

STATISTICAL ANALYSIS PLAN

Protocol KCP-330-027

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC _{0-inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC _{0-t}	area under the concentration-time curve from time zero to time of last concentration measured
BA/BE	bioavailability/bioequivalence
BOR	best overall response
BSA	body surface area
BUN	blood urea nitrogen
C	Cycle
CI	confidence interval
CL/F	apparent clearance
C _{max}	maximum plasma concentration
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCR	disease control rate
CCI	
DOR	duration of response
ECG	Electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FOLFIRI	folinic acid, 5-fluorouracil, and irinotecan
Hb	Hemoglobin
HI	hepatic impairment
IB	Investigator's Brochure

Abbreviation	Definition
ICI	immune checkpoint inhibitor
iRECIST	Immunotherapeutic Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
KRAS	Kirsten rat sarcoma (gene homolog)
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Moderate Hepatic Impairment
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDn	Pharmacodynamics
PDnRO	Pharmacodynamics (XPO1) receptor occupancy
PFS	progression-free survival
PK	Pharmacokinetics
PR	partial response
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SHI	Severe Hepatic Impairment
$t_{1/2}$	terminal half-life
T_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TRAE	treatment-emergent treatment-related adverse event
V_d/F	apparent volume of distribution
WBC	white blood cell
XPO1	exportin 1

1. INTRODUCTION

This statistical analysis plan (SAP) describes the efficacy and safety analyses that will be performed for study KCP-330-027, based on the study protocol version 6.0 dated April 23, 2021. This is a multicenter, open-label, clinical study with a monotherapy period to assess 1) the relative bioavailability/bioequivalence of a new 100 mg tablet vs. the current 5×20 mg tablets at 100mg QW; 2) the PK of selinexor after a single dose of 100 mg (5×20 mg) among patients with normal hepatic function relative to 40 mg (2×20 mg) among patients with moderate and severe hepatic impairment. The second combination therapy period is to access the efficacy, safety and tolerability of selinexor in combination with

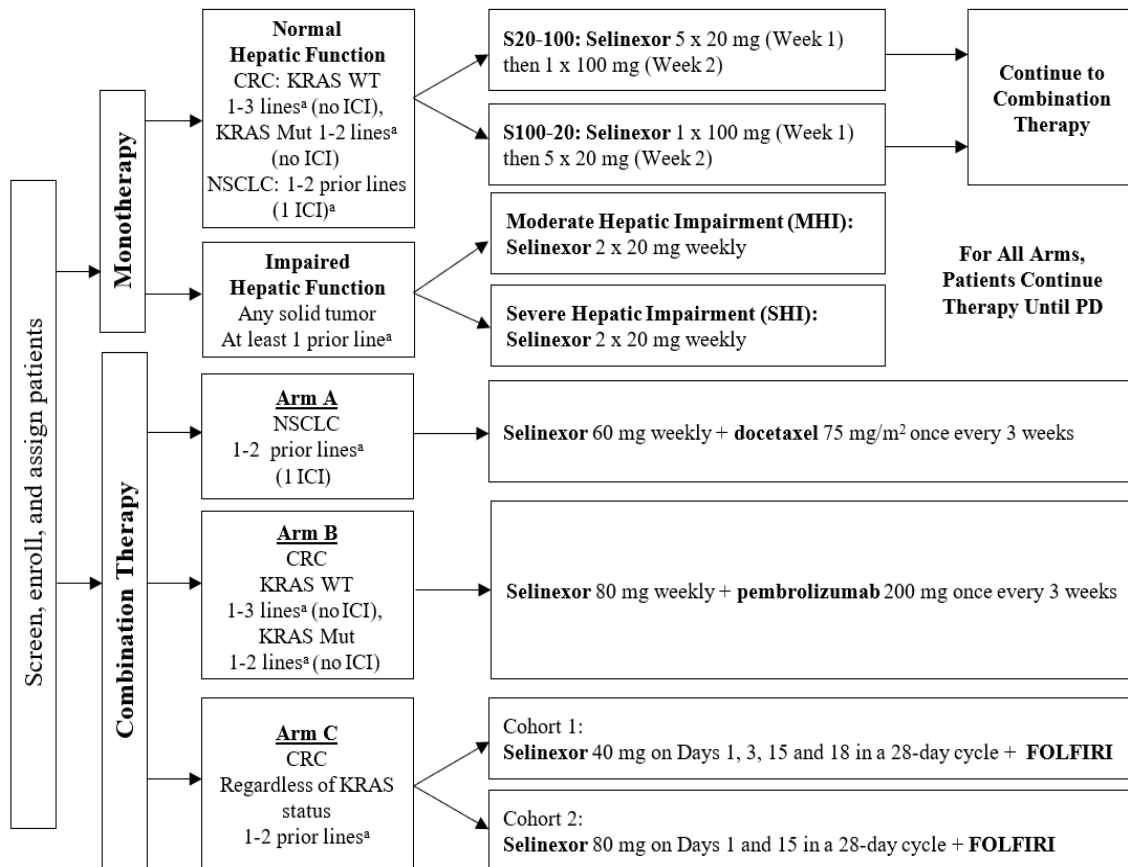
- Arm A: the combination of selinexor with docetaxel in patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) who have received 1-2 prior lines of systemic therapy that included 1 line of therapy with an anti-PD1/L1 monoclonal antibody (mAb).
- Arm B: the combination of selinexor with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

2. OVERVIEW AND INVESTIGATIONAL PLAN

2.1 Study Design

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

Figure 1 Study Design



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

^a Lines of systemic therapy

2.1.1 Monotherapy Part

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

Patients with NSCLC or CRC will be enrolled into the bioavailability/bioequivalence (BA/BE) and with solid tumors in the HI arms; patients in the HI arms are required to have at least 1 prior line of systemic anticancer treatment. Patients with normal hepatic function in the BA/BE arms will continue into the Combination Therapy Part after completing all planned doses and PK sampling in the Monotherapy Part, provided that they meet the Combination Therapy Part reassessment criteria. Patients that do not meet the reassessment criteria will be allowed to continue treatment with monotherapy as per discretion of the Investigator. Patients with MHI or SHI will not switch to combination therapy and will continue with monotherapy treatment, at the discretion of the Investigator, until disease progression or intolerance.

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

Table 2-1 Formulation of Selinexor Used during Each Week of the Monotherapy Part by Treatment Arm

Arm	Planned N	Hepatic Function	Cycle Duration	Week 1 ^a	Week 2 ^a
S20-100	10	Normal	14 days	5 × 20 mg tablet (Tablet A) ^b	1 × 100 mg tablet (Tablet B)
S100-20	10	Normal	14 days	1 × 100 mg tablet (Tablet B)	5 × 20 mg10tablet (Tablet A) ^b
MHI	8	Moderate impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)
SHI	6	Severe impairment	Days 1, 2, 3 (treatment can continue)	2 × 20 mg tablet (Tablet A) ^b	2 × 20 mg tablet (Tablet A)

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

^a If dosing and PK/PDn receptor occupancy (PDnRO) sampling must be repeated due to insufficient PK samples for reasons outlined in Protocol V6, Section 9.3, the repeat dose will be administered after 7 days (5 days minimum, 21 days. maximum) and will be considered the same “study day” as the previous dose (Protocol V6, Section 7.5.3.1) The Sponsor must be notified of any event leading to the collection of insufficient PK samples within 48 hours.

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

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

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

For Week 1 (for all patients) and Week 2 (for patients in the S20-100 and S100-20 arms) following an overnight fast of at least 10 hours, patients will be fed a standard low-fat meal 30 minutes prior to administration of selinexor. Patients should finish the meal within 30 minutes; and, the selinexor dose should be administered 30 minutes after the start of the meal. The start time of fasting and eating must be recorded. Water intake can be allowed ad libitum except for 1 hour before and after drug administration.

Blood sampling for selinexor PK (plasma) analyses will be collected pre-dose (≤ 10 minutes before taking selinexor), 15 min (± 5 min), 30 min (± 5 min), 1 hour (± 5 min), 1.5 hours (± 5 min), 2 hours (± 10 min), 3 hours (± 10 min), 4 hours (± 10 min), 5 hours (± 10 min), 6 hours (± 10 min), 8 hours (± 20 min), 10 hours (± 20 min; optional timepoint), 24 hours (± 1 hour), 30 hours (± 1 hour), and 48 hours (± 2 hour) post selinexor dose. Blood samples for the assessment of protein binding will be collected at 3- and 8-hours post-dose from patients administered Tablet A or Tablet B in the S20-100 and S100-20 arms (Day 1 and Day 8, respectively) and all patients in the MHI and SHI arms. Blood samples for PDn XPO1 receptor occupancy (PDnRO) analyses will be collected on Day 1 (pre-dose [≤ 10 minutes before taking selinexor], 2 hours [± 10 min], 4 hours [± 10 min], 8 hours [± 20 min], 24 hours [± 1 hour], 30 hours [± 1 hour], and 48 hours [± 2 hour] post selinexor dose) and Day 8 (predose [≤ 10 minutes before taking selinexor], 4 hours [± 10 min] and 8 hours [± 20 min] post selinexor dose) from patients in the S20-100 and S100-20 arms. PDnRO samples may not be collected from all patients if deemed appropriate by the Sponsor. The exact actual time of dosing and each sample is collected must be recorded.

If insufficient PK samples are collected in Week 1 (for all patients) or Week 2 (for patients in the S20-100 and S10-20 arms), selinexor administration and PK/PDn blood sampling for the same formulation will be repeated after 7 days (5 days minimum, 21 days maximum). For the MHI and SHI arms, dosing can go up to 4 weeks if both doses need to be repeated. When dosing/sampling is repeated, all timepoints need to be collected, including those already obtained, or the patient will need to be replaced. Details for situations where PK sampling of a formulation may be repeated are provided in Protocol V6 Section 10.3.

Safety will be evaluated through reporting of treatment-emergent adverse events (TEAEs), physical examinations, and clinical laboratory testing. Patients will receive best supportive care to manage the main adverse drug reactions of selinexor, which are nausea, anorexia, and fatigue (Protocol V6 Section 7.9). Dose reductions may be made (Protocol V6 Section 7.5), as appropriate, by the Investigator in discussion with the Sponsor's Medical Monitor.

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

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

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

2.1.2 Combination Therapy Part

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

Patients can complete screening assessments up to 21 days prior to the start of selinexor dosing. Laboratory tests will be completed ≤ 3 days before dosing (Protocol V6 Section 9.4.5).

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

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

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

Table 2-2 Dosing Schedules in the Combination Therapy Part

Arm	Plan ned N	Tumo r Type	Numb er Prior Thera pies	Cycle Durati on	Selinexor Dose	Docetaxel Dose	Pembroliz umab Dose	FOLFIRI Dose
A	40	NSCLC	1-2	21 days	60 mg weekly	75 mg/m ² once every 3 weeks	-	-
B	40	CRC	2-3	21 days	80 mg weekly	-	200 mg once every 3 weeks	-
C1	10	CRC	1-2	28 days	40 mg on Days 1, 3, 15 and 17	-	-	Irinotecan 180 mg/m ² ; leucovorin 400 mg/m ² ; 5-FU 400 mg/m ² bolus; then 5-FU 2400 mg/m ² continuous over 46-48 hours (IV) on Day 1 and 15 of a 28-day cycle
C2	10	CRC	1-2	28 days	80 mg on Days 1 and 15	-	-	Irinotecan 180 mg/m ² ; 5-FU 2400 mg/m ² ; leucovorin 400 mg/m ² ;

Arm	Plan ned N	Tumo r Type	Numb er Prior Thera pies	Cycle Durati on	Selinexor Dose	Docetaxel Dose	Pembroliz umab Dose	FOLFIRI Dose
								5-FU 400 mg/m ² bolus; then 5-FU 2400 mg/m ² continuous over 46-48 hours; IV on Day 1 and 15 of a 28-day cycle

2.2 Objectives and Endpoints

This SAP will only discuss the primary and secondary endpoints (Table 2-3) in the combination therapy period, and safety endpoints in the monotherapy period.

Table 2-3 Objectives and Endpoints

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

Objectives	Endpoints
	- area under the free-drug concentration-time curve from time zero extrapolated to infinity (AUC_{∞}) - apparent free-drug clearance (CL_R/F) - apparent free-drug volume of distribution (V_d/F)
- To assess the tolerability of single-agent selinexor at 100 mg once weekly in patients with advanced or metastatic NSCLC and CRC - To assess the tolerability of single-agent selinexor in patients with any type of advanced or metastatic solid cancer indication and moderate or severe hepatic impairment	Based on AE reports, physical examination results (including vital signs), and clinical laboratory results by means of the occurrence, nature and severity of AEs
Exploratory	
CCI	
Combination Therapy Part: Arm A and Arm B	
Primary	
To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	ORR per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab
Secondary	
To assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with NSCLC and with pembrolizumab in patients with CRC	PFS, DOR, DCR, per RECIST 1.1 for selinexor + docetaxel per iRECIST for selinexor + pembrolizumab

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

2.3 Determination of Sample Size

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

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

Combination Arm A enroll approximately 40 patients, Arm B will enroll approximately 40

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

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

2.4 Modifications to The Statistical Section of the Protocol

The DCR will be defined as the proportion of patients who have best response of PR or better as assessed by RECIST1.1 [Arms A, C], or iRECIST [Arm B], or at least 12 continuous weeks of SD before disease progression, death due to any reason, or initiation of a new antineoplastic treatment.

2.5 CHANGES IN THE STATISTICAL ANALYSIS PLAN

Not applicable. This is the original version of the SAP.

3. GENERAL STATISTICAL METHODS AND DATA HANDLING

This SAP outlines the methods to be used in the analysis of clinical data during the combination therapy period in order to answer the study objectives. Populations for analysis, data handling rules, and statistical methods are provided. This SAP does not include endpoints and methods to be used in the relative bioavailability and PK analysis of monotherapy period.

3.1 General Analysis Methods

All summary statistics will be computed and displayed among the corresponding analysis population, and by each assessment time point whenever applicable. Summary statistics for continuous variables will in general include n, median, mean, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be presented with the denominators for the percentages determined based on the analysis population used, unless otherwise specified. For time-to-event variables, the Kaplan-Meier (KM) method will be used for descriptive summaries. Graphical displays may be provided as appropriate.

The safety endpoints during monotherapy and combination therapy period will be summarized separately. Results will be presented by arm and cohort.

3.2 Missing Data Handling in Data Presentation

In general, missing baseline values will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data will be summarized using counts (n) and percentages (%). The denominator will be the total number of people in the corresponding analysis group, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only

3.2.1 Handling of Computation of Treatment Duration if Study Treatment End of Treatment Date is Missing

For the calculation of treatment duration, the date of the last dose of study treatment is equal to the date of last non-zero study treatment dosing reported on the electronic case report form (eCRF) dosing page. If all the dosing dates are missing, then the duration is missing.

3.2.2 Handling of Missing/partial Dates for Adverse Events or Concomitant Medications

In general, the imputation should be conservative such that onset dates should be imputed to be as early as possible and resolution dates as late as possible. However, for categorization purposes, if the partial AE onset date information does not indicate whether the AE started prior to treatment, during the treatment period, or after the treatment period, the AE will be classified as treatment-emergent.

The data imputations are only for categorization purposes or calculation of AE duration, and will not be used in listings.

Refer to the *Karyopharm Biostatistics and Statistical Programming Rule Book* for details on imputation methods.

3.2.3 Handling of Missing Assessment of Relationship of AEs to Study Treatment

If the assessment of the relationship to study treatment is missing, then the relationship to study treatment is considered as related.

3.3 Study Treatment Dosing Date

Study treatment dosing date is the date on which a patient actually received study treatment (partial or complete), as recorded on the study drug exposure eCRF.

The start date of study treatment is defined as the earliest non-zero dose date of any study drug, and the end date of study treatment is defined as the latest non-zero dose date of any study drug.

3.4 Study Day Calculation

Study Day 1 is the date of first study treatment. The day before Day 1 is considered Day -1. There is no Day 0.

A patient is considered as treated in a cycle if the patient received any non-zero dose of study drug in that cycle.

Study day for a given assessment is defined as

- the assessment date – the date of first study treatment + 1 if the assessment date is on or after Day 1, or
- The assessment date – the date of first study treatment if the assessment date is before Day 1

3.5 Baseline Measurement

In general, the baseline value is defined as latest measured value prior to the first dose of study treatment.

In the event that an assessment is performed on the same date as the date of first study treatment and it cannot be determined whether it preceded the first dose, the evaluation time will be assumed to be prior to dosing.

3.6 Visit Windows

For safety data during the combination therapy period that are summarized/plotted by time points, non-missing assessments from all scheduled and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme. Analysis visit windows for combination therapy period are defined in Table 3-1 and Table 3-2.

If there are 2 or more assessments mapped to the same analysis visit for a patient, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments mapped to the same analysis visit with the same distance from the target visit day, the latest one will be selected for the analysis.

Table 3-1 Visit Windows for Clinical Laboratory Tests and Vital Signs for Combination Therapy Period in Arm A and B

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1

Day 22	Day 22	Day 2 to 32
Day 43	Day 43	Day 33 to 53
Day 64	Day 64	Day 54 to 74
...		
(every 21 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 3-2 Visit Windows for Clinical Laboratory Tests and Vital Signs for Combination Therapy Period in Arm C

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
Day 29	Day 29	Day 2 to 43
Day 57	Day 57	Day 44 to 71
Day 85	Day 85	Day 72 to 99
...		
(every 28 days)		
NOTE: Day 1 is the date of first study treatment. Analysis visit and visit window may change for certain parameters depending on the data availability.		

3.7 Subgroups

To explore potential contributors to treatment efficacy and mechanism of action in the study population, subgroup analyses on selected endpoints (e.g. ORR) will be performed when appropriate. For example, CRC patients with or without KRAS mutations may be analyzed separately.

3.8 Pooling of Centers for Statistical Analyses

All participating centers in the study will be pooled together for analyses.

3.9 Computing and Coding Standards

Activities will be performed using the following tools:

Table 3-3 Computing and Coding Standards

Table, listing, and figure production	SAS Version 9.4 or higher
---------------------------------------	---------------------------

Coding	
AEs	MedDRA Version 25.1 or higher
Medical Histories	MedDRA Version 25.1 or higher
Prior and Concomitant Medications	WhoDrugGlobalB3- 202209 or higher
Grading	
AEs	CTCAE Version 5.0
Labs	CTCAE Version 5.0

4 PATIENT INFORMATION

4.1 Analysis Populations

Safety Population for the bioequivalence cohorts in the monotherapy period

All patients who receive at least one dose of selinexor in the monotherapy period in S100-20 or S20-100 arms.

Safety Population for the hepatic impairment cohorts in the monotherapy period

All patients who receive at least 1 dose of selinexor in the monotherapy period in SHI or MHI arm.

Safety Population for the combination therapy period

All patients who receive at least 1 dose of selinexor in the combination therapy period in arm A, B, and C1/C2.

Modified Intent-to-Treat Population for the combination period

All patients who receive at least 1 dose of selinexor in the combination therapy period. This is the same population as the safety population in the combination therapy period.

4.2 Disposition of Patients

The following variables may be used to summarize patient disposition:

- Patients who received at least one dose of study treatment (partial or complete)
- End of treatment status:
 - Patients still on treatment
 - Patients who discontinued treatment and primary reason for treatment discontinuation
- Survival follow-up status
 - Patients in survival follow-up
- End of study status:
 - Patients still on study
 - Patients who discontinued study and primary reason for study discontinuation

4.3 Protocol Deviations

Major protocol deviations will be presented in a listing.

4.4 Demographics, Medical History and Baseline Characteristics

Demographics, medical history and baseline characteristics will generally be summarized among mITT and safety populations, unless otherwise specified.

4.4.1 Demographic Data

Demographic characteristics may include the following:

- Sex (Female, Male)

- Race (Asian, Black, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Country (Israel)
- Age (years)

4.4.2 Baseline Characteristics

Baseline characteristics may include the following:

- Height (cm)
- Weight (kg)
- Body surface area (BSA) (m²)
- BMI (kg/m²)
- Eastern Cooperative Oncology Group (ECOG) performance status

4.4.3 Prior Antineoplastic Therapy

The following variables will be used to summarize prior antineoplastic therapy:

- Type of unique prior anti-NSCLC or anti-CRC regimens
- Number of prior anti-NSCLC or anti-CRC regimens

4.4.4 Medical History - Conditions and Procedures

Medical history other than NSCLC or CRC will be summarized by system organ class (SOC) and Preferred Term (PT) using the number and percentage of patients who have at least one occurrence of a SOC and PT. The summary will be sorted by alphabetic order in SOC, and further by decreasing frequency of PT within each SOC. When more than one PT has the same frequency, the order of presentation will be alphabetical in PTs.

4.4.5 Disease History

Disease history data will be summarized by treatment arm, as well as overall, and will include the following variables:

- Time since first initial diagnosis to the first dose date
- Stage of tumor at initial diagnosis
- Stage of tumor at study entry

4.5 Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE).

Prior medications are any medications received by the patient prior to the first dose of study treatment. Prior medications can be discontinued before the first dose of study treatment or can be ongoing during treatment period.

Concomitant medications are any treatments received by the patient concomitantly with study treatment, from the first dose of study treatment to last dose of study treatment + 30 days.

Note that a medication can be classified as both a prior medication and a concomitant medication.

Concomitant medications will generally be summarized for mITT populations. Concomitant medications will be summarized according to the WHO DDE by the ATC level 2 (therapeutic level), level 4 (generic level) and preferred name. A patient taking the same drug multiple times will only be counted once.

Please refer to Section 3.2.2. for details on data handling rules related to computation, dates and imputation for missing dates.

4.6 Extent of Study Treatment Exposure and Compliance

Extent of exposure and compliance will be summarized for mITT populations.

4.6.1 Extent of Study Treatment Exposure

The extent of exposure for the study treatment will be assessed using the duration of study treatment exposure. The following will be assessed separately for each study drug (selinexor, docetaxel, pembrolizumab, and FOLFIRI):

- Duration of exposure
- Total dose received
- Average dose received per week
- Occurrence of dose reduction
- Occurrence of dose interruption
- Occurrence of missed dose

Duration of study treatment exposure is defined as the date of last study treatment – date of first study treatment + 1.

Average dose received per week is defined as total dose received divided by duration of exposure times measured in weeks.

4.6.2 Treatment Compliance

Study treatment compliance is defined as

$$\frac{\text{number of actual study treatment doses taken}}{\text{number of study treatment doses prescribed}} \times 100$$

A study treatment dose is considered prescribed if any study drug is prescribed. The number and percentage of patients with study treatment compliance $\geq 70\%$ will be provided. Note that the number of prescribed study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Selinexor compliance is similarly defined as

$$\frac{\text{number of actual selinexor doses taken}}{\text{number of selinexor doses prescribed}} \times 100$$

The number of scheduled selinexor doses does not include doses missed due to treatment interruption or other reasons not related to patient choice. The number and percentage of patients with selinexor compliance $\geq 70\%$ will be provided.

5 EFFICACY

The primary efficacy analysis will be conducted using the mITT population. Patient response at each time point will be assessed by PIs.

5.1 Primary Efficacy Endpoint

5.1.1 Overall Response Rate (ORR)

ORR is defined as the proportion of patients who have a response of partial response (PR) or complete response (CR) as assessed by RECIST/iRECIST criteria (v1.1) before disease progression or initiating a new antineoplastic treatment.

ORR can be computed based on best overall response (BOR) of each patient. BOR is only censored by EOT+ 30 days, or confirmation of PD, new antineoplastic treatment event, database cut. The gap of assessment is not censoring event for BOR.

For descriptive purposes, a two-sided exact 95% CI of ORR will also be presented. The number and percentage of patients in the following response categories will also be presented, along with exact 95% CIs: CR, PR, SD, and NE.

5.2 Secondary Efficacy Endpoint

5.2.1 Progression-free Survival (PFS)

PFS is defined as the time from the starting date of the combination therapy until the date of first PD determined by PI per RECIST or iRECIST, or death due to any cause, whichever occurs first. The outcome and censoring definitions are provided in Table 5-1, Table 5-2 for RECIST and iRECIST respectively. The number and percentage of censored patients will be reported. The 25th, 50th (median), and 75th percentiles for PFS and associated 95% CIs will be estimated based on the KM method, and the KM curves will be provided.

5.2.2 Duration of Response (DOR)

DOR is defined for patients with PR or CR as the duration from the date of first PR or better to the date of first PD or death due to any cause, whichever occurs first. Details on the outcome and censoring definitions used for DOR are provided in Table 5-1, Table 5-2.

The number and percentage of censored patients will be reported. The 25th, 50th (median), and 75th percentiles for DOR and associated 95% CIs will be estimated based on the KM method, and the KM curves will be provided.

5.2.3 Disease control rate (DCR)

DCR is defined as the proportion of patients who have best response of PR or better, or at least 12 continuous weeks of SD before disease progression or initiating a new antineoplastic treatment.

For descriptive purposes, a two-sided exact 95% CI will also be presented.

5.2.4 Overall Survival (OS)

OS is defined as time since the starting date of the combination therapy until death due to any cause. If death event did not occur during the follow-up period, the patient is censored at the date of discontinuation from the study, or date of last participating visit (e.g., a telephone

contact with patient status being alive) on or before database cut-off date, whichever occurs first.

Table 5-1 Outcome and Censoring Definition for DOR and PFS per RECIST

Situation	Date of event or censoring	Outcome
No baseline disease assessment	Date of first combination therapy	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first combination therapy	Censored
No PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. documented treatment discontinuation + 30 days, e. start of new treatment, f. A gap of 2 or more consecutively missed scheduled disease assessment whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events listed in the left column	Censored
Investigator-determined PD without a gap of 2 or more consecutively missed scheduled disease assessment before PD.	Date of PD	Event
Death before Investigator-determined PD and without a gap of 2 or more consecutively missed scheduled disease assessment before death.	Date of death	Event

Table 5-2 Outcome and Censoring Definition for DOR and PFS per iRECIST

Situation	Date of event or censoring	Outcome
No baseline disease assessment	Date of first combination therapy	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first combination therapy	Censored
No event been called on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. documented treatment discontinuation + 30 days, e. start of new treatment, f. A gap of 2 or more consecutively missed scheduled disease assessment (>140days between two assessments). whichever occurs first	Date of last adequate disease assessment prior to the earliest occurrence of the events listed in the left column	Censored
Investigator-determined iCPD without a gap of 2 or more consecutively missed scheduled disease assessment before iCPD, and without an iUPD immediately before it.	Date of iCPD	Event
Investigator-determined iUPD without an iCPD before it or a gap of 2 or more consecutively missed scheduled disease assessment before this iUPD, which is followed immediately by iCPD, EOT due to PD, death, or new antineoplastic treatment.	Date of iUPD	Event
Death before Investigator-determined iUPD/iCPD and without a gap of 2 or more consecutively missed scheduled disease assessment before death.	Date of death	Event

6 SAFETY

Safety analyses will be based on the reported AEs and other safety information, such as ECG, vital signs, physical examination, ECOG performance status, and clinical laboratory assessments. Safety analyses will be performed using the safety population and will be descriptive; no statistical testing is planned.

6.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient receiving a pharmaceutical product regardless of a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

All AEs (including serious adverse events [SAEs]) will be coded to a PT and associated primary SOC using the Medical Dictionary for Regulatory Activities (MedDRA).

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale. An AE with a CTCAE grade of 3 or higher is considered a severe AE. The severity of the AE is different from the seriousness of the AE.

6.1.1 Definitions

- A **treatment-emergent AE (TEAE)** is an AE that was not present prior to the initiation of study treatment or was present and worsened in intensity or frequency following exposure to study treatment, from the first dose to 30 days after the last dose (inclusive) or the day before the start of a new antineoplastic treatment, whichever occurs first. Additionally, any AE that occurs 30 days after the last dose of study treatment is considered a TEAE if considered by the Investigator as related to any study treatment.
- A **serious AE (SAE)** is 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
- A **treatment-emergent treatment-related AE (TRAE)** is any TEAE that is considered by the Investigator to be related to any study treatment.

6.1.2 Analysis Methods

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to classify the AE as treatment emergent. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is not treatment emergent. Details on classification of AEs with missing or partial onset dates are provided in Section 3.2.2.

AE summaries will include number and percentage of patients who have experienced a TEAE. The denominator for percentages is the total number of patients in the treatment Arm. Multiple occurrences of the same event in the same patient will be counted only once in the tables.

Unless otherwise specified, sorting order will follow the alphabetic order in SOC, and further by decreasing frequency of PTs within each SOC. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

6.1.2.1 Analysis of TEAE and TRAE

An AE overview summary table will be provided, which will include the number of patients with any:

- TEAEs
 - Grade 3/4
 - Serious
 - Leading to dose modification (i.e., reduction or interruption) of any study drug
 - Leading to dose reduction of any study drug
 - Leading to dose interruption of any study drug
 - Leading to study treatment discontinuation
 - Leading to death
- TRAEs
 - Same subcategories as for TEAEs

TEAEs will be summarized by primary SOC and PT and will include the following categories:

- All TEAEs
- All TEAEs, by causality
- All TEAEs, by maximum grade
- TEAEs leading to dose modifications of study treatment
- TEAEs leading to study treatment discontinuation

6.1.2.2 Analysis of SAEs

Treatment-emergent SAEs will be summarized by primary SOC and PT and will include the following categories:

- All treatment-emergent SAEs
- All treatment-emergent SAEs, by causality
- Treatment-emergent SAEs leading to dose modifications of study treatment
- Treatment-emergent SAEs leading to study treatment discontinuation

6.2 Death

The following summaries on death events will be provided:

- An overview of all death events and primary cause of death
- TEAEs leading to death (death as an outcome on the AE page as reported by the Investigator), by primary SOC and PT

- TEAEs leading to death and are related to study treatment, by primary SOC and PT

6.3 Laboratory Safety Variables

6.3.1 Definitions

Blood samples for clinical laboratory tests will be taken as specified in the study protocol, and measurements in conventional units will be converted using the international system of units (SI). Clinical laboratory data includes the following:

- Hematology: hemoglobin (Hb), hematocrit, white blood cell (WBC) count, lymphocytes, neutrophils, and platelets
- Serum chemistry: sodium, potassium, urea, BUN, creatinine, creatinine clearance, glucose, calcium, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin (direct and indirect), direct bilirubin, indirect bilirubin, total protein.
- Coagulation parameters: prothrombin time, international normalization ratio and activated partial thromboplastin time

6.3.2 Analysis of Laboratory Variables

Whenever applicable, severity of selected clinical laboratory measures will be determined based on the CTCAE criteria. The worst toxicity grade in hematology and chemistry will be summarized by toxicity grade. 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 presented.

For key laboratory parameters, measurements over time (actual values and/or change from baseline) may be plotted for individual patients and/or summarized across patients (e.g., using boxplots).

6.4 Vital Signs, ECOG, and Physical Examination Variables

Physical examinations (PEs) include height, weight, and vital signs (heart rate, systolic and diastolic blood pressure, and body temperature). An ECOG performance status assessment will be performed as specified in the study protocol.

The actual value and change from baseline over time will be summarized for vital signs. Abnormal vital signs results will be summarized in the threshold/range analyses.

Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status will be presented.

7 REFERENCES

Karyopharm Biostatistics and Statistical Programming Rule Book, Karyopharm Therapeutics Inc.

FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. 2001.

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