment Assessment

Patient's assignment to either MHI or SHI arms, will be based on patient's degree of hepatic impairment. The assessment of hepatic function will be done according to NCI organ dysfunction working group (NCI-ODWG) criteria:

- Normal hepatic function: Total bilirubin and AST $\leq$ ULN
- Mild hepatic impairment: Total bilirubin $>$ ULN to $1.5 \times$ ULN or AST $>$ ULN
- Moderate hepatic impairment (MHI): Total bilirubin $>1.5-3 \times$ ULN, any level of AST
- Severe hepatic impairment (SHI): Total bilirubin $>3 - 10 \times$ ULN, any level of AST

9.3. Pharmacokinetic and Pharmacodynamic Receptor Occupancy Assessments

Blood samples of approximately 2 mL and 10 mL will be collected for measurement of plasma concentrations of selinexor (PK) and XPO1 receptor occupancy (PDnRO), respectively, at the time points listed in Table 9 and Table 10. PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor. Additional blood samples of approximately 5 mL will be collected from all patients at 3 hours and 8 hours post selinexor dose (Day 1 and Day 8 for S20-100 and S100-20 Arms, and Day 1 for MHI/SHI Arms) for the purpose of conducting protein binding assessments. Instructions for the collection and handling of biological samples are provided in the Laboratory Manual. The actual date and time (24-hour clock time) each sample is collected and selinexor is dosed will be recorded.

Table 9: PK and PDn Receptor Occupancy Blood Sampling Time Points for Patients with Normal Hepatic Function (S20-100 and S100-20 Arms)

Time Point	PK (Days 1-3, 8-10) 2 mL	PK [Protein Binding] (Day 1 or 8) ^a 5 mL	PDnRO (Days 1-3) 10 mL	PDnRO (Day 8) 10 mL
Initiate low-fat meal 30 min prior to dosing (meal should be completed prior to dosing) ^b				
Pre-dose (≤ 10 min prior to dosing for PK/PDnRO samples)	X		X	X
0 min (30 min after start of meal)	Administration of selinexor ^c			
15 min (± 5 min)	X			
30 min (± 5 min)	X			
1 hr (± 5 min)	X			
1.5 hr (± 5 min)	X			
2 hr (± 10 min)	X		X	
3 hr (± 10 min)	X	X		

Time Point	PK (Days 1-3, 8-10) 2 mL	PK [Protein Binding] (Day 1 or 8)^a 5 mL	PDnRO (Days 1-3) 10 mL	PDnRO (Day 8) 10 mL
4 hr (± 10 min)	X		X	X
5 hr (± 10 min)	X			
6 hr (± 10 min)	X			
8 hr (± 20 min)	X	X	X	X
10 hr (± 20 min; optional)	X			
24 hr (± 1 hr)	X		X	
30 hr (± 1 hr)	X		X	
48 hr (± 2 hr)	X		X	

^a Blood samples for protein binding assessments will be collected from patients at 3 hours (±10 min) and 8 (±20 min) hours after the administration of Tablet A (i.e., 5 × 20 mg) Tablet B (1 × 100 mg) during Days 1 and 8 in the S20-100 and S100-20 arms, respectively.

^b Patients should finish the meal in 30 minutes or less.

^c Administration of selinexor will be performed 30 minutes after initiating the standardized low-fat meal.

Table 10: PK and PDn Receptor Occupancy Blood Sampling Time Points for Patients with Hepatic Impairment (MHI and SHI Arms)

Time Point	PK (Days 1-3) 2 mL	PK [Protein Binding] (Day 1) 5 mL	PDnRO (Days 1-3) 10 mL	PDnRO (Day 8) 10 mL
Initiate low-fat meal 30 min prior to dosing (meal should be completed prior to dosing) ^a				
Pre-dose (≤10 min prior to dosing for PK samples)	X		X	X
0 min (30 min after start of meal)	Administration of selinexor ^b			
15 min (± 5 min)	X			
30 min (± 5 min)	X			
1 hr (± 5 min)	X			
1.5 hr (± 5 min)	X			
2 hr (± 10 min)	X		X	
3 hr (± 10 min)	X	X		
4 hr (± 10 min)	X		X	
5 hr (± 10 min)	X			
6 hr (± 10 min)	X			

Time Point	PK (Days 1-3) 2 mL	PK [Protein Binding] (Day 1) 5 mL	PDnRO (Days 1-3) 10 mL	PDnRO (Day 8) 10 mL
8 hr (± 20 min)	X	X	X	
10 hr (± 20 min; optional)	X			
24 hr (± 1 hr)	X		X	
30 hr (± 1 hr)	X		X	
48 hr (± 2 hr)	X		X	

^a Blood samples for protein binding assessments will be collected from patients at 3 hours and 8 hours after the administration of selinexor during Day 1 only.

^b Patients should finish the meal in 30 minutes or less.

^c Administration of selinexor will be performed 30 minutes after initiating the standardized low-fat meal

If any PK sampling timepoints are missed, the site must notify the Sponsor within 24 hours. More broadly, the Sponsor must be notified of any event leading to the collection of insufficient PK samples (as described below) within 48 hours.

If ≥ 3 blood samples are not drawn for a patient within 1 PK assessment (for D1-D3 or D8-D10), the patient will repeat the same formulation 7 days (5 days minimum, 21 days maximum) later and the PK/PDnRO all samples for that formulation, will be collected. The all subsequent planned doses during the Monotherapy Part will be postponed accordingly. The Sponsor's PK scientist will evaluate and decide whether PK/PDnRO blood sampling must be repeated, and additional week of dosing with the same formulation is required. In any case, selinexor doses need to be 7 days apart (5 days minimum, 21 days maximum).

If a patient must receive a strong inhibitor or strong inducer of CYP3A ≤ 3 days of dosing in which PK samples will be collected, then selinexor will be administered as planned but no samples for PK/PDnRO will be collected. In such cases, selinexor administration and PK/PDn blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum) as described above.

If a patient experiences emesis during the first 6 hours of dosing, no further PK/PDnRO blood samples will be collected. In such a case, an additional dose, of similar formulation, will be administered after 7 days (5 days minimum, 21 days maximum), and blood samples will be collected as described above. For additional instructions regarding vomited doses see Section 7.4.2.

Plasma samples will be analyzed via a validated HPLC/MS-MS method for plasma selinexor concentration.

Plasma PK samples will be shipped to a bioanalytical laboratory for analysis. Details for collection and processing of PK/PDnRO blood samples can be found in the Laboratory Manual.

Plasma samples will be analyzed via a validated HPLC/MS-MS method for plasma selinexor concentration.

9.3.1. Patients with Hepatic Impairment

For patients with hepatic impairment (MHI and SHI arms), dose escalation can only occur once per cycle (up to a dose of 80 mg), after analysis of the patient's tolerability and PK data and after documented approval from the Sponsor is received.

The PK parameters of total selinexor total and free-drug concentration will be assessed ([Table 11](#)).

Table 11: PK Parameters of Total Selinexor and Free Drug Concentration

PK Parameter	Definition
λ_z	Terminal elimination rate constant
AUC_{0-t}	area under the concentration-time curve from time zero to the last non-zero concentration
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-last} + C_t/k_{el}$, where: C_t = the last observed nonzero concentration
AUC_u	free-drug area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $(AUC_{0-last} + C_t/k_{el}) * f_u$, where: C_t = the last observed nonzero concentration
% extrapolated AUC	proportion of AUC_{0-inf} based on extrapolated results, calculated as $C_t/k_{el}/AUC_{0-inf} * 100$
C_{max}	maximum observed concentration, taken directly from the plasma concentration data
$C_{max,u}$	maximum observed free-drug concentration, calculated as $C_{max} * f_u$
F_u	fraction of unbound drug
T_{max}	time of first observation of C_{max} , taken directly from the plasma concentration data
$t_{1/2}$	elimination half-life, calculated as $\ln(2)/k_{el}$
CL/F	apparent clearance
CL_R/F	apparent renal clearance
CL_u/F	apparent free-drug clearance
V_d/F	apparent volume of distribution, calculated as $Dose / (k_{el} * AUC_{0-inf})$, uncorrected for fraction absorbed; reported normalized by patient body weight (kg)
V_u/F	apparent free-drug volume of distribution

9.4. Safety Assessments

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

9.4.1. Physical Examinations

Full physical examinations will be performed prior to receiving first dose of study drug and at the EOMT Visit. All other physical examinations during the study should be limited, symptom-directed physical examinations, including body systems as appropriate. The physical examination can be conducted on or 1 day prior to the Monotherapy Part D1.

Height will be measured without shoes and in centimeters at Screening. Weight will be measured with indoor clothing and without shoes in kilograms. Body surface area will also be measured as indicated in the SOA.

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 D1 dosing 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 and entered into the AE eCRF.

9.4.2. Vital Signs

Vital signs will include systolic and diastolic blood pressure (BP), pulse measurements, and body temperature (°C or °F). Assessments will be performed as indicated in the SOA.

9.4.3. ECOG Performance Status

The ECOG performance status assessment ([Appendix 2](#)) will be performed as indicated in the SOA. Results from prior testing of KRAS status is required for patients with CRC. To be collected for patients with NSCLC, if available.

9.4.4. Electrocardiogram (ECG)

Standard 12-lead electrocardiogram (ECG) will be performed at Screening, and as clinically indicated during the study.

Patients must rest for at least 5 minutes prior to any ECG recording. The Investigator will interpret the ECG using 1 of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant.

The time of performing ECG and following parameters will be recorded in the eCRF: heart rate, PR interval, QRS interval, QT interval, and QT corrected using Fridericia's formula.

9.4.5. Clinical Safety Laboratory Assessments

Clinical laboratory tests ([Table 12](#)) will be performed by the sites' local laboratories. In addition, laboratory tests will be collected and analyzed at times specified on the SOA. More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion and these should be recorded on the eCRF.

Table 12: Clinical Safety Laboratory Tests

Hematology (Blood sample: whole blood; EDTA tests)				
Hemoglobin	Hematocrit	WBC count	Lymphocytes ^a	Neutrophils ^a
Platelets	Reticulocytes ^a			
Serum Chemistry (Blood sample: Serum)				
Glucose	Calcium	BUN/urea	Creatinine	Sodium
Potassium	Albumin	Alkaline phosphatase	Total bilirubin ^b	Total protein
AST	ALT	LDH ^c		
Coagulation Test (Blood sample: whole blood) – Hepatic impairment arms only				
Prothrombin time	International normalization ratio	Activated thromboplastin time		

ALT: alanine transaminase; AST: aspartate transaminase; BUN: blood urea nitrogen; EDTA: ethylenediaminetetraacetic acid; LDH: lactate dehydrogenase; WBC: white blood cell.

^a Absolute counts will be collected, not percent values.

^b If the total bilirubin concentration is increased $>1.5 \times \text{ULN}$, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

^c Per Investigator's discretion.

The Investigator or designee will review the laboratory report after receipt of the results and assess and document 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, manifest clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be documented in the eCRF.

The clinical significance will be documented on the laboratory report 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 End of Treatment (EOT) visit that is considered clinically significant will be followed according to accepted medical standards for up to 30 days following EOT visit (30-day Safety Visit) or until resolution of the abnormality or return to baseline levels. Toxicity will be assessed using the NCI CTCAE, v. 5.0.

Estimated creatinine clearance is calculated using the Cockcroft-Gault formula:

- $(140 - \text{age}) \times \text{body weight (kg)} / (72 \times \text{creatinine [mg/dL]}) \times (0.85 \text{ if the patient is female})$

9.4.6. Adverse Events and Serious Adverse Events

Detailed information related to the collection and reporting of AEs and SAEs is in Section 10.

9.4.6.1. Pregnancy Testing

Childbearing potential status of female patients will be documented in the patient medical file by the study staff. Female patients of childbearing potential will be informed as to the potential risks of conception while participating in this study

Pregnancy testing will be performed only for females of childbearing potential. A negative serum hCG pregnancy test must be obtained at Screening (within 3 days before selinexor administration) and throughout the study as indicated in the SOA. Pregnancy testing may be performed as needed, if clinically indicated during the study.

Female patients of childbearing potential in the Monotherapy Part must use highly effective methods of contraception throughout the study and for 30 days following the last dose of study drug. Female patients of childbearing potential in the Combination Therapy Part must use highly effective methods of contraception throughout the study and for 4 months following the last dose of study drug.

9.5. Anti-tumor Activity Assessments

CT or MRI scans will be performed at the time points specified in the SOA. Computed tomography scans with contrast are preferred. The method used at Screening for a given patient should be used consistently throughout the study for that patient. CT scans with contrast are preferred.

Baseline tumor assessment will be performed during Screening. As the Monotherapy Part is as short as 2 weeks, no additional tumor assessments will be performed during this period.

For patients in the S20-100 and S100-20 arms that continue to the Combination Therapy Part, anti-tumor activity will be assessed at the time points specified in the SOA and will continue for up to 1 year after the 30-day Safety Visit, if applicable.

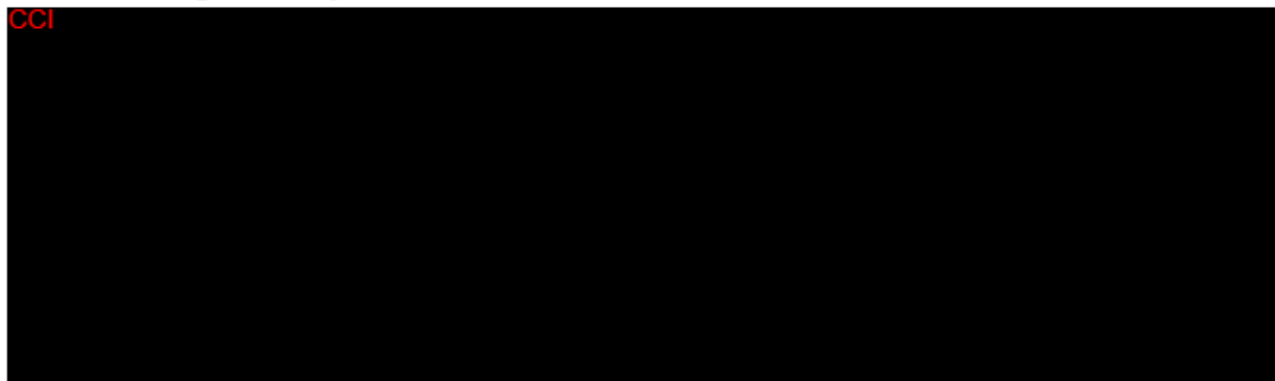
For patients in the MHI or SHI arms, anti-tumor activity will be assessed at the time points specified in the SOA and will continue for up to 1 year after the 30-day Safety Visit, if applicable.

As part of the medical history documentation, every effort should be made to obtain the latest historic scans available (preferably CT), and to use them to perform lesion identification, characterization and measurement. This historic information will be reported in the EDC disease assessment table as the pre-baseline timepoint.

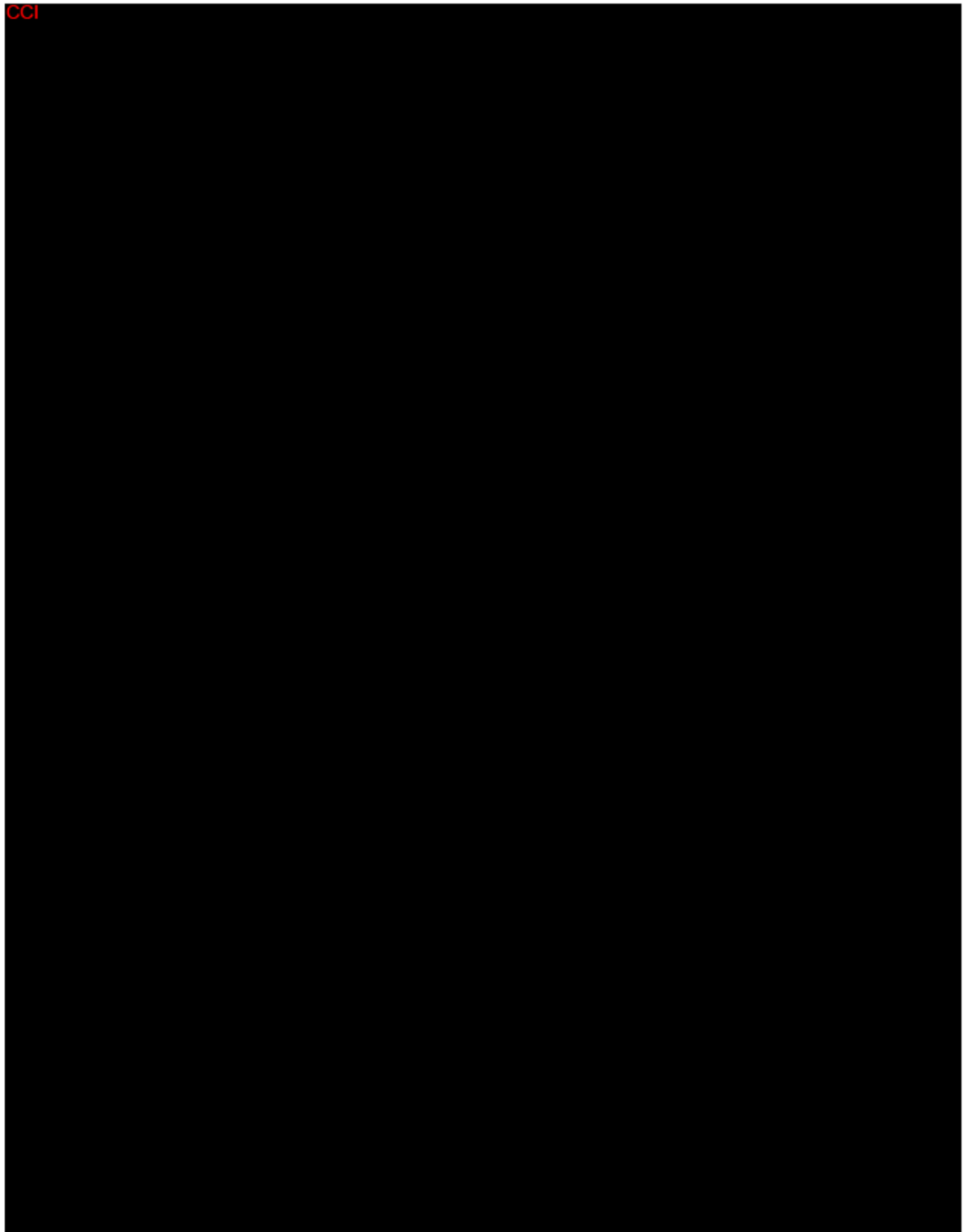
Response assessment will be determined per RECIST 1.1 for the monotherapy treatment arms and combination Arms A, B, and C ([Appendix 1](#)), and per iRECIST for combination Arm B ([Appendix 4](#)) at the time points specified.

9.6. Exploratory Assessments

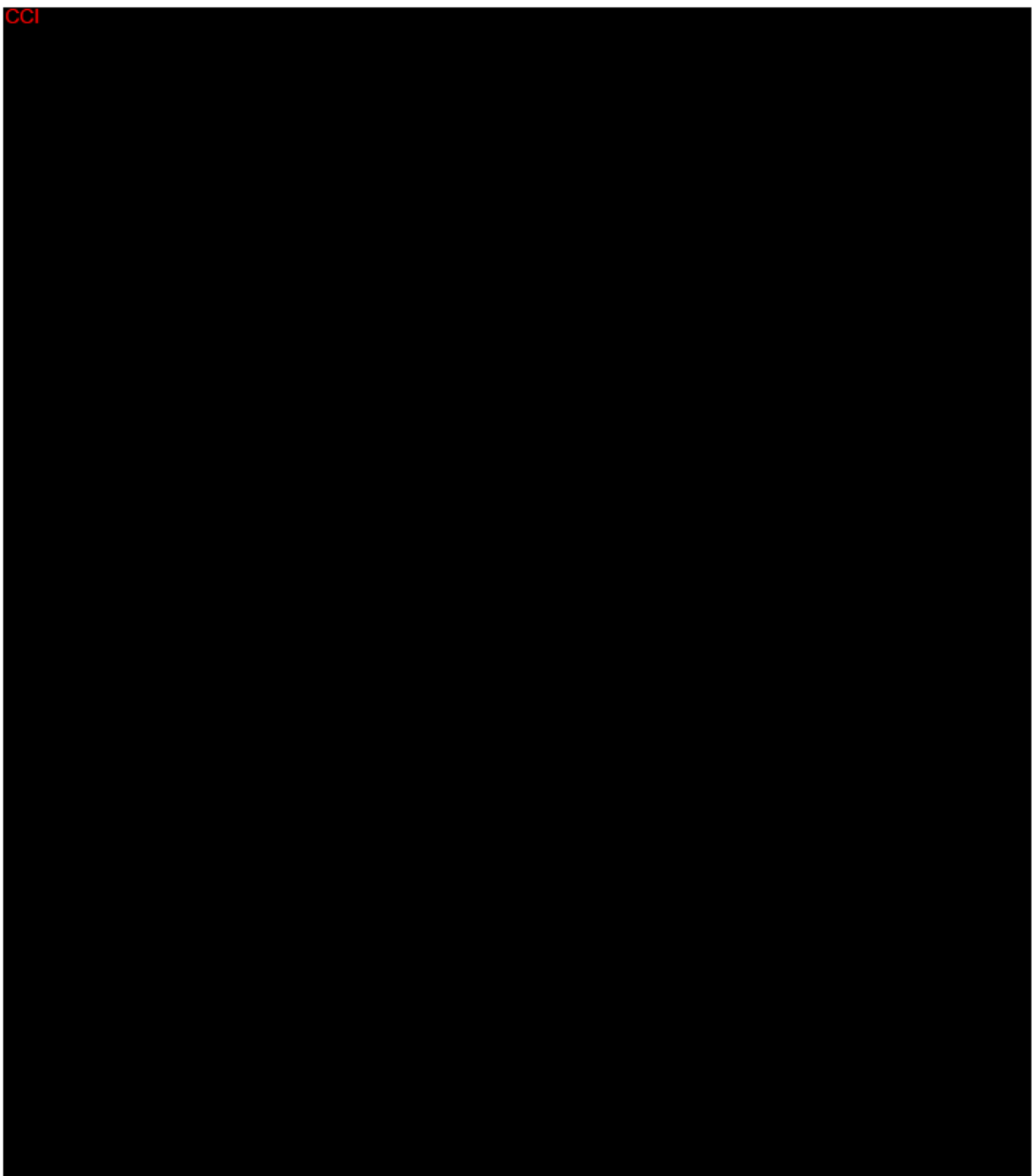
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9.7. Post-treatment Assessments

See the SOA for more information on the tests to be performed at each of the following timepoints.

9.7.1. End of Treatment

For the S20-100 and S100-20 arms:

- For the Monotherapy Part, the EOMT visit takes place on D15 ($\pm 1D$) of the Monotherapy Part, unless supplement PK sample collection is required and then the Monotherapy Part will continue for a third week, having the EOMT at D22 ($\pm 1D$).
- For the Combination Therapy Part, the EOT visit takes place ≤ 6 days after the last dose of study drug or the date at which the decision was made to discontinue treatment. In the case of dose interruption, EOT could be as long as 28 days after the last dose of study drug.

For the MHI and SHI arms:

- The EOT visit takes place ≤ 6 days after the last dose of study drug or the date at which the decision was made to discontinue treatment. In the case of dose interruption, the EOT visit could be as long as 28 days after the last dose of study drug.

9.7.2. 30-day Safety Visit

The 30-day Safety Visit takes place 30 days ($\pm 4D$) after the last dose of study drug. If the EOT visit is delayed due to a dose interruption before discontinuation, the 30-day Safety Visit may be performed together with the EOT visit, if both visits fall within 26-34 days following study drug discontinuation.

9.7.3. Response and Survival Follow-up

Follow-up will continue for 1 year after the 30-day Safety Visit. For patients who discontinued due to PD, follow-up will be limited to survival follow-up.

10. ADVERSE EVENTS

10.1. Reporting of Adverse Events

10.1.1. 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.
- *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 10.2.3 for additional information about SAE reporting.)

- *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.
- *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 but are not specifically mentioned as occurring with the particular drug under investigation

See Section 10.2.3 for additional information about SAE reporting.

10.1.2. Recording of Adverse Events

AEs must be recorded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 5.0), where possible, and include the start and end date, severity (grade), the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.

All AEs that begin or worsen after first dosing, will be recorded as AEs. Any AEs which were experienced prior to dosing will be added to the patient's medical history and recorded as such.

All SAEs will be reported once the ICF is signed.

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

AEs (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. AEs will also be recorded when they are volunteered by the patient, or through physical examinations, laboratory tests, or other clinical assessments.

10.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment and thus considered to be clinically significant), should be documented and recorded as AEs. 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 an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, the laboratory test abnormal result should not be recorded as a separate additional event.

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.

10.1.3. 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>).

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 10.1 and/or as per the opinion of the Investigator.

10.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment (for each study drug), 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 making a definitive or reasonably possible relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

10.2. Serious Adverse Events

See Section 10.1 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).

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

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g., an overnight stay for social reasons) or other medical procedures, 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 in which case it must be documented as an SAE.

Progression of the malignancy/disease (including fatal outcomes), events that are clearly consistent with the expected pattern of progression of the underlying disease, should NOT be reported as an SAE throughout the study (Section 10.2.3). Any sudden and 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.

10.2.2. 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, completed query forms and follow-up reports, 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) for key data elements that are required for expedited reporting.

10.2.3. 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 Department within 24 hours of learning of its occurrence, by completing the study 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) or +49-89-9218-5650 (Germany)

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm Pharmacovigilance Department if the Investigator suspects that the SAE has a causal relationship to the study treatment. 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.

The Investigator will be responsible for notifying his/her IRB/ IEC of all SAEs, if applicable per local regulatory requirements.

10.2.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

All SUSARs 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 local regulatory requirements.

10.3. Procedures for Handling Special Situations

10.3.1. Pregnancy and Breastfeeding

Note: Pregnancy is not considered to be an AE; however, it is important to follow-up and report pregnancies that occur during studies. A medical untoward 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).

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 patient or female patient's partner
- Sexual abstinence

A serum pregnancy test will be performed on each female patient of childbearing potential ≤ 3 days before the first dose of study drug, on D1 of every cycle while on treatment, and again at EOT visit. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The Investigator must immediately notify the Sponsor's Medical Monitor of the event and record the pregnancy on the study Pregnancy Form. The initial information regarding a pregnancy must be forwarded to Karyopharm Pharmacovigilance Department by email or fax within 24 hours of first knowledge of its occurrence (for contact information refer to Section 10.2.3).

The pregnancy should be followed up to determine the outcome, including any spontaneous or voluntary termination, details of the birth, and, if relevant, any birth defects, congenital abnormalities, or maternal and/or newborn complications. A formal consent for collecting information regarding the pregnancy outcomes should be obtained from the patient (or patient's female partner).

All pregnancies occurring within 30 days after the patient's last dose of study drug must be reported to Karyopharm Pharmacovigilance Department, 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 (including pregnancy of patient's partner).

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 10.2.3).

A pregnancy in a female partner of a male patient must be reported to Karyopharm Pharmacovigilance Department within 24 hours of learning of its occurrence (as described in Section 10.2.3). A formal consent to collect 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.

10.3.2. 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 on an SAE report form and emailed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE.

10.3.2.1. 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 then Sponsor 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 Department at pharmacovigilance@karyopharm.com, 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.

10.3.2.2. 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.

Misuse is situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

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 at pharmacovigilance@karyopharm.com, within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible.

10.3.2.3. Occupational Exposure

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

All occurrences of occupational exposure with any study treatment are to be recorded on an SAE report form and sent to Karyopharm Pharmacovigilance at pharmacovigilance@karyopharm.com, 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 as soon as possible.

11. 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 final report.

11.1. General Considerations

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters.

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, as well as 2-sided 95% confidence intervals (CIs), unless otherwise stated.

For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

11.1.1. Procedures for Handling Missing Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the clinical study report (CSR).

For AEs, missing data will be imputed per the rules outlined in the SAP.

For HI analyses, missing data will be dealt with per rules in SAP.

11.2. Statistical Hypotheses

For the Monotherapy Part, hypothesis testing will be used for relative bioavailability analysis and the exploratory objective of bioequivalence following FDA's guidelines. No formal hypothesis testing will be used for other study data, such as demographics and safety data.

11.3. Sample Size Determination

A total of 20 patients with either NSCLC or CRC with normal hepatic function will be enrolled and randomized with a 1:1 ratio to the S100-20 and S20-100 arms to evaluate the relative bioavailability of the new 100-mg tablet formulation (Tablet B) relative to the current 5×20 mg tablet formulation (Tablet A). Evaluation of these data will also serve as a pilot BE study (BE of Tablet B with Tablet A as the reference) to inform the feasibility and design of a future BE study. Moreover, these 20 patients with normal hepatic function will serve as the reference group for the evaluation of patients with hepatic impairment in the MHI and SHI arms.

The sample size for the hepatic impairment arms are 6 for the severe (SHI) and 8 for the moderate (MHI) hepatic impairment arms.

Combination Arm A enroll approximately 40 patients, Arm B will enroll approximately 40 patients, and Arm C will enroll up to 26 patients to assess the tolerability, safety, and anti-tumor activity of that arm.

Safety data in Arm C will be evaluated upon completion of the first cycles for the first 6 patients enrolled in Cohort 1 and 6 patients in Cohort 2. Based on these results, recruitment will continue on the selected cohort.

11.4. Populations for Analyses

11.4.1. PK Analysis Population

All patients in the Monotherapy Part who receive at least 1 dose of selinexor and have at least 1 post-dose PK measurement without important protocol deviations/violations or events thought to significantly affect the PK of selinexor (e.g., vomited at or before 6 hours; wrong dose administered; prohibited concomitant medication; etc.; see Section 9.3). The PK scientist and study statistician will evaluate the strategy for dealing with data affected by protocol deviations or events before any formal statistical analysis is performed.

11.4.2. Safety Population

All patients who received at least 1 dose of study treatment in monotherapy or combination therapy periods.

11.4.3. Modified Intent-to-Treat Population in the monotherapy period (mITT mono)

All patients who received at least 1 dose of selinexor in the monotherapy period in S100-20 or S20-100 arms. SHI and MHI patients are not included.

11.4.4. Modified Intent-to-Treat Population in the combination therapy period (mITT combo)

All patients who received at least 1 dose of selinexor in the combination therapy period. All arms in the combo period (A, B, C1, C2) are included.

11.5. Statistical Analyses

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

11.5.1. Relative Bioavailability and Bioequivalence Analyses

Bioequivalence analyses will be performed on the PK Population following FDA's guidance "Statistical Approaches to Establishing Bioequivalence." Standard noncompartmental PK parameters will be calculated based on plasma concentration data for selinexor from individual patients.

11.5.2. Safety Analyses

All safety analyses will be performed using the Safety Population. 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 NCI CTCAE, v.5.0. Investigators will provide their assessment on causality (i.e., whether the AE is related or not related to selinexor). Treatment-emergent AEs, serious adverse events (SAEs), AEs of at least Grade 3 in severity, AEs related to selinexor, and AEs leading to withdrawal of treatment will be summarized 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.

Analysis of AEs, laboratory data, and vital signs will be outlined in the SAP.

11.5.3. Efficacy Analyses

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, as well as 2-sided 95% CIs, unless otherwise stated.

For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented.

11.5.4. Hepatic Impairment Analyses

For the analyses of the hepatic impairment arms, descriptive demographic statistics will be provided for each hepatic function group. Regression modeling will be performed for comparison among hepatic function groups and association between hepatic function groups and PK parameters. Pharmacokinetic parameters will be the dependent variable and age, gender, race, and baseline body weight may be included as covariates. Estimates of the mean difference between hepatic function groups and corresponding 95% confidence intervals (CIs) will be calculated.

11.5.5. Exploratory Analyses

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12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1. Ethical and Administrative Obligations

12.1.1. Regulatory and Ethical Considerations

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization (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 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 all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Sponsor monitors, auditors, designated agents of Sponsor, 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, which will be submitted and approved retrospectively.

12.1.2. 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 and per local regulatory requirements
- Notifying the IRB/IEC of SUSARs or other significant safety findings as required per local regulatory requirements
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, 21 CFR and European regulation 536/2014 for clinical studies (as applicable), and all other applicable local regulatory requirements

12.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information 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 at the beginning of the study, at the time of study closure, and for 1 year after completion of the study.

12.3. Informed Consent Process

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/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 and the form signed, will be captured in the patient's CRFs.

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

Females of childbearing potential and male patients with childbearing potential partners will 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 as per inclusion criteria. 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.
- 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 process and date of obtaining the patient's informed consent must be documented in the patient's source documents. 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 during their participation in the study, as long as the changes made include safety information or other information relevant to the patient and/or may affect the patient's consent to continue participating in the study.
- A copy of the ICF must be provided to the patient or the patient's legally authorized representative, and the originally signed document must be filed at the site.

The ICF will contain a separate section that addresses the use of remaining mandatory and optional samples for CCI. Patients will be made aware that they are free to refuse to participate in this CCI study and may withdraw their consent at any time and for any reason at any time.

12.4. Data Collection and Management

12.4.1. Data Confidentiality

The Investigator must ensure anonymity of the patients. Each patient will be assigned a unique identifier. Originally 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 the Sponsor 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, where applicable, 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.

12.4.2. Data Collection

Data collection is the responsibility of the clinical study staff at the site, under the supervision of the Investigator. 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 study eCRF is the primary data collection instrument for the study. 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 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.

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

12.4.3. Site Monitoring

Before study initiation, Sponsor personnel (or designee) 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 eCRFs, adherence to the protocol and to ICH GCP, progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to Sponsor 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 eCRFs must be traceable to source documents in the patient's file.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries.

Monitoring will be performed according to the standard and processes described in the study-specific monitoring plan.

12.4.4. Database Management and Quality Control

Sponsor personnel (or designee) will review the eCRF data entered by site 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 locked and signed-off by the Investigator.

For EDC studies, after database lock, the Investigator will receive PDFs of patient data on electronic media for archiving at the investigational site.

12.5. 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 ClinTrials.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.

12.6. Source Documents

Each participating site will maintain appropriate medical and research records for this study (i.e., source documents), in compliance with Section 4.9 of the ICH E6 GCP, local 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 as initially recorded, including 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 ICH GCP - 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 Sponsor 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.

12.7. 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 and database lock. A study site will be considered closed when all required documents and study supplies have been collected, the Trial Master File has been audited and considered complete for the study site, the database is locked or all site eCRFs are signed/locked 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 intervention development

12.8. 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.

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14. APPENDICES

APPENDIX 1. RECIST 1.1

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 <10 mm.

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 PD.

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.

Table 14: 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
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.

Table 15: 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
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.

Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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.

Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

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. 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](#).

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: 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. IRECIST: GUIDELINES FOR RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS

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 pseudo-progression. 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 (i.e., the date of iUPD) provided that iCPD is confirmed at the next assessment or patient discontinued treatment due to disease progression following the iUPD 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 16](#): Comparison of RECIST 1.1 and iRECIST illustrates comparisons between RECIST 1.1 and iRECIST, and [Table 17](#) provides guidance for assigning timepoint response without or with previous iUPD.

Table 16: 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.		

Table 17: 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. ^a Previously identified in assessment immediately before this timepoint.		