CLINICAL STUDY PROTOCOL

XPORT-CRC-041 (SeRAS)

A Phase 2 Open-Label Multicenter Study to Evaluate the Safety and Efficacy of Selinexor with or without Pembrolizumab versus Standard of Care in Previously treated Metastatic Colorectal Cancer with RAS mutations

Study Number:	XPORT-CRC-041
Study Phase:	Phase 2
Investigational Product:	Selinexor (KPT-330)
IND Number:	CCI [redacted]
Indication:	Previously treated metastatic colorectal cancer with RAS mutation type
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. +1 (617) 658-0600
Protocol Date and Version:	20 April 2021, Version 1.0 26 May 2021, Version 2.0

CONDUCT

In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL APPROVAL SIGNATURE PAGE

I have read and understand the contents of this clinical protocol for Study XPORT-CRC-041 dated 26 May 2021 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPD

PPD **PhD** **Date**

PPD

Karyopharm Therapeutics Inc.

PPD

PPD **, MD** **Date**

PPD

Karyopharm Therapeutics Inc.

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study XPORT-CRC-041 dated 26 May 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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CCI [redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
ARC	absolute reticulocyte count
AST	aspartate transaminase
AUC	area under the concentration-time curve
BID	twice daily
BIW	biweekly
BOR	best overall response
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C	cycle
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
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
DLBCL	diffuse large B-cell lymphoma
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response

Abbreviation	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
EORTC-QLQ-C30	The European Organization for Research and Treatment of Cancer quality of life questionnaire
EOT	end of treatment
FCSI	Functional Assessment of Cancer Therapy Colorectal Cancer Symptom Index
FDA	Food and Drug Administration
5-FU	fluorouracil
GCP	Good Clinical Practice
Hb	hemoglobin
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IkBα	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
ITT	intent to treat
IO	immunotherapy
IRB	Institutional Review Board
IV	intravenous(ly)
KRAS	Kirsten rat sarcoma
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
min	minute

Abbreviation	Definition
mL	milliliter
MM	multiple myeloma
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NA	not applicable
NCCN	National Comprehensive Cancer Network®
NCI	National Cancer Institute
NFkB	nuclear factor kappa B
NK1	Neurokinin-1
NRAS	neuroblastoma rat sarcoma
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
CCI [redacted]	
PFS	progression-free survival
PHI	protected health information
PO	orally
PR	partial response
QoL	quality of life
QW	once weekly
RAS	rat sarcoma
REB	research ethics board
RECIST	Response Evaluation Criteria in Solid Tumors
CCI [redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SI	International System of Units

Abbreviation	Definition
SINE	selective inhibitor of nuclear export
SOA	schedule of assessments
SOC	standard of care
TEAE	treatment-emergent adverse event
TSP	tumor suppressor protein
ULN	upper limit of normal
US	United States
WBC	white blood cell
WT	wild type
XPO1	exportin 1

1. PROTOCOL SUMMARY

Sponsor:	**Investigational Product:**	**Study Phase:**
Karyopharm Therapeutics Inc.	Selinexor (KPT-330)	Phase 2

Title of Study: A phase 2 open-label multicenter study to evaluate the safety and efficacy of **se**linexor with or without pembrolizumab versus standard of care in previously treated metastatic colorectal cancer with **RAS** mutations (SeRAS).

Protocol Number: XPORT-CRC-041

Study Location:

Approximately 10-15 US sites in a multicenter study

Study Rationale:

In the US, colorectal cancer is the third leading cause of cancer-related deaths in men and in women, and the second most common cause of cancer deaths when men and women are combined (ACS 2020). More than 1.9 million new cases were diagnosed in 2020. Approximately 20% of new colorectal cancer patients have metastatic disease at the time of diagnosis. Another 20% of patients progress to have metastatic colorectal cancer (mCRC) and have a significant lower survival rate (Li 2020). Patients with advanced or mCRC are typically treated with 5-FU and oxaliplatin or irinotecan-based regimens in first- and second-line disease management. Despite initial response rates around 60% with first line chemotherapy, mCRC remains incurable, with recurrence after 8-12 months and overall survival of approximately 30 months (Saltz 2008; Douillard 2010; Loupakis 2014; van Cutsem 2011; Venook 2017). Second line chemotherapy in recurrent mCRC yields considerably less efficacy with response rates of 5-36%, progression-free survival (PFS) of 5-7 months, and overall survival (OS) of 11-14 months (Giantonio 2007; Bennouna 2013; Sobrero 2008; Peeters 2014).

Mutations in RAS proteins (KRAS, NRAS, HRAS) occur in between 33-69% of patients with CRC (Prior 2020; Tate 2019; Sanchez-Vega 2018; Serebriiskii 2019). The presence of oncogenic *RAS* alterations leads to poor response from conventional treatments and poor clinical outcomes. While options for the third line therapy of mCRC are very limited, patients who have *RAS*-mutated CRC lack effective therapies and are treated with agents that demonstrate only modest survival gains. Currently regorafenib (Stivarga®) and combination treatment of trifluridine and tipiracil (Lonsurf®) are the only third and later line treatments for patients with mCRC including those with RAS mutations. However, patients with KRAS mutant tumors had shorter median overall survival (OS) in the CORRECT and RECOURSE studies (Tabernero 2015; Van Cutsem 2018). Currently there are no approved therapies for targeting RAS mutations in cancer while several investigational agents are in development targeting $KRAS^{G12C}$ mutation in patients with heavily pre-treated solid tumors including patients with CRC with RAS mutations (Hong 2020).

Anti-EGFR targeted therapies, cetuximab and panitumumab, are indicated for EGFR expressing, RAS wild type mCRC but have shown poor results for mCRC in patients with KRAS mutations (Saif 2009; Lievre 2008; Amado 2008; Douillard 2013; Van Cutsem 2009). Pembrolizumab, an anti-PD-1 mAb, is approved as the first-line treatment of patients with unresectable, metastatic microsatellite instability-high (MSI-H), or deficient mismatch repair (dMMR) colorectal cancer, which includes approximately 5% of CRC patients (Overman 2018). It is the first immunotherapy approved for this patient population as a first-line treatment and which is administered to patients without administering chemotherapy. Pembrolizumab demonstrated a statistically significant improvement in PFS compared with chemotherapy (16.5 months for pembrolizumab versus 8.2 months for chemotherapy) in patients with MSI-H/dMMR CRC in the KEYNOTE-177 study (Andre 2020). Among patients with treatment refractory CRC treated with immune checkpoint inhibitors, PFS is increased among patients with MSI-H/dMMR vs MSS/pMMR (~ 2 months to not reached in follow-up versus ~ 2 months) (Overman 2018; Le 2020; Le 2015).

Selinexor is a first-in-class, oral selective inhibitor of nuclear export. Preclinical data have demonstrated sensitivity of RAS-mutant NSCLC cell lines to exportin-1 (XPO1) inhibitors (Kim 2016). Inhibition of XPO1 leads to nuclear retention of IkBα, decreased NFkB target gene expression and selective lethality in RAS mutant tumors (Kim 2016). CRC is associated with alterations in the ubiquitin-proteosome system and associated with APC, p53, Fbw7, and Smad4. Additionally, XPO1 is highly co-expressed in CRC tumors as compared to the adjacent normal epithelium. In vitro models demonstrated inhibition of CRC cell growth with the use of selinexor (Wu 2017; Aladhraei 2019). Furthermore, results from several nonclinical studies show that selinexor can upregulate immune function and sensitize tumors to PD-1/PD-L1 blockade (Farren 2017; Elloul 2016; Trott 2016). Clinical activity of selinexor in KRAS mutant NSCLC and CRC has been observed in other studies (Abdul Razak 2016). 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 study KCP-330-027, the combination of selinexor 80 mg weekly with pembrolizumab, 200 mg every three weeks was used to treat 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. The results to date (31 March 2021) suggest that patients with RAS (KRAS and NRAS) mutant tumors have better clinical outcomes than those with wild type tumors and support further clinical evaluation of the combination of selinexor with a PD-1/PD-L1 inhibitor in CRC patients. These results indicate a potential for effective treatment using selinexor in combination with pembrolizumab in previously treated mCRC patients with RAS mutations.

The activity of selinexor as monotherapy and the synergistic anti-tumor activity of selinexor and PD 1/L1 blockade seen in nonclinical studies in the hard to treat patients with RAS mutated mCRC, make selinexor an ideal candidate to be evaluated for this unmet medical need. Selinexor demonstrated preliminary evidence of activity in patients with RAS mutant mCRC, both as monotherapy (Abdul Razak 2016) and in combination with pembrolizumab in KCP 330-027. In addition, selinexor has a manageable safety profile in monotherapy as well as a lack of overlapping toxicities in combination therapy. Based on these preliminary yet promising results, this study aims to evaluate the combination of selinexor with pembrolizumab in chemotherapy-refractory CRC with RAS mutations.

Objectives and Endpoints:

The following objectives will be assessed in patients with RAS mutated mCRC:

Objectives	**Endpoints**
Primary	
• To evaluate preliminary anti-tumor activity of selinexor with pembrolizumab versus standard of care (SOC)	• Progression-free survival (PFS), as assessed by the investigator per RECIST 1.1 assessed from randomization until disease progression or death from any cause, whichever occurs first
Secondary	
• To evaluate preliminary anti-tumor activity of selinexor with pembrolizumab versus SOC	• Overall survival (OS), defined as time to death due to any cause from the randomization date • ORR, defined as the proportion of patients who achieve complete response (CR) or partial response (PR), per RECIST 1.1 as

	defined by the Investigator based on radiologic criteria • PFS at 6 months, OS percent in 6 months, OS percent in 12 months, DOR, and DCR per RECIST 1.1
• To evaluate preliminary anti-tumor activity of selinexor only versus SOC	• Overall survival (OS), defined as time to death due to any cause from the randomization date • ORR, defined as the proportion of patients who achieve complete response (CR) or partial response (PR), per RECIST 1.1 as defined by the Investigator based on radiologic criteria. • PFS at 6 months, OS percent in 6 months, OS percent in 12 months, DOR, and DCR per RECIST 1.1 • Progression-free survival (PFS) per RECIST 1.1 assessed by the investigator from the randomization date
• To describe the safety and tolerability of selinexor with and without pembrolizumab	• Safety and tolerability of study treatment will be evaluated based on AE reports, vital signs, clinical laboratory results, electrocardiogram (ECG) and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Exploratory	
CCI [redacted]	

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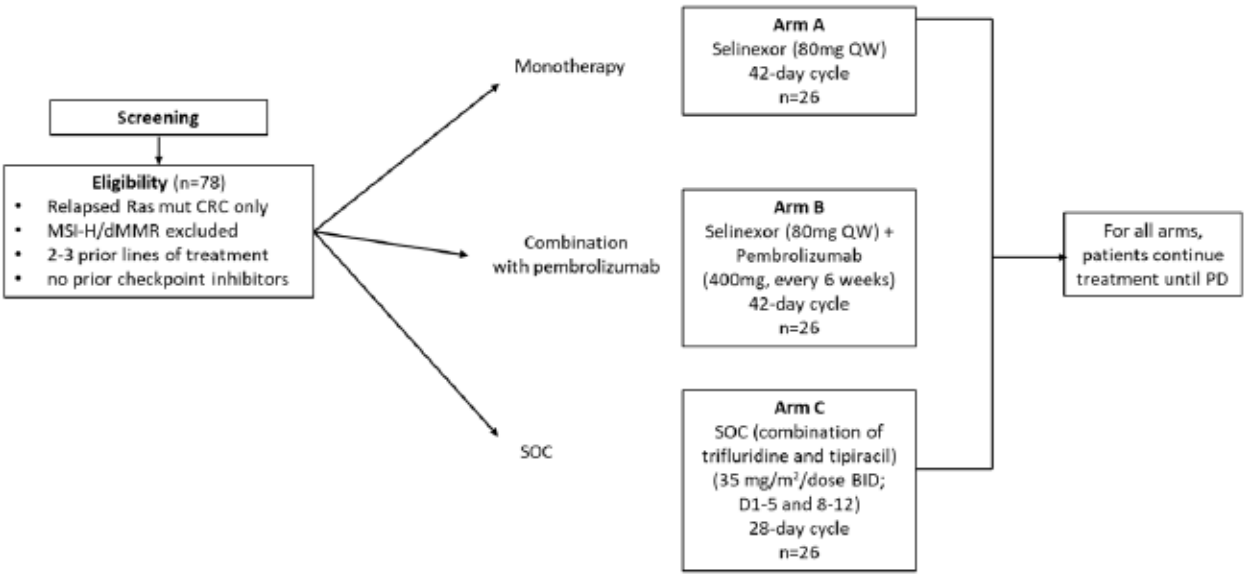
Study Schema:



BID=twice daily; dMMR= deficient mismatch repair; MSI-H=microsatellite instability high; PD=progressive disease; QW=once weekly, SOC=standard of care, CRC= colorectal cancer.

Number of Patients (planned): Approximately 78 patients will be enrolled with 26 patients in each of the 3 arms.

Eligible patients must fulfill all inclusion criteria and no exclusion criteria.

Inclusion Criteria

1. Patient has histologically proven diagnosis of unresectable metastatic colorectal cancer with a known RAS mutation
2. Patient has measurable disease according to RECIST 1.1 criteria
3. Has received 2-3 prior lines of systemic anticancer treatment (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy)
4. Patients with stable previously treated brain metastases are allowed.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 at the time of screening
6. Age ≥18 years at the time of signing informed consent.
7. Life expectancy of at least 3 months.
8. Female patients of childbearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active throughout the study and for 4 months after the last dose of selinexor or pembrolizumab or 6 months after trifluridine and tipiracil.
9. Written informed consent signed in accordance with federal, local, and institutional guidelines

Exclusion Criteria

1. Prior treatment with a SINE compound or selinexor
2. Prior treatment with immune checkpoint inhibitors
3. Patients with microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR).
4. Known allergy to any of study drugs (selinexor, pembrolizumab, and trifluridine and tipiracil) or the excipient of pembrolizumab
5. Significant cardiovascular impairment, defined as:
    i. Left ventricular ejection fraction ≤40%
    ii. Active congestive heart failure (New York Heart Association [NYHA]) Class ≥3
    iii. Unstable angina or myocardial infarction within 3 months of enrollment
    iv. Serious and potentially life-threatening arrhythmia
6. Impaired hematopoietic function (any of the following would result in exclusion):
    i. Absolute neutrophil count (ANC) <1500/mm^3
    ii. Platelet count <100,000/mm^3
    iii. Hemoglobin (Hb) <10 g/dL
7. Significant renal impairment, defined as: calculated creatinine clearance (CrCl) of <30 mL/min using the formula of Cockcroft and Gault
8. Impaired hepatic function defined as: total bilirubin > 1.5 × ULN and AST >2.5 x ULN, ALT > 2.5 x ULN; for Arm B, unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be ≤ 4 x ULN
9. Patients with a diagnosis of immunodeficiency or are receiving systemic steroid therapy (>10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy. Patients with active autoimmune disease requiring systemic treatment during the past 2 years.
    - Patients with controlled Type I and Type II diabetes mellitus, and endocrinopathies such as hypothyroidism on stable 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 allowed

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.

10. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:
    i. 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
    ii. Have ongoing clinically significant anti-cancer therapy-related toxicities CTCAE Grade >1. In specific cases, patients whose toxicity has stabilized or with Grade 2 non-hematologic toxicities can be allowed following documented approval by the Sponsor's Medical Monitor
    iii. Had last dose of previous anti-cancer therapy ≤14 days prior to Day 1 dosing
    iv. Palliative radiotherapy >14 days prior to the study is allowed
    v. Received investigational drugs in other clinical trials within 28 days, or 5 half-lives of the investigational drug (whichever is shorter), prior to C1D1
    vi. Live-attenuated vaccine against an infectious disease (e.g., nasal spray influenza vaccine) ≤14 days prior to the intended C1D1
11. Female patients who are pregnant or lactating
12. Active, ongoing or uncontrolled active infection requiring parenteral antibiotics, antivirals, antifungals within 1 week of Screening
13. Patients with autoimmune disease, a medical condition that requires systemic corticosteroids or other immunosuppressive medication; or a history of interstitial lung disease
14. Any gastrointestinal dysfunctions that could interfere with the absorption of selinexor (e.g., bowel obstruction, inability to swallow tablets, malabsorption syndrome, unresolved nausea, vomiting, diarrhea CTCAE > grade 1)
15. In the opinion of the Investigator, patients who are below their ideal body weight and would be unduly impacted by changes in their weight
16. Serious psychiatric or medical conditions that could interfere with participation in the study or in the opinion of the Investigator would make study involvement unreasonably hazardous
17. Concurrent therapy with approved or investigational anticancer therapeutic including topical therapies

Study Treatment/Treatment Groups, Dose, and Mode of Administration:

Selinexor will be provided in tablet formulations for oral administration. Pembrolizumab therapy, 400 mg IV once every 6 weeks, per the Keytruda® USPI.

All patients will receive study drug as follows:

Arm A: Selinexor 80 mg QW PO on Day 1 of each week (Days 1, 8, 15, 22, 29, and 36 of 42-day cycle)

Arm B: Selinexor 80mg QW PO on Day 1 of each week (days 1, 8, 15, 22, 29, and 36) in combination with pembrolizumab 400 mg IV once every 6 weeks

Arm C: Standard of care (28-day cycle) - trifluridine and tipiracil: 35 mg/m^2 /dose orally twice daily (max 80 mg / dose) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle

Statistical Methods:

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[redacted]

Given the above assumptions, the total sample size is approximately 78 patients with 26 in each arm.

Analysis Populations:

Intent-to-Treat Population (ITT): All patients randomized to study treatment. Patients will be analyzed in the treatment arm to which they will be randomized.

Safety Population: All patients who have been assigned to study treatment and who have received ≥1 dose of study drug. Patients will be analyzed according to the treatment arm received.

Efficacy Analyses:

All efficacy analyses will be performed using the ITT Population. The analysis of time-to-event endpoints (PFS, OS) will be based on Kaplan-Meier method for estimation of summary statistics and will include the median event times and associated 95% CIs, as well as the number and percentage of censored patients. In addition, Cox proportional hazards regression models will be used to estimate a HR for the risk of progression in the selinexor only arm or selinexor and pembrolizumab arm versus the SOC control arm.

Safety Analyses:

All safety analyses will be performed using the Safety Population. The safety and tolerability of the three treatment arms will be evaluated by means of drug-related adverse events (AE) reports, physical examinations, and laboratory safety evaluations. The grading of the severity of the AEs will be done according to NCI CTCAE, v5.0. 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 other study drugs, and AEs leading to withdrawal of treatment will be summarized. 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 efficacy, AEs, laboratory data, and vital signs will be outlined in the statistical analysis plan.

1.1. Schedule of Assessments

Table 1: Arm A (Selinexor Monotherapy) and Arm B (Selinexor and Pembrolizumab) (42-day Cycle)

Activity/ Assessment	Screening (<21 D of C1D1)	C1D1 ±1D	C1D3	C1D15/D29 ±3D	C2D1 ±2D	C2D15/D29 ±3D	C3-4D1 ±3D	≥C5D1 ±3D	EOT Up to 6 days After Discontinuation Decision	30-D Safety Visit ±4D	Response and Survival FU ±14D
Procedures											
Informed consent signed	X										
Eligibility confirmation by Sponsor	X										
Demographics	X										
Inclusion/Exclusion criteria	X										
Medical history[a]	X										
Physical examination[b]	X	X			X		X	X	X		
Vital signs[c]	X	X			X		X	X	X		
Weight[d]	X	X			X		X	X	X		
Height	X										
ECOG performance status[e]	X	X			X		X	X	X		
Nutritional consultation[f]	X	Throughout, as needed									
ECG	X	As clinically indicated									
Supportive care		As clinically indicated (Section 6.5.2.1)									
Concomitant medications review	X	Throughout									
Adverse events[g]	X	Throughout									X
Telephone contact[h]			X							X	X
Anti-neoplastic therapy									X	X	X
CCI											
Laboratory											
Serum chemistry and hematology[j]	X	X		X	X	X	X	X	X		

Activity/ Assessment	Screening (<21 D of C1D1)	C1D1 ±1D	C1D3	C1D15/D29 ±3D	C2D1 ±2D	C2D15/D29 ±3D	C3-4D1 ±3D	≥C5D1 ±3D	EOT Up to 6 days After Discontinuation Decision	30-D Safety Visit ±4D	Response and Survival FU ±14D
Pregnancy test[k]	X	X			X		X	X	X		
BioBank											
CCI [redacted]											
Anti-tumor Activity											
Tumor assessment by CT/MRI scans[o]	X	Tumor assessment will be performed every 6 weeks for 6 months, then every 9 weeks for 6 months, then every 3 months thereafter							X		
CEA[p]	X	every 6 weeks for 6 months, then every 9 weeks for 6 months, then every 3 months thereafter							X		
Drug Administration											
Selinexor		Selinexor will be administered weekly on Day 1 of each week (Days 1, 8, 15, 22, 29, 36 of 42-day cycle)									
Pembrolizumab		Pembrolizumab will be administered on Day 1 once every 6 weeks									

Abbreviations: C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; CEA = carcinoembryonic antigen; ECG = electrocardiogram; CCI [redacted]
CCI [redacted]

[a] 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 anti-cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history and smoking history will be obtained and documented. CCI [redacted]
[b]Full physical examination will be performed prior to receiving first dose of study drug (C1D1) and at the EOT Visit. All other physical examinations during the study should be limited, and symptom-directed physical examinations.
[c]Vital signs include systolic and diastolic blood pressure, pulse measurements, and body temperature (°C or °F).
[d]Indoor clothing and without shoes.
[e]ECOG performance status criteria are provided in Appendix 2.
[f]Patients must be given documented nutritional consultation per local practice to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening period of the study and prior to administration of study drug on C1D1. Nutritional consultation is to be provided throughout, as needed.
[g]Adverse event must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v5.0) 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 9.1 for additional details.

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

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[j] Serum chemistry and hematology must be conducted ≤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 8 for a list of lab tests. Labs will be repeated every 2 weeks for 2 cycles and thereafter once per cycle

[k] Female patients of childbearing potential must have a negative serum hCG pregnancy test ≤3 days before first dose C1D1.

CCI

[o] 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. Tumor assessments at screening and every 6 weeks from C1D1 for the first 6 months and then every 9 weeks till 1 year. After one year, tumor assessment frequency can be reduced to once every 3 months at the Investigator's discretion. Tumor assessment should be obtained at EOT if possible, for patients who discontinue treatment for other than PD

[p] CEA should be obtained at same time points as imaging assessments

Table 2: Arm C: Standard of Care: trifluridine and tipiracil (28-day Cycle)

Activity/ Assessment	Screening (<21 D of C1D1)	C1D1 ±1D	C1D3	C1D15 ±3D	C2D1 ±2D	C2D15 ±3D	C3-4D1 ±3D	≥C5D1 ±3D	EOT up to 6 days After Discontinuation Decision	30-D Safety Visit ±4D	Response and Survival FU ±14D
Procedures											
Informed consent signed	X										
Eligibility confirmation by Sponsor	X										
Demographics	X										
Inclusion/Exclusion criteria	X										
Medical history[a]	X										
Physical examination[b]	X	X			X		X	X	X		
Vital signs[c]	X	X			X		X	X	X		
Weight[d]	X	X			X		X	X	X		
Height	X										
ECG performance status[e]	X	X			X		X	X	X		
ECG	X	As clinically indicated									
Nutritional consultation[f]	X	Throughout, as needed									
Concomitant medications	X	Throughout									X
Adverse events[g]	X	Throughout									X
Telephone contact[h]			X							X	X
Anti-neoplastic therapy									X	X	X
Laboratory											
Serum chemistry and hematology[i]	X	X		X	X	X	X	X	X		
Pregnancy test[j]	X	X			X		X	X	X		
BioBank											
CCI [redacted]											

Activity/ Assessment	Screening (<21 D of C1D1)	C1D1 ±1D	C1D3	C1D15 ±3D	C2D1 ±2D	C2D15 ±3D	C3-4D1 ±3D	≥C5D1 ±3D	EOT up to 6 days After Discontinuation Decision	30-D Safety Visit ±4D	Response and Survival FU ±14D
Anti-tumor Activity											
Tumor assessment by CT/MRI scans[m]	X	Tumor assessments will be performed every 6 weeks for 6 months, then every 9 weeks for 6 months, then every 3 months thereafter							X		
CEA[n]	X	every 6 weeks for 6 months, then every 9 weeks for 6 months, then every 3 months thereafter							X		
Drug Administration											
Trifluridine and tipiracil[o]		X	X		X		X	X			

Abbreviations: C = cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; MRI = magnetic resonance imaging; CEA = carcinoembryonic antigen; ECG = electrocardiogram; CCI [redacted]

[a] 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 anti-cancer therapies, including the start date, end date/ongoing. All current medical history/conditions by at least the month/year. A complete ophthalmic history and smoking history will be obtained and documented. CCI [redacted]
[b] Full physical examination will be performed prior to receiving first dose of study drug (C1D1) and at the EOT Visit. All other physical examinations during the study should be limited, and symptom-directed physical examinations.
[c] Vital signs include systolic and diastolic blood pressure, pulse measurements, and body temperature (°C or °F).
[d] Indoor clothing and without shoes.
[e] ECOG performance status criteria are provided in Appendix 2.
[f] Patients must be given documented nutritional consultation per local practice to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with study drug. This must be completed within the Screening period of the study and prior to administration of study drug on C1D1. Nutritional consultation is to be provided throughout, as needed.
[g] Adverse event must be recorded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v5.0) 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 9.1 for additional details.
[h] Telephone contact will be made on C1D3 to evaluate supportive care medications, concomitant medications, and adverse events, and to adjust supportive care as appropriate. After discontinuation of study treatment, follow-up phone calls will be performed 30 days and every 3 months until 12 months documenting start of new therapy and survival status.
[i] Serum chemistry and hematology must be conducted ≤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 8 for a list of lab tests. Labs will be repeated every 2 weeks for 2 cycles and thereafter once per cycle
[j] Female patients of childbearing potential must have a negative serum hCG pregnancy test ≤3 days before first dose C1D1.
CCI [redacted]

CCI

[m]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. Tumor assessments at screening and every 6 weeks from C1D1 for the first 6 months and then every 9 weeks till 1 year. After one year, tumor assessment frequency can be reduced to once every 3 months at the Investigator's discretion. Tumor assessment should be obtained at EOT if possible, for patients who discontinue treatment for other than PD

[n] CEA should be obtained at same time points as imaging assessments

[o] Trifluridine and tipiracil 35 mg/m^2 /dose orally twice daily (max 80 mg / dose) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Trifluridine and tipiracil should be taken with food

2. INTRODUCTION

2.1. Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer worldwide and is the fourth leading cause of cancer-related deaths, with an estimated 850,000 deaths in 2018 (Bray 2018). More than 1.9 million new cases were diagnosed in 2020. Approximately 20% 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). 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) mismatch repair enzymes (dMMR). Immune checkpoint inhibitors are approved for approximately 5% of CRC patients with MSI-H/dMMR tumors and survival may be prolonged by adding biologic agents.

While anti-EGFR targeted therapies, cetuximab and panitumumab, are indicated for EGFR expressing, RAS wild type mCRC, these therapies have shown poor results for mCRC in patients with KRAS mutations (Saif 2009). A recent meta-analysis demonstrated no clinically significant difference in PFS with anti-EGFR monoclonal antibody therapy between KRAS G13D and other KRAS mutant colorectal cancer tumors (Rowland 2016). It is now well established in the literature that KRAS mutations confer resistance to anti-EGFR targeted therapies (Lièvre 2008; Amado 2008; Douillard 2013; Van Cutsem 2009). Per NCCN guidelines, patients with RAS mutations should not be treated with cetuximab or panitumumab due to potential for toxicity without any expectation of benefit. Cetuximab or panitumumab are approved in RAS wild type only in the EU per Summary of Product Characteristics (SmPC).

Current available options include monotherapy with an immune checkpoint inhibitor (CPI) that targets the programmed death receptor-1 (i.e., nivolumab or pembrolizumab). Pembrolizumab (intravenous injection) is approved as the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) colorectal cancer. It is the first immunotherapy approved for this patient population as a first-line treatment which is administered to patients without chemotherapy.

Per NCCN guidelines, regorafenib or trifluridine and tipiracil with or without bevacizumab or participation in a clinical trial is recommended for patients with advanced/mCRC who have progressed after all standard therapies (NCCN 2020). Regorafenib (Stivarga®) and trifluridine and tipiracil (Lonsurf®)were FDA approved based on the results of the CORRECT and RECOURSE studies respectively (Grothey 2013; Mayer 2015). Both studies met their primary survival endpoints with significant improvement in survival versus placebo (6.4 months for regorafenib versus 5.0 months for placebo and 7.1 months for trifluridine and tipiracil versus 5.3

months for placebo). Lacking alternatives, these modest gains in survival have become the standard of care (SOC) for most patients reflecting the poor prognosis for this indication.

The KRAS mutation occurs in approximately 35%-45% of CRC. The presence of oncogenic KRAS alterations has been proposed to portend poor response to conventional treatment and poor clinical outcomes. To date, pharmacologic attempts to inhibit KRAS directly have proven unsuccessful. 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). $KRAS^{G12C}$ 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 do not affect cancers with other type of KRAS mutations. Therefore, novel concepts are needed to improve treatment in KRAS mutant cancers.

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; Aladhraei 2019). In 40 CRC samples from patients, XPO1 overexpression was observed in 52.5% of CRC and was 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, Velichkova 2005; Ki 2008; Neufeld 2009; Ferreiro-Neira 2016; Cheng 2018).

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 µM to 10 µM). Inhibition of XPO1 led to nuclear retention of IkBα, 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).

2.2. Study Rationale

Patients with advanced/metastatic CRC (mCRC) are typically treated with 5-FU and oxaliplatin or irinotecan-based regimens in first- and second-line disease management. Treatment selection

depends on clinical factors and molecular markers. Despite initial response rates around 60% with first line chemotherapy, mCRC remains incurable. After progression free survival (PFS) of about 8-12 months, the disease recurs with and overall survival (OS) remains poor around 30 months (Saltz 2008; Douillard 2010; Loupakis 2014; Van Cutsem 2011; Venook 2017). Second line chemotherapy in recurrent mCRC yields considerably less efficacy with response rates of 5-36%, PFS lasing 5-7 months, and OS of 11-14 months (Giantonio 2007; Bennouna 2013; Sobrero 2008; Peeters 2014). The options for the third line therapy of mCRC are very limited. Additionally, patients who have RAS-mutated CRC lack effective therapies and are treated with agents that demonstrate only modest survival gains. Response rate and survival in patients with mutations in RAS proteins remains an unmet medical need due to the poor antitumor responses, few treatment options, and the aggressive nature of the tumors leading to a shorter survival. Currently regorafenib and combination of trifluridine and tipiracil are third and later lines treatments for patients with mCRC including those with RAS mutations. Immune checkpoint inhibitors are approved for approximately 5% of CRC patients with MSI-H/dMMR tumors. Anti-EGFR targeted therapies, cetuximab and panitumumab, are only indicated for EGFR-expressing KRAS wild-type mCRC in the EU per SmPC. Pembrolizumab, an anti-PD-1 mAb, is approved as the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) colorectal cancer. In a study of pembrolizumab in CRC, regardless of MSI status but with PD-L1-positive disease, the ORR was only 4% (1 out of 23 enrolled and treated). In a review of the patient with a tumor response, it was noted that patient who responded was the only one with MSI-H disease. In the study KEYNOTE-016, patients with microsatellite stable (MSS) disease had an ORR of 0% (95% CI: 0, 20), while those patients with mismatch repair–deficient colorectal adenocarcinomas had an ORR of 40% (95% confidence interval [CI], 12, 74) (Li 2015). Further studies using pembrolizumab have limited the population to MSI-H only; the population for which pembrolizumab received approval. Results from study KCP-330-027 indicate a potential for effective treatment using selinexor in combination with pembrolizumab in previously treated mCRC patients with RAS mutations.

This study aims to evaluate the combination of selinexor with pembrolizumab in chemotherapy-refractory CRC with RAS mutations. The single agent activity of both selinexor and pembrolizumab in RAS mutant CRC, along with the safety and early indications of efficacy of this combination support the study design in this niche indication where there is acute need for effective treatment.

2.3. Selinexor

Selinexor (Xpovio®) is a first-in-class oral selective inhibitor of nuclear export (SINE) compound, specifically inhibiting exportin-1 (XPO1, also called Chromosome Region Maintenance protein 1/CRM1) and has been validated as a target for therapeutic intervention in cancer. Inhibition of XPO1 leads 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 is FDA approved as a treatment (80 mg twice weekly [BIW]) in combination with low-dose dexamethasone in patients with penta-refractory multiple myeloma, and as a monotherapy (60 mg BIW) for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior lines of therapy. Selinexor is also approved in

combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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 (Etchin 2013) and their functions are largely spared.

Mutations in RAS proteins (KRAS, NRAS, HRAS) are very common in human cancer and occur in ~33% of patients with CRC, according to the COSMIC results, and up to ~69% according to The Cancer Genome Atlas (Prior 2020; Tate 2019; Sanchez-Vega 2018; Serebriiskii 2019). The presence of oncogenic RAS alterations leads to poor response from conventional treatments and poor clinical outcomes. Pharmacologic attempts at inhibiting RAS directly have proven not so successful to date.

Preclinical data have demonstrated sensitivity of RAS-mutant NSCLC cell lines to XPO1 inhibitors (Kim 2016). Therapeutic activity of selinexor has been observed in cancers with RAS mutations. Clinical activity of selinexor in KRAS mutant NSCLC and CRC has been observed in other studies. 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).

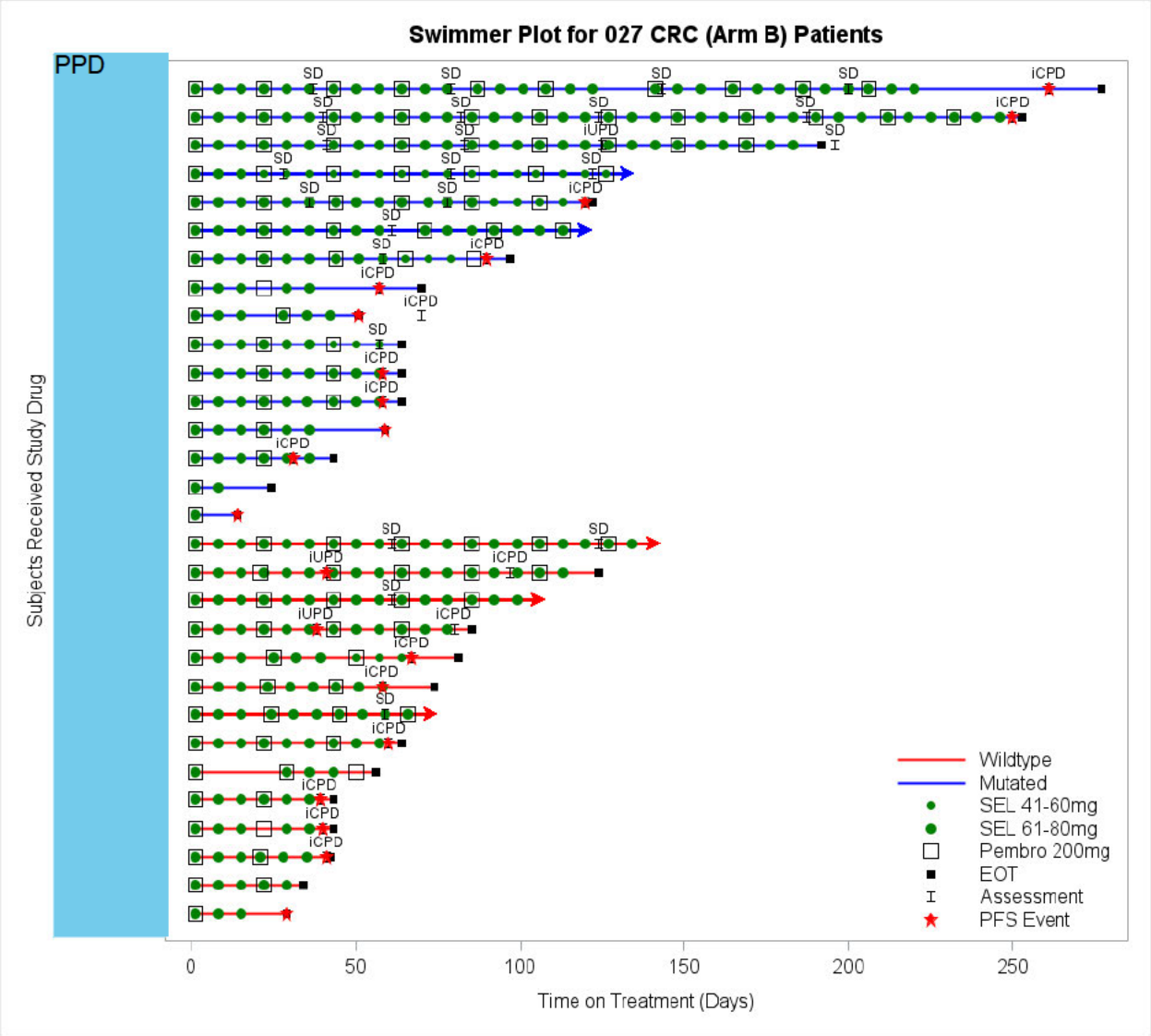
Rationale for use of Selinexor in Combination with Pembrolizumab

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 anti-PD-1 or anti-PD-L1 blockade has been assessed in *in vivo* studies and demonstrated synergistic anti-tumor activity in an aggressive murine colon cancer model (Elloul 2016) as well as other solid tumor models (Farren 2017; Trott 2016) (2) a combination of selinexor and anti-PD-1 or anti-PD-L1 mAb shows significant immunomodulatory activity, inducing changes in the frequency and phenotype of immune cell populations, including increased frequency of NK cells, increased frequency of differentiated TH1 cells, and increased frequency of activated T-cells (Farren 2017); (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)

In study KCP-330-027 the combination of selinexor 80 mg weekly with pembrolizumab, 200 mg every three weeks was used to treat 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. 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 progression of disease. In this group, 11

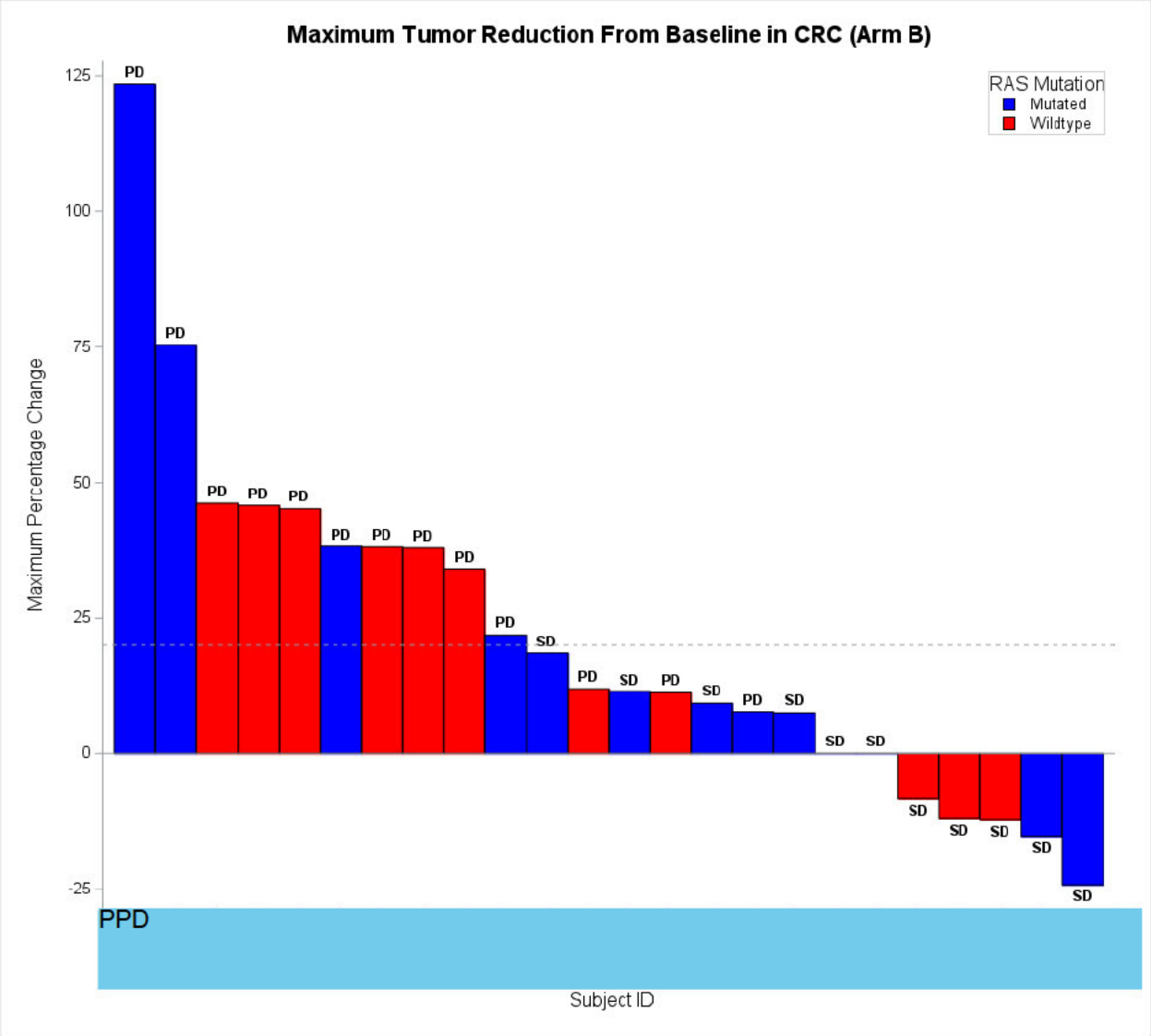
patients had stable disease as their best overall response (BOR), and 8 of these 11 patients with stable disease (73%) had RAS mutant tumors (Figure 1, Figure 2). Notably none of the RAS mutated tumors were MSI-H. Disease stabilization was achieved in various RAS mutant tumors including NRAS mutant, KRAS G12V and G12D. The mPFS in patients with RAS mutated CRC was 12.9 weeks, 95% CI (8.3, NA) versus RAS WT 7.1 weeks, 95% CI: (5.7, NA) (p = 0.20; HR 0.55 [95% CI 0.21, 1.41]). At least one TEAE and one treatment related adverse event (TRAE) were observed in at least 96.7% and 86.7% of patients respectively. The most frequent cause of discontinuation of treatment was due to disease progression (PD). Among patients with TRAEs, 20% had dose modifications and 20% dose interruptions. 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 were 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 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 and warrants further study.

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



CRC=colorectal cancer; PD= progressive disease; SD=stable disease, SEL=selinexor; Pembro= pembrolizumab; EOT=end of treatment

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



CRC=colorectal cancer; PD= progressive disease; SD=stable disease.

Furthermore, 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-uveal type, 9 of them were naïve to prior immunotherapy (IO) and the other 9 were refractory to IO therapy. It is a heterogenous population including heavily treated patients with up to 5 lines of IO treatment. The ORR among patients with IO naïve and IO refractory non-uveal melanoma was 56% versus 33%, respectively. The longest duration of treatment has been 15.4 months for one patient, while the longest duration of response for one patient with CR is almost 13 months with the patient still on study. Adverse events in the study included nausea (68%), vomiting (52%), and anemia (48%). The other AEs were consistent with those reported

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

In the above-described study (NCT02419495), a total of 31 melanoma patients were treated with combinations of selinexor 60-120 mg total weekly dose (once or twice weekly) and pembrolizumab 2 mg/kg or 200 mg IV once every three weeks (Q3W). Of those, 25 patients were treated with selinexor 60 mg BIW. 3 patients out of the 25 patients discontinued due to adverse events. Overall, these results demonstrate that selinexor in combination with pembrolizumab is well-tolerated.

Selinexor appears to overcome resistance to IO, acquired resistance in IO refractory melanoma in the Phase 1b (NCT02419495) and innate resistance in MSS/pMMR CRC in KCP-330-027. Mechanisms of resistance may differ but the hypothesis that selinexor may sensitize IO refractory/resistant tumors is intriguing. Microsatellite instability is infrequent in RAS (Birgisson 2015), and, therefore, patients with RAS mutant CRC will in most cases be deprived of the benefit of IO.

The activity of selinexor as monotherapy and the synergistic anti-tumor activity of selinexor and PD 1/L1 blockade seen in nonclinical studies in the hard to treat patients with RAS mutated mCRC, make selinexor an ideal candidate to be evaluated for this unmet medical need. Selinexor demonstrated preliminary evidence of activity in patients with RAS mutant mCRC, both as monotherapy (Abdul Razak 2016) and in combination with pembrolizumab in KCP 330 027. In addition, selinexor has a manageable safety profile in monotherapy as well as a lack of overlapping toxicities in combination therapy. Based on these preliminary yet promising results, this study aims to evaluate the combination of selinexor with pembrolizumab in chemotherapy-refractory CRC with RAS mutations.

2.4. Dose Justification (Monotherapy and Combination)

Selinexor has been evaluated as a single agent or in combination with other anti-cancer agents in >3700 patients with hematologic or solid-tumor malignancies who received at least 1 dose of selinexor. Among these patients, 2310 were treated on company-sponsored trials (CSTs) and 1201 patients were treated on investigator-sponsored trials (ISTs). Based on the robust available clinical safety and efficacy data from these clinical trials, selinexor shows a reasonably wide therapeutic range, with single agent activity ranging from ~6 mg/m^2 to ≥85 mg/m^2 BIW (approximately 10 mg to 145 mg PO BIW) which was initially observed from the two phase 1 studies and subsequently confirmed in multiple phase 2 and phase 3 clinical trials.

In dose escalation studies in patients with advanced hematologic and solid tumor malignancies (Studies KCP-330-001 and KCP-330-002, respectively), selinexor was dosed once or twice weekly and exhibited linear PK and dose-proportional exposure (maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC]). Based on the observation from the Phase 1 study (KCP-330-002) and several other phase 2 studies in solid tumors, the revised recommended Phase 2 dose (RP2D) of selinexor as single agent for many solid tumors is 60 mg BIW or 80 mg once weekly (QW).

A dose of 80 mg selinexor QW in combination with pembrolizumab 400 mg every 6 weeks has been selected for this study based on the once weekly dosing regimen of 80 mg selinexor in combination with pembrolizumab at the standard approved dose 400 mg once every 6 weeks in the KCP-330-027 study (NCT04256707). Five patients are ongoing on the combination

treatment as of 31Mar 2021. Median treatment duration is 3.2 cycles (21-day cycle) with the longest duration of treatment in 2 patients with KRAS and NRAS mutation (8 and 9 months, respectively, on the combination). Overall, this combination regimen was well tolerated in the 30 patients treated in this study with no dose limiting toxicities. Side effects were generally reversible and manageable with supportive care, dose holds and dose modifications. There were no deaths from drug-related toxicity. These findings indicate that selinexor 80 mg once weekly with pembrolizumab 400 mg once every six weeks is a tolerable regimen in patients with advanced, heavily pretreated CRC.

2.5. Benefit/Risk Assessment

Broad antitumor activity has been observed with selinexor treatment in preclinical and clinical studies. The information about selinexor's mechanism of action and its efficacy observed in the KCP-330-027 study (NCT04256707) in patients with advanced or metastatic colorectal cancer (CRC), indicates that selinexor 80 mg once weekly with pembrolizumab 400 mg IV once every six weeks has activity in RAS mutated CRC; however, further investigation is warranted to elucidate clinical benefit. Adverse events in the study were consistent with those reported previously for selinexor and pembrolizumab administered separately with no clear overlapping toxicities. AEs noted during the trial include hematological, fatigue, nausea/diarrhea, low sodium/potassium attributed as possible/definite to either selinexor or pembrolizumab or possible with both treatments.

In addition, selinexor is currently being evaluated in combination with other agents (targeted therapies and chemo-/radiotherapy). As these clinical trials proceed, more data will become available to assess both the added efficacy and possible adverse events resulting from these combinations to better inform potential trials combining selinexor with immune checkpoint blockade. In ongoing clinical studies, the most common non-hematologic AEs reported as related to selinexor have been predominantly nausea, vomiting, diarrhea, fatigue, anorexia and weight loss, and these AEs were assessed as low-grade and manageable with dose modification or supportive care. Hyponatremia (typically asymptomatic), confused state and dizziness have also been reported. On the other hand, hematological AEs including thrombocytopenia, neutropenia and anemia, which can be higher grade, were reported primarily in patients with hematologic malignancies. Any potential overlapping toxicity, such as thrombocytopenia, will be monitored closely by careful physical examination and clinical laboratory testing on Day 1 and Day 15 of Cycle 1 and Cycle 2 with dose adjustments as per prespecified dose modifications (see Table 4).

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

Pembrolizumab is approved for use in the treatment of patients with unresectable or metastatic MSI-H or dMMR CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as a result of an accelerated approval based upon the tumor response rate and durable response. Early studies using pembrolizumab did not demonstrate activity in CRC with RAS mutations or without microsatellite instability. Nonclinical models demonstrated combination activity of selinexor and pembrolizumab. The results seen in Study KCP-330-027 confirmed the activity of the combination in this otherwise pembrolizumab nonresponding population.

Please refer to the Prescribing Information for more information regarding pembrolizumab.

3. STUDY OBJECTIVES AND ENDPOINTS

The following objectives will be assessed in patients with RAS mutated mCRC:

Objectives	Endpoints
Primary	
• To evaluate preliminary anti-tumor activity of selinexor with pembrolizumab versus standard of care (SOC)	• Progression-free survival (PFS), as assessed by the investigator per RECIST1.1 assessed from randomization until disease progression or death from any cause, whichever occurs first
Secondary	
• To evaluate preliminary anti-tumor activity of selinexor with pembrolizumab versus SOC	• Overall survival (OS), defined as time to death due to any cause from the randomization date • ORR, defined as the proportion of patients who achieve complete response (CR) or partial response (PR), per RECIST 1.1 as defined by the Investigator based on radiologic criteria • PFS at 6 months, OS percent in 6 months, OS percent in 12 months, DOR, and DCR per RECIST 1.1
• To evaluate preliminary anti-tumor activity of selinexor only versus SOC	• Overall survival (OS), defined as time to death due to any cause from the randomization date • ORR, defined as the proportion of patients who achieve complete response (CR) or partial response (PR), per RECIST 1.1 as defined by the Investigator based on radiologic criteria • PFS at 6 months, OS percent in 6 months, OS percent in 12 months, DOR, and DCR per RECIST 1.1 • Progression-free survival (PFS) per RECIST 1.1 assessed by the investigator from the randomization date

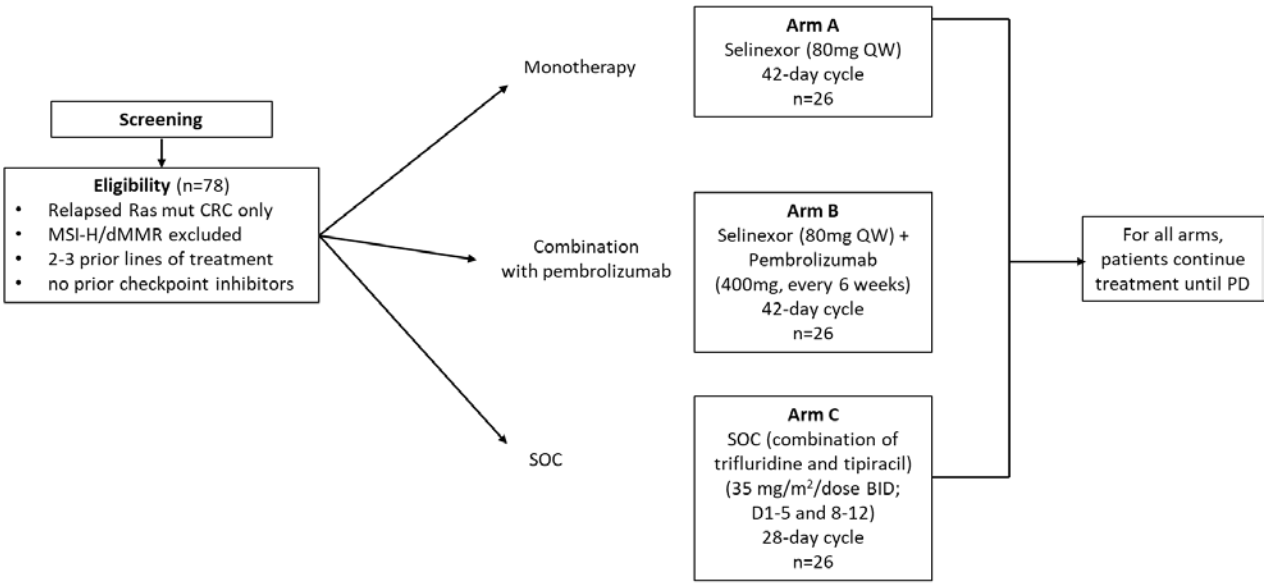
Objectives	Endpoints
• To describe the safety and tolerability of selinexor with and without pembrolizumab	• Safety and tolerability of study treatment will be evaluated based on AE reports, vital signs, clinical laboratory results, electrocardiogram (ECG) and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Exploratory	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2, open-label, multicenter study that will evaluate the efficacy and safety of selinexor and pembrolizumab in patients with advanced or metastatic CRC. The study schema is depicted in Figure 3.

Figure 3: Study Schema



SOC = Standard of care, PD = progressive disease; MSI-H = microsatellite instability high; dMMR = deficient mismatch repair; QW = once weekly; BID=twice daily; CRC=colorectal cancer

Approximately 78 patients with advanced or metastatic CRC will be enrolled, and randomized to Arm A, B or C based on the following stratification factor:

- ECOG performance status 0 or 1 versus 2

All eligible patients in Arm A will be treated with selinexor 80 mg QW orally as a monotherapy on Day 1 of each week of a 42-day cycle. Arm B patients will be treated with selinexor at the same dose as Arm A in combination with pembrolizumab 400 mg IV once every 6 weeks. Arm C patients will be administered the standard of care treatment trifluridine and tipiracil 35 mg/m^2/dose orally BID (max 80 mg / dose) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Trifluridine and tipiracil should be taken with food.

Primary efficacy will be assessed by PFS, as assessed by the investigator per RECIST1.1 for selinexor plus pembrolizumab and for SOC assessed from randomization until disease progression or death from any cause, whichever occurs first. Objective response rate (ORR) defined as the proportion of patients who achieve complete response (CR) or partial response

(PR), per RECIST 1.1 as defined by the Investigator based on radiologic criteria. Assessments will be performed per timepoints as mentioned in SoA.

Safety and tolerability of study treatment will be evaluated based on AE reports, vital signs, clinical laboratory results, electrocardiogram (ECG) and physical examination findings, by the occurrence, nature, and severity of AEs as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Timepoints will be performed as mentioned in SoA.

Patients will receive study treatment until disease progression (PD), intolerable toxicity, or withdrawal from the study. Disease response/progression will be based on tumor assessments at timepoints specified in the SoA.

4.2. End of Treatment

The EOT visit will occur ≤30 days post-treatment discontinuation. After discontinuation of study treatment, patients will be followed for PFS approximately every 3 months after EOT visit until PD, death or initiation of the subsequent treatment (if a patient discontinues from the treatment due to reasons other than PD), and for survival every 3 months after end of treatment visit for 12 months or until withdrawal of consent, death, or the end of study (i.e., when the last patient in the study has been followed up on study treatment for at least 1 year or completed at least 6 months of survival follow-up period after their last dose of study treatment, has withdrawn consent, has died, or has been lost to follow-up, whichever occurs first). The duration of the study will be approximately 3 years.

4.3. Safety Follow-Up Visit and Survival Follow-Up Visit

A safety follow-up visit must be performed within 30 days after EOT. The purpose is to assess patient status, follow-up on any AEs that were not resolved at the EOT Visit.

Survival follow-up visit will be performed every 3 months from EOT and will continue for 12 months.

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

5. STUDY POPULATION

Eligible patients must fulfill all inclusion criteria and no exclusion criteria.

5.1. Inclusion Criteria

1. Patient has histologically proven diagnosis of unresectable metastatic colorectal cancer with a known RAS mutation.
2. Patient has measurable disease according to RECIST 1.1 criteria.
3. Has received 2-3 prior lines of systemic anticancer treatment (adjuvant or neoadjuvant therapy is not counted as one line of systemic therapy).
4. Patients with stable previously treated brain metastases are allowed.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 at the time of screening.
6. Age ≥ 18 years at the time of signing informed consent
7. Life expectancy of at least 3 months.
8. Female patients of childbearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active throughout the study and for 4 months after the last dose of selinexor or pembrolizumab or 6 months after trifluridine and tipiracil.
9. Written informed consent signed in accordance with federal, local, and institutional guidelines.

5.2. Exclusion Criteria

1. Prior treatment with a SINE compound or selinexor.
2. Prior treatment with immune checkpoint inhibitors.
3. Patients with microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR).
4. Known allergy to any of study drugs (selinexor, pembrolizumab, and trifluridine and tipiracil) or the excipient of pembrolizumab.
5. Significant cardiovascular impairment, defined as:
    i. Left ventricular ejection fraction ≤40%
    ii. Active congestive heart failure (New York Heart Association [NYHA]) Class ≥3
    iii. Unstable angina or myocardial infarction within 3 months of enrollment
    iv. Serious and potentially life-threatening arrhythmia
6. Impaired hematopoietic function (any of the following would result in exclusion):
    i. Absolute neutrophil count (ANC) <1500/mm^3
    ii. Platelet count <100,000/mm^3

iii. Hemoglobin (Hb) <10 g/dL

7. Significant renal impairment, defined as: calculated creatinine clearance (CrCl) of <30 mL/min using the formula of Cockcroft and Gault.
8. Impaired hepatic function defined as: total bilirubin > 1.5 × ULN and AST > 2.5 x ULN, ALT > 2.5 x ULN; for Arm B, unless bilirubin elevation is related to Gilbert's Syndrome for which bilirubin must be ≤ 4 x ULN.
9. Patients with a diagnosis of immunodeficiency or are receiving systemic steroid therapy (>10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy. Patients with active autoimmune disease requiring systemic treatment during the past 2 years.
    - Patients with controlled Type I and Type II diabetes mellitus, and endocrinopathies such as hypothyroidism on stable 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 allowed.

    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.
10. Insufficient time since or not recovered from procedures or anti-cancer therapy, defined as:
    i. 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.
    ii. Have ongoing clinically significant anti-cancer therapy-related toxicities CTCAE Grade >1. In specific cases, patients whose toxicity has stabilized or with Grade 2 non-hematologic toxicities can be allowed following documented approval by the Sponsor's Medical Monitor.
    iii. Had last dose of previous anti-cancer therapy ≤14 days prior to Day 1 dosing.
    iv. Palliative radiotherapy >14 days prior to the study is allowed.
    v. Received investigational drugs in other clinical trials within 28 days, or 5 half-lives of the investigational drug (whichever is shorter), prior to C1D1.
    vi. Live-attenuated vaccine against an infectious disease (e.g., nasal spray influenza vaccine) ≤14 days prior to the intended C1D1.
11. Female patients who are pregnant or lactating.
12. Active, ongoing or uncontrolled active infection requiring parenteral antibiotics, antivirals, antifungals within 1 week of Screening.
13. Patients with autoimmune disease, a medical condition that requires systemic corticosteroids or other immunosuppressive medication; or a history of interstitial lung disease.
14. Any gastrointestinal dysfunctions that could interfere with the absorption of selinexor (e.g., bowel obstruction, inability to swallow tablets, malabsorption syndrome, unresolved nausea, vomiting, diarrhea CTCAE > Grade 1).

15. In the opinion of the Investigator, patients who are below their ideal body weight and would be unduly impacted by changes in their weight.
16. Serious psychiatric or medical conditions that could interfere with participation in the study or in the opinion of the Investigator would make study involvement unreasonably hazardous.
17. Concurrent therapy with approved or investigational anticancer therapeutic including topical therapies.

5.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study as they did not meet the inclusion/exclusion criteria. 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.

6. STUDY TREATMENT

6.1. Study Treatments Administered

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

Table 3: Study Treatment

Treatment Name	Selinexor (Xpovio®)	Pembrolizumab (Keytruda™)	Standard of Care (Trifluridine and Tipiracil)
Dose Formulation	Tablet	Solution	Tablet
Unit Dose Strength	20 mg	25 mg/mL	15 or 20 mg
Dosage Level	80 mg, single dose once weekly on Day 1	400 mg once every six weeks on Day 1	35 mg/m^2 /dose twice daily (max 80 mg / dose) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle
Route of Administration	PO	IV	PO

PO=orally; IV=intravenous.

6.2. Study Drug Dosing and Administration

6.2.1. Labeling

All labels (selinexor, pembrolizumab, and Lonsurf (trifluridine and tipiracil) 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.

Refer to the Pharmacy Manual for information on pembrolizumab and trifluridine and tipiracil labeling and additional information.

6.2.2. Dispensing Directions

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

6.2.3. Dosing Information

Selinexor tablets should be taken orally with at least 120 mL (4 fluid ounces) of water. Selinexor can be taken with or without food. In order to avoid contact with skin, tablets must be swallowed whole and should not be crushed. For additional details on drug formulation, preparation, and administration, please refer to the Pharmacy Manual and the Investigator's Brochure.

Pembrolizumab (Arm B) will be administered at the site, only by authorized site personnel. Trifluridine and tipiracil (Arm C) should be taken with food and should be taken at home unless there is a site visit on the dosing day as appropriate.

6.3. Preparation/Handling/Storage/Accountability

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

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

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

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

6.4. Study Treatment Compliance

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

6.5. Concomitant Medication

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

6.5.1. Prohibited Concomitant Medications

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

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

6.5.2. Permitted Concomitant Medications

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

Based on our current limited clinical information, there are no known contraindications associated with selinexor and the available authorized COVID vaccines. While Karyopharm is unable to offer COVID vaccinations to patients at this time, patients are not prohibited to receive vaccination through available sources at any time while being treated with selinexor. If a patient receives the concomitant COVID vaccine, each dose, the manufacturer of the vaccine, and the date of vaccination should be recorded and the respective prescribing information of the authorized COVID vaccines should be referred. As always, all AEs, including their causalities, as well as noted laboratory abnormalities will be recorded. There may be concurrent known adverse events, such as fatigue and nausea associated with the authorized COVID vaccines and selinexor. All causalities associated with the treatment emergent events should be reported according to the clinical discretion of the investigator. Based on our current limited clinical information, there are no known contraindications associated with selinexor and the available authorized COVID- vaccines.

6.5.2.1. Anti-emetic Agents

In order to minimize nausea, unless contraindicated all patients must receive 2 anti-emetics initially. A 5-HT3 antagonist (ondansetron 8mg or equivalent), starting 30-60 minutes before administration of study drug and continued 2-3 times daily for at least 2 days after dosing, as needed.

In addition to 5-HT3 antagonist, patients receiving selinexor, single agent and selinexor and pembrolizumab arms, 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.

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 per discussion with the medical monitor. An NK-1 antagonist, or another anti-emetic agent should be used as per the label per NCCN Guidelines Alternative; or an additional anti-emetic agent may be used if the patient does not tolerate or has inadequate anti-emetic effect with 5-HT3 antagonists and olanzapine.

6.6. 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 must be completed within the Screening period of the study and prior to administration of study drug on C1D1. The Investigator or any study staff can provide the nutritional consultation, in person or by telephone. Nutritional/supportive care is to be provided throughout, as needed, and per local guidance.

6.7. Restrictions

6.7.1. Diet

There are no dietary restrictions during this study. Selinexor should be administered with about 4 oz (120 mL) of water. Patients can drink water as desired. Throughout the study, patients on study drug should maintain adequate caloric and fluid intake.

6.8. Dose Modifications

6.8.1. Selinexor Dose Modifications

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

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

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

Table 4 summarizes the selinexor dose levels for modification; Table 5 describes supportive care and dose adjustment guidelines for hematologic adverse reactions. Table 6 describes dose adjustment guidelines for non-hematologic adverse reactions. Deviations from the guidelines are permitted after discussion between the Sponsor and the treating physician.

Table 4: Selinexor Dose Modification Steps for Adverse Reactions

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

Table 5: Dose Modification for Hematologic Adverse Reactions

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

Adverse Reaction[a]	Occurrence	Action
Hemoglobin level < 8.0 g/dL	Any	Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	Interrupt selinexor. Monitor hemoglobin until levels return to 8 g/dL or higher. Restart selinexor at 1 dose level lower (see Table 4). Administer blood transfusions and/or other treatments per clinical guidelines.
[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.		

Table 6: Selinexor Dose Modification Guidelines for Non-Hematologic Adverse Reactions

Adverse Reaction[a]	Occurrence	Action
Hyponatremia		
Grade 1 or 2 (sodium level < normal to 130 mmol/L)	Any	Maintain dose Rule out other causes including drug (e.g. diuretic) effects Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL) Treat hyponatremia per institutional guidelines including dietary review Consider addition of salt tablets to patient's diet
Grade 3 (sodium levels 120 to 129 mmol/L) without symptoms	Any	Rule out other causes including drug (e.g., diuretic) effects Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150mg/dL) If (corrected) sodium is Grade ≤ 3 and continues to be asymptomatic, then patient may continue current dosing provided that IV saline and/or salt tablets are provided
Grade 3 (sodium levels 120 to 129 mmol/L) with symptoms *OR* Grade 4 (sodium levels < 120 mmol/L)	Any	Rule out other causes including drug (e.g., diuretic) effects Be certain that reported sodium level is corrected for concurrent hyperglycemia (serum glucose > 150 mg/dL)

Adverse Reaction[a]	Occurrence	Action
		Interrupt selinexor dosing until resolved to Grade 1 or baseline and without symptoms. Reduce selinexor by 1 dose level
Fatigue		
Grade 2 lasting > 7 days *OR* Grade 3	Any	Interrupt selinexor. Monitor until fatigue resolves to Grade 1 or baseline. Restart selinexor at 1 dose level lower (see Table 4).
Nausea and Vomiting		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) *OR* Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	Maintain selinexor and initiate additional anti-nausea medications.
Grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher vomiting (6 or more episodes per day)	Any	Rule out other causes. Use additional anti-nausea medications to supplement the protocol-required 5-HT3 antagonists Additional options can be found in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (CPGO) for antiemesis and anorexia/cachexia (palliative care). Interrupt selinexor dosing. Initiate additional anti-nausea medications. Monitor until resolved to Grade ≤ 2 or baseline and reduce selinexor by 1 dose level (see Table 4).
Diarrhea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	Maintain selinexor and institute supportive care.
	2nd and subsequent	Reduce selinexor by 1 dose level (see Table 4). Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	Interrupt selinexor and institute supportive care. Monitor until diarrhea resolves to Grade 2 or lower. Restart selinexor at 1 dose level lower (see Table 4).
Weight Loss and Anorexia		
Weight loss of 10% to less than 20%	Any	Interrupt selinexor and institute supportive care.

Adverse Reaction[a]	Occurrence	Action
OR anorexia associated with significant weight loss or malnutrition		Monitor until weight returns to more than 90% of baseline weight. Restart selinexor at 1 dose level lower (see Table 4).
Other Non-Hematologic Adverse Reactions		
Grade 3 or 4	Any	Interrupt selinexor. Monitor until resolved to Grade 2 or lower, restart selinexor at 1 dose level lower (see Table 4).
[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.		

6.8.2. Pembrolizumab Dose Modifications

For AEs related to pembrolizumab, refer to dose adjustment guidelines in the respective drug's prescribing information. If an AE requires interruption of pembrolizumab but not selinexor, selinexor treatment may continue. Pembrolizumab dosing will be done on Day1 of any given 42-day cycle. If an AE requires interruption of only pembrolizumab, but the AE does not require interruption of selinexor, then pembrolizumab may remain interrupted as long as is necessary to allow the patient to recover from the AE that caused the drug interruption. If it is determined that the patient should no longer receive pembrolizumab, the patient may continue treatment with single agent selinexor, at the discretion of the Investigator.

6.8.3. Trifluridine and tipiracil Dose Modifications

Trifluridine and tipiracil dose modifications will be determined based on dose adjustment guidelines in the drug's prescribing information.

6.9. Missed or Vomited Selinexor Doses

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

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

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

7. DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. 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 v 1.1 (Appendix 1)
- 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 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.

7.2. 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.
- Any patient who does not withdraw from the study but who stops attending study visits and does not respond to 3 documented contact attempts will be considered lost to follow-up.

7.3. 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 IECs, IRBs, Investigators, and regulatory authorities.

8. 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. 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.

8.1. 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 11.3). 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.

8.2. Baseline Assessments

8.2.1. Demographics

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

8.2.2. 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 RAS mutations, EGFR mutations, 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. CCI

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

Definitive chemoradiotherapy followed by adjuvant therapy would be counted as one line of systemic therapy.

CCI

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.

8.3. Efficacy Assessments

8.3.1. Response Criteria

CT or MRI

CT or MRI scans will be performed at the time points specified in the SoA. Computed tomography (CT) scans with contrast are preferred. The method used at Screening for a given patient should be used consistently throughout the study for that patient. 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 30 days prior to C1D1 may be allowed to be used for the baseline scan following discussion with the Sponsor's Medical Monitor. Tumor assessments will be performed as specified in the SoA.

Baseline tumor assessment will be performed during Screening. 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 electronic data capture (EDC) disease assessment table as the pre-baseline timepoint.

Response assessment will be determined per RECIST 1.1 for all arms (Appendix 1) at the time points specified by the investigator.

8.3.2. Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA) is an oncofetal protein that is overexpressed by approximately 85% colorectal cancers and detectable in serum (Mayer 1978). ASCO & NCCN clinical practice guidelines recommend serial monitoring of the CEA level while patients are on active treatment (Chiorean 2020). Reductions and elevations in CEA levels may help identify response and resistance to treatment before imaging, are prognostic and correlate with outcomes.

Increasing CEA levels are associated with poor outcomes (Herrera 1977) while decreasing levels are associated with better survival (Shani 1978).

Blood samples will be collected from all patients participating in this study for monitoring CEA levels, as indicated in the SoA.

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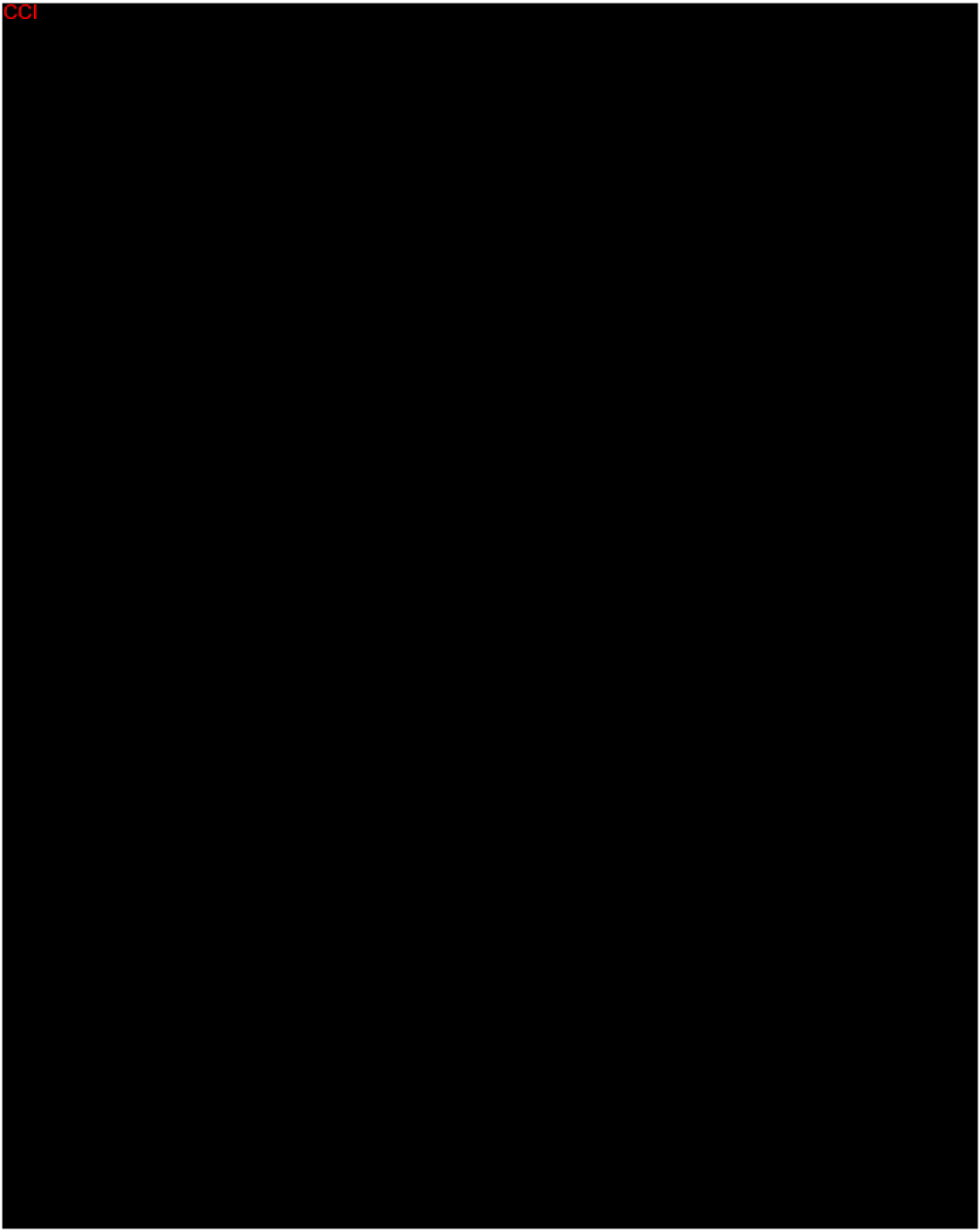

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[redacted]

8.5. Safety Assessments

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

8.5.1. Physical Examinations

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

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

Height (without shoes) in centimeters and weight (indoor clothing without shoes) in kilograms (kg) will be measured during the physical examinations.

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 Day1 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.

8.5.2. Vital Signs

Vital signs will include:

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

Assessments will be performed as indicated in the SoA.

8.5.3. ECOG Performance Status

The ECOG performance status (Oken 1982) will be assessed at Screening to determine eligibility of the patient and also during the study as indicated in the SoA (Appendix 2).

8.5.4. Electrocardiogram

Standard 12-lead ECG will be performed at Screening. Electrocardiograms may also be performed 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 the ECG was performed, and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using either Bazett's or Fridericia's formula.

8.5.5. Clinical Safety Laboratory Assessments

Clinical laboratory tests (Table 8) will be performed by the sites' local laboratories Samples 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 8: Clinical Safety Laboratory Tests

Hematology (Blood sample: whole blood; EDTA tests)				
Hemoglobin	Hematocrit	WBC count	Lymphocytes[a]	Neutrophils[a]
Platelets				
Serum Chemistry (Blood sample: Serum)				
Glucose	Calcium	BUN/urea	Creatinine	Sodium
Potassium	Albumin	Alkaline phosphatase	Total bilirubin[b]	Total protein
AST	ALT	LDH[c]		

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 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

[c] Per Investigator's discretion.

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

The Investigator or designee will review the laboratory report 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.

If any abnormal laboratory value or test result constitutes an AE, then these must be recorded on the AE eCRF. Values will be documented in the eCRF until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline. Any laboratory value that remains abnormal at the EOT visit that is considered clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline levels. For lab parameters included in the CTCAE, toxicity will be assessed using the NCI CTCAE, v5.0.

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

8.5.6. Adverse Events and Serious Adverse Events

Detailed information related to the collection and reporting of AEs and SAEs is in Section 9.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to study treatment or study procedures, or that caused the patient to discontinue study drug (Section 9.1).

8.5.6.1. Pregnancy Testing

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

8.6. Other Assessments

8.6.1. Collection of Information on Antineoplastic Therapy

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

8.6.2. Telephone Contacts

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

8.7. Post-treatment Assessments

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

9. ADVERSE EVENTS

9.1. 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 9.2.3 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 9.2.3 for additional information about SAE reporting.

9.1.1. Recording of Adverse Events

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

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

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

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

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

9.1.2. Laboratory Test Abnormalities

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

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

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (considered to be severe per NCI CTCAE, v5.0) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 9.1 and/or as per the opinion of the Investigator. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRF.

9.1.3. 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, v5.0 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Events that are not specifically defined in CTCAE v5.0 should be assessed according to the guidance provided on page 2 of the CTCAE v5.0 document

9.1.4. 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.

9.2. Serious Adverse Events

See Section 9.1 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).

9.2.1. 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 9.2.3). 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.

9.2.2. 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.

9.2.3. Reporting of Serious Adverse Events

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

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

If the SAE is to be reported via a paper SAE Report Form, upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

Fax: +1-617-334-7617 (USA)

+49-89-9218-5650 (Germany)

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

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

9.2.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Karyopharm 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 national regulatory requirements in participating countries.

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

9.3. Procedures for Handling Special Situations

9.3.1. 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) during the dosing period and for a period of at least 4 months after the end of treatment.

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 pregnancy test will be performed on each premenopausal female patient of childbearing potential prior to the first dose of study drug, at Screening, and again at treatment discontinuation during the EOT. A negative serum hCG pregnancy test must be documented within 3 days prior to first study dose on C1D1.

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

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

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

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

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

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

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

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

9.3.2.1. 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.

9.3.2.2. 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.

9.3.2.3. Occupational Exposure

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

All occurrences of occupational exposure with any study treatment are to be recorded on an SAE Report Form and sent to Karyopharm Pharmacovigilance, regardless of whether or not an AE or SAE has occurred due to the occupational exposure. If the occupational exposure is associated with an SAE, the SAE Report Form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted within 24 hours of awareness.

10. 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.

10.1. General Considerations

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

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

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

10.1.1. Procedures for Handling Missing Data

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

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

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

10.2. Statistical Hypotheses

Details of statistical hypotheses will be provided in the SAP.

10.3. Sample Size Determination

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Given above assumptions, the total sample size is approximately 78 patients with 26 in each arm.

10.4. Populations for Analyses

10.4.1. Intent to Treat Population

Intent-to-Treat Population (ITT): All patients randomized to study treatment. Patients will be analyzed in the treatment arm to which they will be randomized.

10.4.2. Safety Population

All patients who have been assigned to study treatment and who have received ≥1 dose of study drug. Patients will be analyzed according to the study treatment received.

10.5. Statistical Analyses

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

10.5.1. Efficacy Analyses

All efficacy analyses will be performed on the ITT Population. The analysis of time-to-event endpoints (PFS, OS) will be based on Kaplan-Meier method for estimation of summary statistics and will include the median event times and associated 95% CIs, as well as the number and percentage of censored patients. In addition, Cox proportional hazards regression models will be used to estimate a HR for the risk of progression in the selinexor only or selinexor and pembrolizumab arm versus the SOC control arm, and the selinexor and pembrolizumab arm versus selinexor only arm comparisons.

Details will be specified in the SAP.

10.5.2. Safety Analyses

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

The safety and tolerability of selinexor will be evaluated by means of drug-related AE reports, physical examinations, and laboratory safety evaluations. The grading of the severity of the AEs will be done according to CTCAE, v5.0. Investigators will provide their assessment as either the AE is related or not related to study drug.

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

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

Continual monitoring of safety data will be performed by the independent Data Safety Monitoring Board (DSMB). Adverse events and concomitant medications will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug, respectively.

10.5.2.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class and preferred term.

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

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

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

SAEs will be summarized in the same manner as TEAEs.

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

10.5.2.2. Laboratory Data

Clinical laboratory values will be expressed using SI units.

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

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

10.5.2.3. Vital Signs and Physical Examinations

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

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

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

10.5.2.4. Concomitant Medications

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

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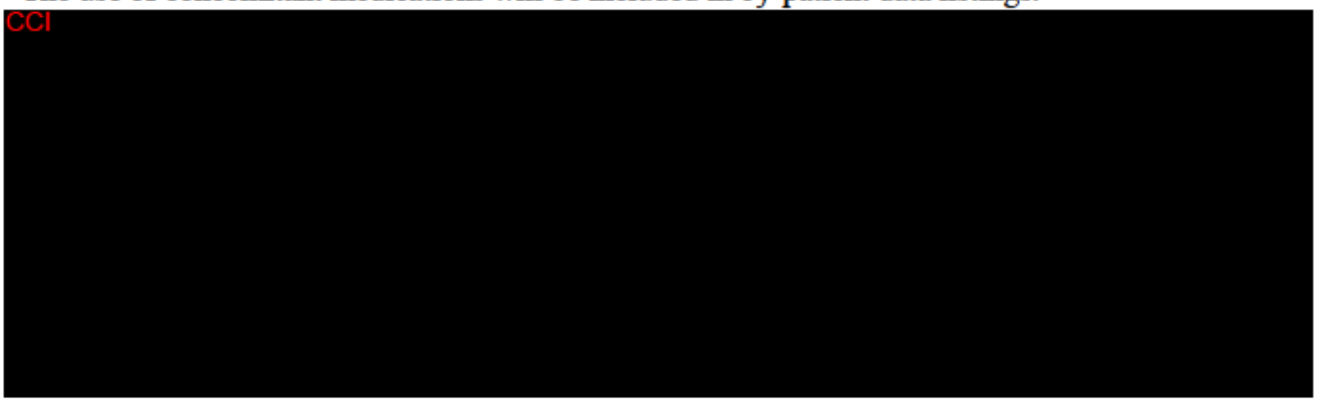

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Ethical and Administrative Obligations

11.1.1. Regulatory and Ethical Considerations

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

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

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

11.1.2. 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

11.2. 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.

11.3. Informed Consent Process

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

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- 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.

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Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. If required by local regulations, in addition to the primary ICF, there will be a separate form for female partners of participating male patients who are sexually active and accept risks.

11.4. Data Collection and Management

11.4.1. 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.

11.4.2. Data Collection

Data collection is the responsibility of the clinical study staff at the site, under the supervision of the site Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies

should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. An audit trail will be maintained by the eCRF system.

11.4.3. Site Monitoring

Before study initiation, Karyopharm personnel (or designated contract research organization [CRO]) will review the protocol with the Investigators and their staff (e.g., at a site initiation visit). During the study, the monitor will visit the site regularly to check the completeness of patient records, accuracy of entries on the CRFs, adherence to the protocol and to Good Clinical Practice (GCP), progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

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

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

11.4.4. Data Captures

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

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

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

11.4.5. Database Management and Quality Control

Karyopharm personnel (or designated CRO) will review the eCRF data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of

the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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

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

11.5. Structure of Committees

11.5.1. Data Safety Monitoring Board

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

The DSMB will be composed of at least 2 oncologists (at least one of whom specializes in CRC) and a statistician. Following their initial meeting, the DSMB will meet approximately every 6 months to review clinical data and provide recommendations to the Sponsor on whether the study should continue. The DSMB may also meet more frequently, if needed.

11.6. Dissemination of Clinical Study Data

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

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

11.7. 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.

11.8. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion 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

11.9. Publication Policy

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

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

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

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13. APPENDICES

APPENDIX 1. RECIST VERSION 1.1

(Modified from Eisenhauer 2009)

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

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <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 9: 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 10: 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.

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 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. Ultrasound 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, indinavior/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.