STATISTICAL ANALYSIS PLAN

Protocol KCP-9274-901

A PHASE 1 OPEN-LABEL STUDY OF THE SAFETY, TOLERABILITY AND EFFICACY OF KPT-9274, A DUAL INHIBITOR OF PAK4 AND NAMPT, IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES OR NON-HODGKIN'S LYMPHOMA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Please refer to the signature page at the end of this document.

The undersigned has developed this statistical analysis plan (SAP):

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The undersigned have reviewed this SAP and approve it in its entirety:

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DOCUMENT HISTORY

Version	Date	Author(s)	Brief Summary of Changes
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AECI	adverse event of clinical interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomic therapeutic class
BSA	body surface area
°C	degrees Centigrade
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EoS	End of Study
EoT	End of Treatment
ER	Extended Release
°F	degrees Fahrenheit
FDA	Food and Drug Administration
HI	hematological improvement
HNSTD	highest non-severely toxic dose
ICF	informed consent form
Karyopharm	Karyopharm Therapeutics Inc.
kg	kilogram
m^2	square meters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified intent-to-treat
mL	milliliter
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
CCI	[redacted]

Abbreviation	**Definition**
PDx	patient derived xenograft
PFS	progression-free survival
PK	pharmacokinetic
PP	per protocol
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment emergent adverse event
TTP	Time to progression
ULN	upper limit of normal
WBC	white blood cell
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. OVERVIEW AND INVESTIGATIONAL PLAN

1.1. STUDY DESIGN

This is a first-in-human, multi-center, open-label clinical study with separate Dose Escalation and Expansion Phases to assess preliminary safety, tolerability, and efficacy of KPT-9274, a dual inhibitor of PAK4 and NAMPT, in patients with advanced solid malignancies (including sarcoma, colon, lung, etc.) or NHL for which all standard therapeutic options considered useful by the investigator have been exhausted and with progressive disease on study entry.

The Dose Escalation Phase will include two parts, Part A and Part B.

- Part A will be performed to determine the RP2D and MTD of KPT-9274 alone (note that the RP2D may be ≤ the MTD and will be used for the Dose Expansion Phase of the study).
- Part B will be performed to determine the RP2D and MTD of KPT-9274 co-administered with starting dose of 500 mg niacin ER (may be titrated to 2,000 mg of daily dose, per label); the starting dose of KPT-9274 for Part B will be a dose and schedule that has cleared DLT assessment in Part A.

DOSE ESCALATION PHASE

Based on repeat-dose toxicology studies in dogs and rats, a starting dose of 10 mg of KPT-9274 was selected. This provides a 6-fold safety window relative to the expected highest non-severely toxic dose (HNSTD) in dogs.

Patients will receive oral KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle. During Part B of the Dose Escalation Phase, patients will receive a starting dose of 500 mg niacin ER (may be titrated to 2,000 mg of daily dose per label) co-administered with each dose of KPT-9274. For the purposes of dose escalation decisions, a standard 3+3 dose escalation design will be used during both Part A and Part B.

Based on preclinical and early clinical data, patients will be enrolled according to their NAPRT1 status at a ratio of 2:1 (NAPRT1 negative: NAPRT1 positive). The NAPRT1 status must be determined prior to enrollment based on evaluation of a fresh tumor biopsy or archival tissue taken ≤ 6 months of screening.

Part A: KPT-9274

The initial cohort, Cohort 1, will consist of 3 enrolled patients who will be treated at 10 mg. If these patients do not experience a DLT during Cycle 1, the KPT-9274 dose will be escalated to 20 mg for another group of 3 patients (Cohort 2) upon approval during a dose decision meeting. Dose escalation will continue based on a standard 3+3 design at the dose levels specified in the table below.

Part B: KPT-9274 + Niacin ER

The initial cohort, Cohort 1 + niacin ER (Cohort 1B), will consist of 3 enrolled patients who will be treated at a dose and schedule of KPT-9274 that has cleared DLT assessment in Part A, co-administered with a starting dose of 500 mg niacin ER (may be titrated to 2,000 mg of daily dose, per label).

Part A and Part B:

Dose escalation will continue independently in Parts A and B until the MTD in each part is determined. The MTD is defined as the highest dose at which ≤1 patient experiences a DLT in Cycle 1. A RP2D equal to or less than the MTD will be declared for each part and used for the Dose Expansion Phase.

In both Parts A and B, patients must complete a minimum of 1 cycle of treatment, defined as receiving ≥ 75% of KPT-9274 doses during Cycle 1 (e.g., ≥9 of 12 doses in the 3 doses/week schedule), or have a DLT within the first cycle of treatment to be evaluable for dose escalation decisions. Dose escalation decisions will occur when the cohort of patients has met these criteria.

The table below describes the starting dose of KPT-9274 and the dose cohorts that may be evaluated during Part A of the Dose Escalation Phase of this study. A similar dose escalation plan will be used in Part B; however, the starting dose of KPT-9274 will be based on a dose and schedule that has cleared DLT assessment in Part A. To better evaluate the safety, tolerability, and PK of KPT-9274, additional cohorts of patients may be enrolled on alternate dosing schedules, at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

Part A: KPT-9274 Dose Escalation Levels

Cohort	**KPT-9274**
	Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle
1 (starting dose)	10mg
2	20mg
3	30mg
4	40mg
5+	Increases at 20 mg per cohort

DOSE EXPANSION PHASE

After completion of the Dose Escalation Parts A and B, Dose Expansion in up to 65 additional patients with advanced solid malignancies and NHL may be conducted to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274 ± niacin ER. Note that preliminary clinical results may define the patient population (i.e., specific indications) selected for enrollment in the Dose Expansion Phase.

After declaring the RP2D for KPT-9274 single agent and KPT-9274 + niacin ER, based on the safety and tolerability results of the Dose Escalation Phase, a decision will be made whether expansion (4 groups, ~45 patients total) will be conducted at the RP2D of KPT-9274 single agent or at the RP2D of KPT-9274 + niacin ER. If the ~45 patient expansion is conducted at the RP2D of KPT-9274 + niacin ER, an optional expansion with < 20 patients at the RP2D of KPT-9274 single agent may also be initiated.

At least 1 clinical response (minimum of stable disease ~16 weeks) must be seen in any of the first 10 patients treated at the RP2D in order to fully enroll either expansion cohort. These 10 patients include the patients enrolled under the 3+3 design for DLT assessment; if necessary, additional patients will be enrolled to a maximum of 10 patients. If no clinical responses are observed, the study will be stopped for futility. If a clinical response is observed at any time, then enrollment of the full expansion cohort may proceed. Initiation of the KPT-9274 + niacin ER escalation will not be dependent upon demonstration of clinical benefit of the single agent, but futility at the KPT-9274 + niacin ER RP2D will be assessed prior to full expansion using the same criterion as described above for the single agent KPT9274.

The KPT-9274 ± niacin ER expansion cohort will consist of 4 groups of approximately 45 patients (please note that these expansion groups may change based on escalation results) including:

- I. NAPRT1 deficient tumor group, approximately 10 patients
- II. NAPRT1 positive tumor group, approximately 10 patients
- III. Either NAPRT1 deficient or positive tumor group, approximately 10 patients
- IV. IDH1 mutant tumor group, approximately 15 patients

Please note that the composition of the expansion groups (e.g., number of patients with NAPRT1 positive vs NAPRT1 deficient tumors) may change based on the results from the escalation phase. An additional, optional KPT-9274 single agent expansion cohort will consist of ~ 20 patients with any tumor mutational status.
Patients in the Dose Expansion Phase may be treated with the RP2D of KPT-9274 ± niacin ER according to the same schedule administered in the Dose Escalation Phase of the study. Patients who are in Part A or Part B of the Dose Escalation Phase being treated at the RP2D ± niacin ER dose chosen for expansion will be included in the efficacy and safety analyses of the Dose Expansion Phase.

Part C: KPT-9274 + Nivolumab
After sufficient data from Part A is available, Dose Finding with the potential for Expansion in patients with melanoma will be conducted to further explore safety, tolerability and preliminary evidence of antitumor activity of the RP2D (or any DLT-cleared dose) of KPT-9274 + nivolumab.
DOSE FINDING PHASE
This Arm will treat approximately 20 patients with melanoma who progressed on an anti-PD-1 or anti-PD-L1 antibody in a prior line of therapy. Two dose levels of KPT-9274 (30 and 40 mg) in combination with nivolumab will be tested in parallel. Patients will be enrolled first into the 30 mg cohort. Patients will be treated with 30 or 40 mg KPT-9274 three times a week every other day (Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26) during each 28-day cycle in combination with a standard dose and schedule of nivolumab (480 mg on Day 1 of each 28-day cycle). A maximum of 10 patients may be enrolled at each dose level. Treatment will continue until disease progression, unacceptable AEs or toxicity that cannot be managed by supportive care, patient's withdrawal of consent, Investigator decision to discontinue study treatment, pregnancy, death, or Sponsor decision to terminate the study. A safety review committee will evaluate all available data from both cohorts after the last patient enrolled has been observed for at least 2 cycles to determine the RP2D. Additional dose levels (20 mg or 60 mg) might be evaluated if an optimal dose is not identified and the safety review committee is in agreement. The definition of a DLT is the same as described in Parts A and B. Response will be assessed every 8 weeks per RECIST 1.1 criteria.

KPT-9274 Dose Finding (Part C)

Cohort	KPT-9274	**Nivolumab**
	Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle	Day 1 in a 28-day cycle
1	30 mg	480 mg
2	40 mg	480 mg

1.2. OBJECTIVES

1.2.1. Primary Objectives

Parts A and B
Dose Escalation

- To determine the Recommended Phase 2 Dose (RP2D)* and the maximum tolerated dose (MTD)* for KPT-9274 administered alone (Part A) and with co-administration of niacin ER (Part B).

*A RP2D equal to or less than the MTD will be declared based on safety and tolerability data and used for expansion.

- To evaluate the safety and tolerability, including dose-limiting toxicities (DLT), of KPT-9274 ±niacin ER.

Dose Expansion

- To evaluate the safety and tolerability of the RP2D and schedule(s) for KPT-9274 ± niacin ER.
- To determine preliminary evidence of anti-tumor activity of KPT-9274 at the RP2D ± niacin ER in patients with advanced solid malignancies or NHL according to Response Evaluation Criteria in Solid Tumors, Version 1.1 or Lugano Classification, respectively.

Part C

- To evaluate the safety, tolerability, and RP2D of KPT-9274 + nivolumab in patients with melanoma.

1.2.2. Secondary Objectives

Parts A and B

Dose Escalation

- To define the preliminary evidence of anti-tumor activity of KPT-9274 alone (Part A) and with co-administration of niacin ER (Part B) in patients with advanced solid malignancies or NHL.

Dose Escalation and Dose Expansion

- To determine the pharmacokinetic (PK) profile of KPT-9274, including, but not limited to, maximum plasma concentration, time-to-peak plasma concentration, terminal half-life, and plasma clearance

Part C

- To determine the preliminary evidence of anti-tumor activity of KPT-9274 + nivolumab in patients with melanoma.
- To characterize the PK of KPT-9274 when administered with nivolumab in patients with melanoma.

1.2.3. Exploratory Objectives

CCI

[redacted]

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. The endpoints and methods to be used in the analysis of PK, CCI [redacted] studies will be addressed in separate plans.

1.3. ENDPOINTS

1.3.1. Efficacy Endpoints

Disease response will be evaluated according to RECIST 1.1 (advanced solid malignancies and melanoma) or Lugano Classification (NHL) and will include the following:

- **Objective response rate (ORR):** proportion of patients who have a response of partial response (PR) or complete response (CR).
- **Duration of response (DOR):** the duration of time from first meeting CR or PR measurement criteria (whichever occurs first) until the first date that PD recurrence is objectively.
- **Disease control rate (DCR):** DCR proportion of patients who have a response of CR, PR, and Stable Disease (SD) $\geq$ 16 weeks.
- **Duration of disease control:** the duration of time from date of first study treatment until the first date that PD is objectively documented.
- **Progression-free survival (PFS):** the duration of time from date of first study treatment until the first date that PD is objectively documented or death due to any cause.
- **Overall survival (OS):** the duration of time from date of first study treatment until death from any cause.
- **Time to Progression (TTP):** The duration of time from date of first study treatment until the first date that PD is objectively documented or death due to PD.

1.3.2. Safety Endpoints

The safety and tolerability of KPT-9274 ± niacin ER and KPT-9274 + nivolumab will be evaluated by means of DLTs, AE reports, physical examination results, electrocardiogram results and laboratory safety evaluations. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, will be used for grading of AEs.

1.4. DETERMINATION OF SAMPLE SIZE

- **Sample size for Part A and B:**

The sample size for the Dose Escalation Phase is based on a standard 3+3 design for the purpose of determining the RP2D and MTD (Part A) and the RP2D and MTD of KPT-9274 co-administered with niacin ER (Part B). Each cohort in Parts A and B of the Escalation Phase will consist of 3 or 6 patients per cohort.

For the Dose Expansion Phase, up to 65 additional patients may be enrolled at the RP2D for KPT-9274 single agent or KPT-9274 + niacin ER (up to 45 patients in the KPT-9274 ± niacin ER cohort; if Dose Expansion is conducted with KPT-9274 + niacin ER then an optional cohort of up to 20 additional patients in the KPT-9274 single agent cohort).

Assuming that 9 dose levels of KPT-9274 are evaluated during both Part A and Part B of the Dose Escalation Phase and up to 65 additional patients are enrolled in the Dose Expansion Phase, the total combined enrollment is estimated to be 175 patients.

- **Sample size for Part C:**

Two dose levels of KPT-9274 (30 and 40 mg) + nivolumab will be tested. A maximum of 10 patients may be enrolled at each dose level. Additional dose levels (20 mg or 60 mg) might be evaluated if an optimal dose is not identified and the safety review committee is in agreement.

1.5. STUDY PLAN

For each patient that signs the informed consent, the study consists of:

- Screening/baseline visit: occurs within 30 or 14 days prior to the start of therapy (i.e., Day -30 to Day -1, Day -30 to Day -14, or Day -14 to Day -1).
- Treatment period: There is no maximum treatment duration. Treatment cycles last 28 days and patients may continue to receive KPT-9274 until the patient has confirmed PD, withdraws consent, is lost to follow-up, experiences intolerable toxicity which precludes further treatment with KPT-9274, or treatment is discontinued at the discretion of the patient, Investigator, or Karyopharm. Patients who have objective disease progression but have evidence of overall clinical benefit may, at the request of the treating physician, continue treatment with KPT-9274 after discussion with the Medical Monitor.
- Follow-up period: durability of response and survival phone call will be made to patient every 3 months up to one year after treatment period.

Please refer to the protocol for the detailed schedule of assessment and study activities.

1.6. INTERIM ANALYSIS

No interim analysis is planned for this study.

1.7. MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The current SAP is based on Protocol Version 5.0 dated 1 March 2020. No modifications were made to the statistical section of the protocol.

1.8. STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This is the first version of SAP.

2. GENERAL STATISTICAL METHODS AND DATA HANDLING

This statistical analysis plan (SAP) outlines the methods to be used in the analysis of clinical data 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 analysis of PK, CCI [redacted]; these will be included in a separate plan.

2.1. GENERAL ANALYSIS METHODS

All summary statistics will be computed and displayed among the corresponding analysis population, and by each scheduled assessment time point whenever applicable. Summary statistics for continuous variables will minimally 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 method will be used for descriptive summaries. Graphical displays will be provided as appropriate.

2.2. MISSING DATA HANDLING IN DATA PRESENTATION

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

- Categorical data at baseline will be summarized using counts (n) and percentages (%). Denominator will be the total number of people in a corresponding treatment arm, based on the population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.
- Continuous data: summaries will be based on observed data only.

2.2.1. 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 study treatment dosing reported on study treatment dosing form. If all the dosing dates are missing, then the duration is missing.

The last dose intake should be clearly identified on the eCRF dosing page and should not be approximated by the last returned package date.

2.2.2. 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 will be imputed to be as late as possible. Impute resolution date first and then impute onset date using imputed resolution date. However, for categorization purpose, if the partial AE onset date information does not indicate whether the AE started prior to treatment or after the treatment-emergent adverse event (TEAE) period, the AE will be classified as treatment-emergent.

These data imputations are for categorization purpose or calculation of AE duration, and will not be used in listings.

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book 2.0 for details on imputation methods.

2.2.3. Handling of Missing or Partial Birth Date for Calculation of Age

Refer to the Karyopharm Biostatistics and Statistical Programming Rule Book 2.0 for details on imputation methods.

2.2.4. 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 in the frequency tables is considered as related.

2.2.5. Handling of Missing Severity of AEs

Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity.

2.3. 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 date of first study treatment is defined as the earliest date of non-zero dose of study treatment.

The date of last study treatment is defined as the latest date of non-zero dose of study treatment.

2.4. OBSERVATION PERIOD

The observation period will be divided by the following:

- The pre-treatment period is defined as the time from the signed informed consent date up to the time before the start date of study treatment.
- The treatment period is defined as the time from the start date of study treatment up to the end date of study treatment +30 days inclusive, or the day before initiation of a new anti-neoplastic treatment, whichever occurs first.
- The post-treatment period is defined as the time beyond the treatment period.

2.5. 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 treatment 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.

2.6. BASELINE MEASUREMENT

For treatment period, the baseline value is defined as the latest value prior to the first dose of study treatment.

In the case an assessment performed on the same date as the first dose, but it is impossible to determine the evaluation time relative to the time of taking the first dose, the evaluation time will be assumed to be following the protocol-defined schedule.

2.7. VISIT WINDOWS

For safety data 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 are defined in Table 2-1-1, Table 2-1-2 and Table 2-1-3. 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, then the latest one is selected for the analysis.

Table 2-1-1 Visit Windows for CBC with Differential and Complete Serum Chemistry (Parts A and B)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
C1D3	Day 3	Day 2 to 5
C1D8	Day 8	Day 6 to 11
C1D15	Day 15	Day 12 to 18
C1D22	Day 22	Day 19 to 23
C1D26	Day 26	Day 24 to 27
C2D1	Day 29	Day 28 to 32
C2D8	Day 36	Day 33 to 39
C2D15	Day 43	Day 40 to 46
C2D22	Day 50	Day 47 to 53
C3D1	Day 57	Day 54 to 63
C3D15	Day 71	Day 64 to 77
C4D1	Day 85	Day 78 to 91
(every 14 days)		
…		
NOTE: Day 1 is the date of first study treatment dose. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-2-2 Visit Windows for Vital Signs (Parts A and B)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
C1D2	Day 2	Day 2
C1D3	Day 3	Day 3 to 5
C1D8	Day 8	Day 6 to 11
C1D15	Day 15	Day 12 to 18
C1D22	Day 22	Day 19 to 22
C1D24	Day 24	Day 23 to 24
C1D25	Day 25	Day 25
C1D26	Day 26	Day 26 to 27
C2D1	Day 29	Day 28 to 32
C2D8	Day 36	Day 33 to 39
C2D15	Day 43	Day 40 to 46
C2D22	Day 50	Day 47 to 53
C3D1	Day 57	Day 54 to 63
C3D15	Day 71	Day 64 to 77
C4D1	Day 85	Day 78 to 91
(every 14 days)		
…		
NOTE: Day 1 is the date of first study treatment dose. Analysis visit and visit window may change for certain parameters depending on the data availability.		

Table 2-3-3 Visit Windows for CBC with Differential, Complete Serum Chemistry Clinical Laboratory Tests and Vital Signs (Part C)

Analysis Visit Name	Target Visit Day	Study Day Range in Window
Baseline	Day 1	Prior to or on Day 1
C1D8	Day 8	Day 2 to 11
C1D15	Day 15	Day 12 to 18
C1D22	Day 22	Day 19 to 25
C2D1	Day 29	Day 26 to 35
C2D15	Day 43	Day 36 to 49
C3D1	Day 57	Day 50 to 63
C3D15	Day 71	Day 64 to 77
C4D1	Day 85	Day 78 to 91
(every 14 days)		
…		
NOTE: Day 1 is the date of first study treatment dose. Analysis visit and visit window may change for certain parameters depending on the data availability.		

2.8. SUBGROUPS

No subgroup analysis is planned due to the small sample size.

2.9. POOLING OF CENTERS FOR STATISTICAL ANALYSES

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

2.10. COMPUTING AND CODING STANDARDS

Activities will be performed using the following tools:

Table, listing, and figure production	SAS Version 9.4 or higher
Coding	
AEs	MedDRA Version 23.1 or higher
Medical Histories	MedDRA Version 23.1 or higher
Prior and Concomitant Medications	WHO DDE Version September 2020 or higher

Grading	
AEs	CTCAE Version 4.03 or higher
Labs	CTCAE Version 4.03 or higher

3. PATIENT INFORMATION

3.1. DISPOSITION OF PATIENTS AND ANALYSIS POPULATIONS

Patient disposition will be summarized in each of the following categories:

- Patients who were enrolled
- Patients who received at least one dose of the study treatment (partial or complete)
- End of treatment:
    - Patients who discontinued treatment and primary reason for discontinuation
- Survival follow-up status
    - Patients willing to continue in Survival Follow-up
- End of study
    - Patients who withdrew from study and primary reason for study withdrawal

A by-patient listing of study completion information, including the reason for study withdrawal may also be provided.

3.1.1. Efficacy Populations

Modified Intent-to-Treat Population

The modified intent to treat (mITT) population for Part A, Part B, and Part C will consist of all patients who receive at least one dose of study treatment.

mITT population will be used for primary analyses of efficacy.

Efficacy evaluable (EE) Population

The efficacy evaluable (EE) population will consist patients who have received at least one post-baseline disease response assessment. This population will be used for supportive inferences for primary analyses of efficacy.

Per-protocol (PP) Population

The per-protocol (PP) population will consist of all patients who have received at least 2 cycles of study treatment, are compliant with study assessments, have received at least 80% of their prescribed study treatment, and have no major protocol violations that would compromise the assessment of efficacy. Major violations will be determined independently of knowledge of response to therapy, and prior to database lock and study analysis. This population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the assessment of efficacy.

3.1.2. Safety Population

All patients who receive at least 1 dose of the study treatment will be included in the safety population. All safety analyses will be performed on the safety population.

DLT Evaluable Population

All patients who complete a minimum of 1 cycle of treatment, defined as having received ≥ 75% of KPT-9274 doses during Cycle 1 (e.g., ≥ 9 of 12 doses in the 3 doses/week schedule), or who have a DLT within the first cycle of treatment, will be included in the DLT evaluable population.

3.2. DEMOGRAPHICS, MEDICAL HISTORY, AND BASELINE CHARACTERISTICS

In general, the baseline value is defined as latest value prior to the first dose of study treatment. Demographics, medical history and baseline characteristics will generally be summarized among mITT and safety populations, unless otherwise specified. P-values on demographic, medical history and baseline characteristic data will not be calculated.

3.2.1. Demographic Data

Demographic variables include sex (female, male), race (American Indian or Alaska Native, Asian, Black or African American, White, Other), ethnicity, and age at study entry.

3.2.2. Prior Antineoplastic Therapy

Prior antineoplastic therapy will be summarized for the mITT population with the following variables:

- Number of unique medication
- Number of prior regimens of antineoplastic therapy
- Best response of most recent prior antineoplastic regimen
- Days since discontinuation of most recent prior antineoplastic therapy to the start of study treatment, which will be calculated as the date of first study treatment – stop date of most recent antineoplastic therapy+1
- Days since most recent disease progression to the start of study treatment

The detailed history of prior systemic therapy including start and end dates of the medication, best response, progression during or after therapy, as well as discontinuations due to, toxicity and/or intolerability may also be provided in a data listing.

3.2.3. Medical/Surgical History

Medical history will be summarized in the mITT population 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.

3.2.4. Disease History

Disease history will be summarized with below variables:

- Duration from initial diagnosis to the start of study treatment
- Disease stage at initial diagnosis
- Primary tumor location

3.2.5. Baseline Characteristics

Baseline characteristics will be summarized including the following variables:

- Baseline height (cm)/ weight (kg)/ body surface area (m^2)/ BMI (kg/m^2)
- Baseline ECOG performance status
- Number of unique ongoing medical history (Preferred Terms) per patient
- Number of unique ongoing medications (Anatomical Therapeutic Class [ATC] Level 4 and standard name) per patient

3.3. CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medication consists of any prescription or over-the-counter preparation, including vitamins, dietary supplements, over-the-counter medications, and oral herbal preparations taken during the study, as well as changes in medication. Patients may continue their baseline medication(s). Concomitant medications include any medications used to treat symptoms, concomitant diseases such as diabetes, hypertension, etc., AEs and intercurrent illnesses that are medically necessary as part of standard care. All concomitant medication(s) must be reported on 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. Concomitant medication will generally be summarized among mITT and safety populations, unless otherwise specified.

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

3.3.1. Prior and Concomitant Medications and Procedures

Prior medications are any treatments received by the patient prior to the first dose of study treatment. Prior medications can be discontinued before 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 first dose of study treatment to last dose of study treatment + 30 days.

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

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

The use of prior and concomitant medications and procedures may also be provided in a data listing.

Please refer to Section 2.2.2 for details on data handling rules related to computation, dates, imputation for missing dates.

3.4. EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE

Study treatment is considered taken when patient actually received any study drug (KPT-9274 and/or niacin and/or nivolumab, partial or complete). Extent of exposure and compliance will generally be summarized among mITT and safety populations, unless otherwise specified.

The extent of exposure for the study treatment will be assessed using the following variable:

- Duration of study treatment exposure

The following will be presented separately for KPT-9274, niacin and nivolumab:

- Duration of exposure
- Total dose received
- Average dose received per week
- Number and percentage of patients with dose reduction
- Number and percentage of patients with dose interruption
- Number and percentage of patients with missed dose

Duration of exposure is defined as the date of last dose - date of first dose + 1.

3.4.1. Treatment Compliance

Study treatment compliance will be summarized descriptively as a quantitative variable, calculated as

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

A study treatment dose is considered scheduled if KPT-9274 and/or niacin and/or nivolumab is scheduled. The number and percentage of patients with study treatment compliance ≥80% will be provided. Note that the number of scheduled study treatment doses does not include doses missed due to treatment interruption or other reasons not related to patient choice.

Treatment compliance will also be presented separately for KPT-9274, niacin, nivolumab as

$$\frac{\text{number of actual doses taken}}{\text{number of doses scheduled}} \times 100.$$

Similarly, the number of scheduled 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 compliance ≥80% for each drug will be provided.

4. EFFICACY

Disease response will be evaluated according to RECIST 1.1 (advanced solid malignancies) or Lugano Classification (NHL) and will include the following endpoints: Time-to-event efficacy endpoints will be performed using the same Kaplan-Meier method for estimation of summary statistics, and will include the 25th, 50th (median) and 75th percentiles, associated two-sided 95% CIs (if estimable), and number of events and censored observations

4.1. EFFICACY ENDPOINTS

Please refer to Table 4-1 below for primary and secondary endpoints and the corresponding definitions

Table 4-1 Efficacy Endpoints and Definitions

Endpoint	Definition
Secondary Endpoints	
Objective response rate (ORR)	Proportion of patients who have a response of partial response (PR) or complete response (CR)
Duration of response (DOR)	The duration of time from first meeting CR or PR measurement criteria (whichever occurs first) until the first date that PD recurrence is objectively documented or death due to any cause Please refer to Table 4-3 for details on the outcome and censoring definitions.
Progression-free survival (PFS)	The duration of time from date of first study treatment until the first date that PD is objectively documented or death due to any cause. Please refer to Table 4-2 for details on PFS outcome status (PFS event vs. censored) and censoring definitions.
Overall survival (OS)	Duration from the date of first study treatment 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 (i.e. withdrawal of consent), or date of last participating visit (e.g., a telephone contact with patient status being alive) on or before database cutoff date, whichever occurs first.
Time to Progression (TTP)	The duration of time from date of first study treatment until the first date that PD is objectively documented or death due to PD

Disease control rate (DCR)	Proportion of patients who have a response of CR, PR, and Stable Disease (SD) ≥ 16 weeks.
Duration of disease control	Duration of disease control is defined among patients achieving disease control as the duration from the date of first meeting the response measurement criteria for disease control to the date of PD or death due to disease progression. Please refer to Table 4-3 for details on the outcome and censoring definitions.

Table 4-2 PFS and DOR outcome and censoring definition

Situation	**Date of event or censoring**	**Outcome**
No baseline disease assessment	Date of first study treatment	Censored
No adequate post-baseline disease status assessment unless death occurs prior to first post-baseline assessment	Date of first study treatment	Censored
Death before PD without a gap of 2 or more consecutively missed scheduled disease status assessment before death	Date of death	Event
PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD	Event
No PD or death on or before a. database cut, b. withdrawal of informed consent, c. lost to follow-up, d. start of new antineoplastic treatment, e. No PD or death before a gap of 2 or more consecutively missed scheduled disease status assessment whichever occurs first	Date of last adequate disease assessment on or prior to the earliest occurrence of the events (a. – e.) listed in the left column	Censored

Table 4-3 TTP and Duration of disease control outcome and censoring definition

Situation	Date of event or censoring	Outcome
No baseline disease assessment	Date of first study treatment	Censored
No adequate post-baseline disease status assessment unless death due to disease progression occurs prior to first post-baseline assessment	Date of first study treatment	Censored
Death due to disease progression before PD without a gap of 2 or more consecutively missed scheduled disease status assessment before death	Date of death	Event
PD without a gap of 2 or more consecutively missed scheduled disease status assessment before progression	Date of PD	Event
No PD or death due to disease progression on or before a. Death due to reasons other than disease progression b. database cut, c. withdrawal of informed consent, d. lost to follow-up, e. start of new antineoplastic treatment, f. No PD or death due to disease progression before a gap of 2 or more consecutively missed scheduled disease status assessment whichever occurs first	Date of last adequate disease assessment on or prior to the earliest occurrence of the events (a. – f.) listed in the left column	Censored

4.2. STATISTICAL METHODS FOR EFFICACY ENDPOINTS

Binary endpoints of ORR and DCR will be calculated by point estimate with a 95% confidence interval (CI) using the exact method.

For time to event endpoints of DOR, PFS, OS, duration of clinical benefit and duration of disease control, the number and percentage of patients who had an event will be reported.

Median event time with 95% CI will be summarized using Kaplan-Meier (KM) method. The KM curve for PFS will be provided by treatment arm.

5. SAFETY

Safety analyses will use safety population. Each tumor type will be analyzed separately with the outputs presented by part and cohort and for all patients combined.

Safety and tolerability of KPT-9274 will be evaluated by means of DLTs (dose escalation cohorts only), AE reports, electrocardiograms and laboratory safety evaluations.

General rules

All safety analyses will be performed using the following common rules:

- The baseline value is the last available value before the first dose of study treatment. Please also refer to Section 2.6 for additional information.
- The analyses of the safety variables will be essentially descriptive, and no statistical testing is planned.
- Unscheduled visit measurements will be used for computation of baseline, worst and last values. The unscheduled visit measurements will also be included in data listings.

5.1. 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 temporarily 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 preferred term (PT) and associated primary system organ class (SOC) using the MedDRA.

The severity of all AEs will be graded according to the NCI CTCAE Grading Scale, Version 4.03. 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. For AEs not covered by CTCAE, the severity will be characterized as “mild,” “moderate,” “severe”, “life-threatening” (corresponding to Grades 1 to 4) according to the following definitions:

- Mild events are usually transient and do not interfere with the patient’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient’s usual daily activities.
- Life-threatening.

5.1.1. Definitions of Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), and Treatment-Emergent Treatment-Related Adverse Events (TRAEs)

5.1.1.1. Treatment-Emergent Adverse Event (TEAE)

- Treatment-emergent adverse events (TEAE) of study treatment are defined as any event that was not present prior to the initiation of study treatment (KPT-9274 and/or niacin

and/or nivolumab) or any event already present that worsens in either intensity or frequency following exposure to study treatment, from the first dose of study treatment to 30 days after the last dose of study treatment inclusive, or the day before the start of a new antineoplastic treatment, whichever occurs first. Additionally, any AEs that occurred 30 days after the last dose of study treatment or after the start of a new antineoplastic treatment will also be considered as TEAE, if assessed by the Investigator as related to any drug of the study treatment.

5.1.1.2. Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence, at any dose, that:

- 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
- Results in a congenital anomaly/birth defect

SAE needs to be clearly documented on the AE form. SAEs that occur at any time between the signing of the ICF up to the first dose of study treatment, must be reported (in addition to SAEs that occur after the first dose of study treatment).

5.1.1.3. Treatment-emergent Treatment-Related Adverse Events (TRAEs)

A TRAE is any TEAE that is related to any study treatment.

5.1.1.4. Adverse Event of Clinical Interest (AECI)

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

5.1.2. Analysis Methods

The primary focus of AE reporting will be on TEAEs.

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to determine 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 2.2.2.

AE summaries will include number (n) and percentage (%) of patients who have experienced an AE. The denominator for computation of percentages is the number of patients in the corresponding 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.

The summary of AEs by causality will generally include the following categories of causality.

- Related to either KPT-9274 or niacin or nivolumab
- Related to KPT-9274 only
- Related to niacin only
- Related to nivolumab only
- Not related to KPT-9274 or niacin or nivolumab

5.1.3. Analysis of TEAE

An TEAE overview summary table will be provided, which will include the number of patients with at least one of the adverse events:

- TEAEs
- Grade 3/4 TEAEs
- Serious TEAEs
- TEAEs leading to dose modifications of study treatment
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment
- TEAEs leading to study treatment discontinuation
- TEAEs leading to death
- TRAE
- Serious TRAEs
- TRAEs leading to dose modifications of study treatment
- TRAEs leading to dose reduction of study treatment
- TRAEs leading to dose interruption of study treatment
- TRAEs leading to study treatment discontinuation
- TRAEs leading to death

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
- Grade 3 or higher TEAEs
- Grade 3 or higher TEAEs, by causality
- TEAEs leading to dose modifications of study treatment

- TEAEs leading to study treatment discontinuation

The most commonly reported (at least 10% of all patients) TEAEs will be presented by PT only and will include the following categories:

- The most commonly reported TEAEs
- The most commonly reported TEAEs related to study treatment

5.1.4. Analysis of SAE

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

All SAE will be provided in a data listing.

5.1.5. Analysis of DLTs

DLT will be summarized in the dose escalation population. A data listing will be provided for DLTs.

5.1.6. Analysis of AECI

Standard MedDRA Query (SMQ), Customized MedDRA Query (CMQ) will be utilized for AECI analysis. Analyses of treatment-emergent AECI will be performed separately for each pre-specified AECI category. Overview summary of all AECI will be summarized similarly as in Section 5.1.3.

The following AECI will be summarized by PT:

- All TEAEs
- Serious TEAEs

The list of AECI categories are provided in Table 5-1. The search strategy of preferred terms for each category will be provided in a separate document.

Table 5-1 AECI Categories

Group Category	AECI Category
Hematologic events	Anaemia
	Neutropenia
	Thrombocytopenia
	Decreased Appetite

Constitutional events	Weight Decreased
Eye disorders events	Blurred Vision
	Cataract
Gastrointestinal events	Nausea
	Vomiting
Infection	Pneumonia
	Opportunistic Infection
	Sepsis
Metabolism and nutrition disorders	Hyponatremia
Nervous system disorders	Neurological Toxicity
Others	Hepatobiliary Disorders
	Cardiac Toxicity

5.2. 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 report 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
- TEAEs leading to death and are related to KPT-9274 only, by primary SOC and PT
- TEAEs leading to death and are related to niacin only, by primary SOC and PT
- TEAEs leading to death and are related to nivolumab only, by primary SOC and PT
- Listing of all TEAEs leading to death
- Listing of all death events

5.3. LABORATORY SAFETY VARIABLES

5.3.1. Definitions

Clinical laboratory data of interest consists of blood analysis, including hematology and serum chemistry and coagulation. Clinical laboratory values in conventional units will be converted using the international system of units (SI).

The laboratory parameters will be classified as follows:

- Hematology test will be performed at screening visit, on day 1 of every cycle, and at the EoT visit.
- Complete Serum Chemistry panel will be measured at Screening Visit on day 1 of every cycle and at the EoT visit.
- Coagulation test will be performed at screening visit and at the EoT visit.

Table 5-2 presents the clinical laboratory tests that will be analyzed.

Table 5-2 Clinical Laboratory Tests

Complete Blood Count with Differential (Blood sample: whole blood; ethylenediaminetetraacetic acid) tests including)				
Hemoglobin	Hematocrit	Mean corpuscular volume	Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
WBC count	WBC differential[1] (Parts A and B Only)	RBC count	Lymphocytes	Monocytes
Neutrophils	Eosinophils	Basophils	Platelets	Reticulocyte count
Complete Serum Chemistry (Blood sample: serum)				
Sodium	Potassium	Chloride	Bicarbonate	Blood urea nitrogen
Creatinine	Glucose	Calcium	Phosphate	Magnesium
ALT	AST	Alkaline Phosphatase	Total bilirubin[2]	Lactate dehydrogenase
Total protein	Albumin	Amylase	Lipase	Creatinine kinase
Urate	Thyroid-stimulating hormone			
Coagulation				
Prothrombin time (Parts A and B Only)	International normalization ratio (Parts A and B Only)	Activated thromboplastin time (Parts A and B Only)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RBC = red blood cell; ULN: upper limit of normal; WBC = white blood cell.

1 WBC differential may be automated or manual as per institutional standards. Blasts should be included.
2 If the total bilirubin concentration is increased > 1.5 × ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.> 1.5 ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

5.3.2. 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

relative to CTCAE classification ranges will be presented. These shift tables will include results from unscheduled visits.

For several key laboratory parameters, box plots on measurements over time as well as by-patient plots for patient-level measurements over time may be presented.

A listing of cases where ALT or AST > 3x upper limit of normal (ULN) with simultaneous total bilirubin > 2x ULN will be presented.

Thresholds/Range analyses for selected laboratory parameters will be conducted. The number and percentage of patients classified into each category based on worst values will be presented.

5.4. VITAL SIGNS, AND ECOG VARIABLES

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

A full physical examination including vital signs will be performed at Screening Visit and EOT visit.

Symptom-directed physical examination, vital signs, and ECOG will be performed as per the schedule of assessments (SOA).

The actual value and change from baseline to each on-study evaluation will be summarized for vital signs including pulse, temperature, systolic blood pressure, diastolic blood pressure, BSA and weight. Shift tables that present changes from baseline to highest on-study and lowest on-study for systolic blood pressure and diastolic blood pressure will be presented. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will also be produced.

Abnormal vital signs results will be summarized in the threshold/range analyses.

All vital sign measurements, physical examination results and ECOG performance status scores may also be provided in data listings.

5.5. ELECTROCARDIOGRAM (ECG)

Standard 12-lead electrocardiogram (ECG) will be performed at screening (day -30 to day -1), C1D1 (pre-dose and 4 hours post-dose), C1D26 (pre-dose and 4 hours post-dose), C2D1, day 1 of odd numbered cycles starting at cycle 3, at the EoT visit, and as clinically indicated at the discretion of the Investigator. Electrocardiograms may also be performed as clinically indicated during the study. Patients must rest for at least 5 minutes prior to the ECG recording. 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 following will be assessed: heart rate, PR interval, QRS interval, and QT corrected using Fridericia's formula (Fridericia, 1920).

Changes from baseline to highest on-study post baseline measurement for PR interval, QRS interval, and QT corrected will be summarized using shift tables. For heart rate, changes from baseline to lowest and highest on-study post baseline measurement will be presented.

Abnormal ECG results will be summarized in the threshold/range analyses.

Electrocardiogram data for each patient may also be provided in a data listing.

5.6. OPHTHALMIC EXAM

An ophthalmic examination by an optometrist or ophthalmologist is required at Screening, at the EoT visit, and if clinically indicated throughout the study (e.g., monitoring of pre-existing cataracts, visual disturbances) at the intervals determined by the Investigator.

All ophthalmic examination findings may be presented in a data listing.

6. REFERENCES

1. Cheson B, Fisher R, Barrington S, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014 Sep 20;32(27):3059-67.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2): 228–47.
3. Fridericia L. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Medica Scandinavica. 1920; 53:469-86.