CLINICAL STUDY 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

Study Name: PANAMA: PAK4 and NAMPT in Patients with Solid MAlignancies or NHL

Study Number:	KCP-9274-901
Study Phase:	1
Investigational Product:	KPT-9274
IND Number:	CCI [redacted]
Indication:	Advanced solid malignancies and non-Hodgkin's lymphoma
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Avenue Newton, MA 02459 USA Tel. + (617) 658-0600
Protocol Date and Version:	16 December 2015, Version 1.0 26 February 2016, Version 2.0 02 May 2016, Version 3.0 15 June 2017, Version 4.0 13 December 2017, Version 4.1 02 February 2018, Version 4.2 (Canada Specific Amendment) 11 March 2020, Version 5.0

CONDUCT

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

SPONSOR INFORMATION

Sponsor Contacts:	PPD , MD PPD Karyopharm Therapeutics Inc. PPD , PhD, MBA PPD Karyopharm Therapeutics Inc.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: KARYOPHARM THERAPEUTICS INC.

I have read and understand the contents of this clinical protocol for Study No. KCP-9274-901 dated 11 March 2020 and agree to meet all obligations of Karyopharm Therapeutics Inc., as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

PPD

PPD PPD, MD PPD

PPD

Karyopharm Therapeutics Inc.

11 March 2020

Date

PPD

PPD **, PhD, MBA**

PPD

Karyopharm Therapeutics Inc.

11 March 2020

Date

INVESTIGATORS' AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. KCP-9274-901 dated 11 March 2020 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practice, ICH E6, and applicable FDA regulatory requirements.

Printed Name of Investigator

Signature of Investigator

Institution

Date

PROTOCOL SYNOPSIS

Sponsor: Karyopharm Therapeutics Inc.	**Investigational Product:** KPT-9274	**Study Phase:** Phase 1

Title of Study:
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

Study Name: PANAMA: PAK4 and **NA**MPT in Patients with Solid **MA**lignancies or NHL

Name of Active Ingredient:
(*E*)-3-(6-aminopyridin-3-yl)-*N*-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylamide

Protocol Number: KCP-9274-901

Study Center(s): Multi-center

Patient Population: Patients with advanced solid malignancies (including sarcoma, colon, lung, etc.) or non-Hodgkin's lymphoma for which all standard therapeutic options considered useful by the investigator have been exhausted and with progressive disease on study entry.

Objectives and Endpoints:
This study will evaluate the safety, tolerability, and efficacy of oral KPT-9274 for the treatment of patients with advanced solid malignancies or non-Hodgkin's lymphoma (NHL).

Objectives	Endpoints
Primary	
Parts A and B • To assess the maximum tolerated dose (MTD) in each Part • To establish a recommended phase 2 dose (RP2D)	*Parts A and B* • MTD/RP2D • Dose limiting toxicities (DLTs) • The occurrence of Grade ≥3 adverse events (AE), all serious adverse events (SAEs), and all AEs leading to treatment discontinuation
Dose Expansion (if conducted) • Preliminary evidence of anti-tumor activity of KPT-9274 at the RP2D ± niacin ER	*Dose Expansion (if conducted)* • Overall response rate (ORR), duration of response (DOR), disease control rate (DCR), duration of disease control, progression-free survival (PFS), overall survival (OS), time to progression (TTP)

Part C • Safety, tolerability, and RP2D	*Part C* • MTD/RP2D • Dose limiting toxicities (DLTs) • The occurrence of Grade ≥3 adverse events (AE), all serious adverse events (SAEs), and all AEs leading to treatment discontinuation
Secondary	
Parts A and B • Preliminary evidence of anti-tumor activity of KPT-9274 at the RP2D ± niacin ER • Pharmacokinetics (PK) *Dose Expansion (if conducted)* • Pharmacokinetics (PK) *Part C* • Preliminary evidence of anti-tumor activity of KPT-9274 + nivolumab • Pharmacokinetics (PK)	*Parts A and B* • ORR, DOR, DCR, duration of disease control, PFS, OS, TTP • Maximum plasma concentration, time-to-peak plasma concentration, terminal half-life, and plasma clearance *Dose Expansion (if conducted)* • Maximum plasma concentration, time-to-peak plasma concentration, terminal half-life, and plasma clearance *Part C* • ORR, DOR, DCR, duration of disease control, PFS, OS, TTP • Area under the curve (AUC) and Maximum concentration (Cmax)
Exploratory	
CCI [redacted]	
Rationale for the Study:	

KPT-9274 is a first-in-class orally bioavailable, non-competitive, small molecule, dual modulator of p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase /PBEF/visfatin (NAMPT). PAK4 is a key downstream effector for RAS and forms a critical link between RAS-driven oncogenic transformation and activation of the WNT/β-catenin signaling pathway. NAMPT is the rate-limiting enzyme in the metabolic scavenging pathway that utilizes nicotinamide to replenish nicotinamide adenine dinucleotide (NAD), an essential metabolic cofactor and second messenger.

Hematologic and solid tumor cells are susceptible to single-agent cytotoxicity by KPT-9274 as they become dependent on both the PAK4 and NAMPT pathways. KPT-9274 demonstrated potent anti-proliferative activity against cancer cell lines with minimal toxicity to normal cells. In mouse xenograft studies, KPT-9274 was well tolerated and resulted in a marked reduction/elimination of tumors, tumor growth inhibition or disease control across a variety of tumors, including colon, pancreatic, lung, sarcoma, multiple myeloma, leukemia, and lymphoma. In approximately half of the tumor types studied, complete elimination of tumors in as short as 3 weeks was observed with no regrowth after cessation of treatment (for up to 3 additional weeks). Moreover, KPT-9274 has shown preliminary efficacy in companion dogs with spontaneous advanced lymphomas and multiple myeloma.

Rationale for adding niacin ER: NAD can be generated by catabolism of tryptophan, salvage of nicotinamide through NAMPT or salvage of exogenous niacin through NAPRT1 (nicotinate phosphoribosyltransferase; a niacin utilizing enzyme). Some cancers lack the enzyme(s) necessary for the *de novo* synthesis of NAD from tryptophan, while NAPRT1 activity is frequently down-regulated by epigenetic modulation or isocitrate dehydrogenase 1 (NADP+), soluble (IDH1) mutation leaving these cancers dependent on NAMPT activity. If tumors have reduced or absent NAPRT1 function, then this tissue may not be able to utilize niacin to make NAD. Therefore, patients with NAPRT1 in normal tissue, but not in their tumors, might benefit from a niacin co-dosing strategy in order to reduce side effects. Pivotal GLP and exploratory non-GLP studies have demonstrated that co-dosing niacin with KPT-9274 can increase tolerability; therefore, KPT-9274 co-administered orally administered with niacin extended release (ER) will be evaluated in the current study. CCI

CCI

Rationale for combining KPT-9274 with Nivolumab: KPT-9274 binds to and reduces the steady state level of the PAK4 protein kinase as well as blocking the activity of NAMPT. In addition, through PAK4 inhibition, KPT-9274 reduces the stability, nuclear transportation and function of β-catenin by inhibiting its phosphorylation on S675. This is consistent with β-catenin being a target of PAK4. Nivolumab is a monoclonal antibody directed against the programmed cell death 1 receptor (PD-1) on lymphocytes. Anti-PD-1 treatment increases the immune response, allowing T cell killing of tumor cells. Nivolumab has been FDA-approved for use in patients with advanced melanoma. There is evidence suggesting that patients most likely to respond to anti-PD-1 treatment are those who have an elevated baseline of CD8+ T cell infiltration within the tumor microenvironment (TME) (Abril-Rodriguez 2020). Those who lack a T cell infiltrate respond poorly. A correlation was reported between hyperactivation of the WNT/β-catenin signaling pathway and T cell exclusion in melanoma patient tumor samples (Spranger et al 2015). Recently, this correlation has been extended to PAK4 overexpression (Abril-Rodriguez 2020). These data suggest that combination therapies in which activated β-catenin is inhibited through PAK4 inhibition simultaneously with targeting PD-1, may be particularly effective therapy. Indeed, in vivo models of mice engrafted with melanoma cells that were treated with KPT-9274 + an anti-PD-1 antibody showed marked tumor growth inhibition compared to either agent alone (Abril-Rodriguez 2020). Therefore, combinatorial treatment with KPT-9274, which blocks β-catenin, with nivolumab may be beneficial to patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1 treatment.

Methodology:

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.

The Dose Escalation and Expansion Phases of the study will be comprised of Screening, Treatment, and Follow-up periods.

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)	10 mg
2	20 mg
3	30 mg
4	40 mg
5+	Increases at 20 mg per cohort

Three patients will be enrolled in each cohort, if 1 of 3 patients in a cohort experiences a DLT, the number of patients in that cohort will be expanded to 6 patients. A maximum of 6 patients will be enrolled per cohort. If ≥ 2 patients in a cohort experience a DLT, the MTD will be defined as 1 dose level lower.

A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities as described in the table below. The CTCAE, Version 4.03 will be used for grading. In addition, > 3 missed (consecutive or nonconsecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

Other events may occur which do not meet the definition of a DLT but are of concern to the Investigators and Karyopharm and may be considered to be DLTs.

Criteria for Defining Dose-Limiting Toxicities

Toxicity	**Any of the following criteria (based on CTCAE [Version 4.03]):**
Non-Hematologic	Grade ≥3 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications.
	Any other Grade ≥3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy.
Hematologic	Grade 4 neutropenia lasting more than 5 days.
	Febrile neutropenia of any duration (ANC < 1.0×10^9 with single temperature >38.3°C or a sustained temperature ≥ 38°C for more than 1 hour).
	Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion.
	Grade 4 anemia, unexplained by underlying disease.
CTCAE Version 4.03 will be used for grading AEs and laboratory abnormalities. Patients may receive supportive care as per local institutional guidelines.	

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 KPT-9274.

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 anti-tumor 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

Pharmacokinetic CCI Samples

Blood samples for pharmacokinetic (PK) and CCI assessments will be collected during both the Dose Escalation and Dose Expansion Phases of the study. Biopsies for Part C will be collected at baseline and at the first response assessment.

Number of Patients (planned):

Approximately 175 patients may be enrolled. However, the number of patients required for completion of study enrollment cannot be defined *a priori* since this depends on the number of patients needed for the dose escalations in Parts A and B. Assuming that 9 dose levels of KPT-9274 are evaluated during both Part A (KPT-9274 single agent) and Part B (KPT-9274 + niacin ER) 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.

Dose Escalation Phase: Each cohort in Parts A and B of the escalation phase will consist of 3 or 6 patients at each dose level.

Dose Expansion Phase: Up to 65 additional patients (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) may be enrolled.

Dose Finding in Part C may include approximately 20 patients with melanoma.

Inclusion/Exclusion Criteria (Part A and B):

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years.
3. Patients with advanced solid malignancies or NHL for which all standard therapeutic options considered useful by the investigator have been exhausted.
4. Patients must have objective evidence of progressive disease on study entry:
   a. Advanced solid malignancies: Measurable disease as defined by RECIST 1.1[1].
   b. NHL: Measurable disease including target lesion(s) as defined by the Lugano Classification[2] for initial evaluation and staging.
5. Patients must have a site of disease amenable to biopsy and be a candidate for biopsy according to the treating institution's guidelines.
6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
7. Adequate hepatic function:
   a. Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3 times ULN),
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their advanced solid malignancy or NHL who must have their AST and ALT ≤ 5.0 times ULN).
8. Adequate renal function: estimated creatinine clearance of ≥ 60 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female.
9. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.
10. Adequate hematopoietic function: total white blood cell (WBC) count ≥ 1500/mm^3, absolute neutrophil count (ANC) ≥ 1000/mm^3, hemoglobin (Hb) ≥ 10.0 g/dL, and platelet count ≥ 75,000/mm^3.
11. Dose Escalation Phase: 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.
12. Dose Expansion Phase (KPT-9274 ± niacin ER cohort only): Patient tumors NAPRT1 and IDH1 tumor status must be determined at the central laboratory prior to enrollment.
    a. Confirmation of NAPRT1 expression and IDH1 mutation based on evaluation of a fresh tumor biopsy or archival tumor biopsy taken ≤ 6 months of screening tests as follows:
       i. NAPRT1 positive for expansion cohort I or III
       ii. NAPRT1 negative for expansion cohort II or III
       iii. IDH1 mutation status for expansion cohort IV

13. Life expectancy of ≥ 3 months.

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study.

1. Female patients who are pregnant or lactating.
2. Time since the last prior therapy for treatment of advanced solid malignancies or NHL**:
   a. Radiation, chemotherapy, immunotherapy or any other anticancer therapy, including investigational anti-cancer therapy ≤ 2 weeks prior to C1D1.
   b. Palliative steroids for disease related symptoms < 7 days prior to C1D1.

**Patients must have recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤ Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor.

3. Patients with known central nervous system (CNS) disease or leptomeningeal involvement, regardless of response to prior therapy, are excluded.
4. Major surgery within four weeks before C1D1.
5. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   a. Unstable angina or acute myocardial infarction ≤ 3 months prior to C1D1;
   b. Clinically significant heart disease (e.g., symptomatic congestive heart failure; uncontrolled arrhythmia, or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen).
6. Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted.
7. Patients with a known history of Human Immunodeficiency Virus (HIV); HIV testing is not required as part of this study.
8. Known, active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen). Testing is not required.
9. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.
10. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent.
11. Active peptic ulcer disease or other active gastrointestinal bleeds.

Inclusion/Exclusion Criteria (Part C):

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years.
3. Patients must have objective and measurable melanoma by RECIST 1.1 after disease progression on a prior anti-PD-1 or anti-PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Adequate hepatic function:

a. Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3 times ULN),

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their advanced solid malignancy who must have their AST and ALT ≤ 5.0 times ULN).

6. Adequate renal function: Estimated creatinine clearance of ≥ 60 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female.
7. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.
8. Adequate hematopoietic function: total white blood cell (WBC) count ≥ 1500/mm^3, absolute neutrophil count (ANC) ≥ 1000/mm^3, hemoglobin (Hb) ≥ 10.0 g/dL, and platelet count ≥ 100,000/mm^3.
9. Life expectancy of ≥ 3 months.

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Female patients who are pregnant or lactating.
2. ≤ 2 weeks since the last prior therapeutic regimen for melanoma. Palliative steroids for disease related symptoms < 7 days prior to C1D1, unless physiologic doses of steroids are used.
3. Patients who have not recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤ Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor.
4. Patients with untreated central nervous system (CNS) disease or leptomeningeal involvement are excluded. Patients without active brain or leptomeningeal metastases after prior treatment with local therapies are eligible provided that the treatment had been done ≥ 2 weeks prior to enrollment.
5. Major surgery within four weeks before C1D1.
6. Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted.
7. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.
8. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent.
9. Active peptic ulcer disease or other active gastrointestinal bleeds.
10. Patients requiring treatment with corticosteroids at doses higher than substitute therapy (> 10 mg prednisone), are unstable with substitute hormonal therapy, or are deemed to be likely to re-occur by the treating physician when administered nivolumab.

Investigational product, dosage and mode of administration:

KPT-9274 is an orally bioavailable small molecule and a tablet solid dosage form for oral administration is being used for clinical studies.

KPT-9274 tablets are designed for immediate-release oral administration and will be supplied in high-density polyethylene (HDPE) bottles with induction seals. KPT-9274 tablets will be film coated for ease of handling and provided in tablet strengths of 5 mg and 20 mg. KPT-9274 will be supplied by Karyopharm. Additional details on KPT-9274 are provided in the Investigator's Brochure. The investigational treatments will be administered as a flat dose and not by body weight or body surface area.

Patients enrolled in Part B of the Dose Escalation Phase and potentially in the Dose Expansion phase will also receive 500 mg of any FDA approved prescription, generic niacin ER for oral use co-administered with each dose of KPT-9274. The starting dose of 500 mg niacin ER may be titrated up to 2,000 mg of daily dose, per label. A list of approved generic niacin ER will be provided in the Pharmacy Manual.

Patients enrolled in Part C (KPT-9274 + nivolumab) will receive nivolumab (480 mg) intravenously on Day 1 of each 28 day cycle per the FDA approved package insert.

Permitted Concomitant Medications:

No significant inhibition of any of the CYP450 enzymes were observed after KPT-9274 treatment. Weak induction of CYPs 1A2, 2B6, and 3A4 were observed in an exploratory pre-clinical study after KPT-9274 treatment. There were no DDIs noted in the first 50 patients treated in Parts A and B. Therefore, the use of any concomitant medication/therapy (except for the medications listed in the prohibited concomitant medication section), including over-the-counter (OTC) medications (excluding herbal supplements, dietary supplements), deemed necessary for the care of the patient is permitted during the study. Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents (e.g., blood product transfusions, antibiotics with [if appropriate] granulocyte-colony stimulating factors [G-CSF] for neutropenic infection), pain medications, anti-emetics, and anti-diarrheals are allowed. Concurrent therapy with growth factors is allowed. The use of any immunosuppressive agents must be discussed between the Investigator and the Karyopharm Medical Monitor on a case-by-case basis.

Hormonal contraceptives are permitted in women of child-bearing potential. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent.

Additionally, the nivolumab product label will be consulted to obtain the permitted concomitant medications for patients in Part C (KPT-9274 + nivolumab).

Supportive Care:

Patients are expected to be aggressively treated to minimize the likelihood and/or severity of side effects at the discretion of the Investigator (consultation with the Karyopharm Medical Monitor is strongly encouraged), particularly GI symptoms and hematopoietic toxicities as observed in KPT-9274 animal toxicology studies. Supportive care including anti-nausea/anti-emetic therapy, acid suppression (e.g., proton pump inhibitors [PPIs] ± H2-blockers), anti-diarrheal therapy, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. For additional options, see NCCN Supportive Care Clinical Practice Guidelines in Oncology. Note: the use of PPIs is allowed in all patients, but the Investigator must consult with the Karyopharm Medical Monitor prior to their use in patients receiving niacin ER. Supportive care recommendations for events such as anemia, arthralgias, and myalgias include the following; (1) anemia: dose interruption, dose reduction, use of growth factors (i.e., erythropoietins), and transfusions; (2) arthralgia: non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, tramadol, and low-dose steroids; and (3) myalgia and flu-like illness: KPT-9274 dosing at night, acetaminophen (including pre-treatment with acetaminophen), NSAIDs, COX-2 inhibitors, and low-dose steroids. For patients in Part A, the addition of niacin ER (up to 2,000 mg daily dose, per label) is allowed after completion of the DLT period in cycle 1 (first 28 days) in an attempt to offset potential side effect (i.e. anemia, arthralgias, myalgias, etc.)

of KPT-9274. Consultation with the Karyopharm Medical Monitor is recommended for questions regarding these recommendations.

Prohibited Concomitant Medications:

The use of niacin or niacin-containing supplements (e.g., multivitamins and energy drinks) is not allowed in the KPT-9274 only cohorts in the Dose Escalation or Expansion Phases. However, for patients in these cohorts that have cleared DLT in cycle 1, niacin ER (up to 2,000 mg co-administered with KPT-9274) may be used as supportive care in an attempt to offset potential side effects (e.g. anemia, arthralgias, myalgias, etc.) of KPT-9274. Prior to initiating niacin ER, patient symptoms and laboratory values should be reviewed and discussed with the Medical Monitor for this study.

Investigational or commercial anticancer agents other than KPT-9274 are not allowed during the study. The initiation of any non-protocol specific anti-tumor treatment is considered an indication of disease relapse/progression and should be recorded appropriately in the eCRFs.

There are exceptions including localized palliative radiation, hormonal therapy for patients with prostate cancer, hormonal contraception for the prevention of pregnancy, and blood products/growth factors. For other possible cases, consult the Karyopharm Medical Monitor.

Treatment Duration:

Treatment cycles are 28 days long. A patient may continue to receive KPT-9274 ± niacin ER (Parts A and B) or KPT-9274 + nivolumab (Part C) until the patient experiences progressive disease, withdraws consent or decides to withdraw from further treatment, is lost to follow-up, experiences intolerable toxicity which precludes further treatment with KPT-9274, or treatment is discontinued at the discretion of the Investigator or the Karyopharm Medical Monitor.

Criteria for Evaluation:

Safety Endpoints:

The safety and tolerability of KPT-9274 ± niacin ER as well as 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.

A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities.

Efficacy Endpoints:

The secondary endpoint of disease response will be evaluated according to RECIST 1.1[1] (advanced solid malignancies) or Lugano Classification[2] (NHL) and will include the following:

- **Overall response rate (ORR):** 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.
- **Disease control rate (DCR):** DCR = proportion of patients who have a response of CR, PR, and Stable Disease (SD) ≥ 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.

Pharmacokinetic Endpoints:

KPT-9274 PK parameters may include, but are not limited to, maximum plasma concentration (C_{max}), area under the curve (AUC), time-to-peak plasma concentration (t_{max}), terminal plasma half-life ($t_{½}$), apparent volume of distribution (V_d/F), and apparent plasma clearance (CL/F).

CCI

Statistical Methods:

Sample size justification

Part A and Part B:The sample size for 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.

Part C:

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.

Analysis methods for efficacy endpoints:Disease response will be assessed according to RECIST 1.1[1] (advanced solid malignancies) and the Lugano Classification for response assessment[2] (NHL). ORR, DOR, DCR, duration of disease control, PFS, OS, and TTP will be evaluated separately for Part A, B and C. The 2-sided, exact 95% confidence interval (CI) of ORR and DCR will be estimated for each arm. The median duration of DOR, duration of diseae control, PFS, OS, and TTP with the 95% CI will be estimated for each arm using the Kaplan-Meier (KM) method.

Analysis methods for safety endpoints

Standard safety analyses will be performed. Details will be described in the Statistical Analysis Plan.

Table 1: Schedule of Assessments: Screening and Cycle 1 (Parts A and B)

If an in-clinic visit is missed during Cycle 1 due to a national or local holiday, the patient should come to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic.

	Screening		Cycle 1											
			Week 1				Week 2		Week 3		Week 4			
	Day -30 to Day -1	Day -14 to Day -1	Day 1	Day 2	Day 3	D4 +1 day	D8	D11 ±1 day	D15	D18 ±1 day	D22	D24	D25	D26
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
Activity/Assessment														
Informed consent[1]	X													
Determination of NAPRT1 and IDH1 status[2]	X													
Inclusion/exclusion criteria	X	X												
Patient History														
Demographics	X													
Medical history[3]	X													
Clinical Assessments														
Patient height	X													
Patient weight	X		X	X	X		X		X		X	X	X	X
Vital Signs (BP, pulse, temp)[4]	X		X	X	X		X		X		X	X	X	X
Complete physical exam	X													
Symptom-directed physical exam			X				X		X		X			X
12-lead ECG[5,8]	X[5]		X[5] (Pre-dose and 4 hours post-dose)											X[5] (Pre-dose and 4 hours post-dose)
Echocardiogram or MUGA[6,8]	X													
Ophthalmic exam[7, 8]	X													
ECOG[8]	X		X											
Rheumatology consultation and testing[23]			As clinically indicated											
Hematology consultation and testing[24]			As clinically indicated											
Clinical Labs														

	Screening		Cycle 1											
			Week 1				Week 2		Week 3		Week 4			
	Day -30 to Day -1	Day -14 to Day -1	Day 1	Day 2	Day 3	D4 +1 day	D8	D11 ±1 day	D15	D18 ±1 day	D22	D24	D25	D26
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
Urinalysis[8]		X	X[21]		X		X		X		X			X
CBC with differential[8]		X	X[21]		X		X		X		X			X
TSH[8, 9]		X	X[21]		X		X		X		X			X
Complete serum chemistry[8]		X	X[21]		X		X		X		X			X
Amylase and lipase[8, 9]		X	X[21]											
Coagulation tests[8]		X							X					
Serum hCG pregnancy test[10]		X												
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[25]	X		As clinically indicated											
NHL Only Procedures														
Disease risk assessment[11]	X													
PET-CT or CT scan[12]	X													
Lymph node core biopsy[2]	X													X ±7 days
Bone marrow aspirate and/or biopsy[13]	X													
EORTC QLQ-C30 and FACT-Lym questionnaires[14]			X											
Advanced Solid Malignancy Only Procedures														
CT or MRI or PET-CT[15]	X													
Tumor biopsy[2]	X													X ±7 days
EORTC QLQ-C30[14]			X											
Study treatment dosing in-clinic[20]			X		X		X		X		X	X		X
PK/CCI														
Blood draws for PK analysis[16]			X	X	X		X		X			X	X	X
CCI														
Adverse events	Continuous													
Concomitant medications	Continuous													
Telephone contact[18]						X		X		X				

Table 2: Schedule of Assessments: Cycles 2 and Beyond (Parts A and B)

If an in-clinic visit is missed during Cycle 2 and beyond, the patient should come to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic.

	Cycle 2								Cycle 3 and Beyond					
	Week 1		Week 2		Week 3		Week 4		Week 1		Week 2	Week 3		Week 4
	D1	D4 ±1 day	D8	D11 ±1 day	D15	D18 ±1 day	D22	D25 ±1 day	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day
Visit Type	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Phone Call**
Activity/Assessment														
Clinical Assessments														
Patient weight	X		X		X		X		X			X		
Vital Signs (BP, pulse, temp)[4]	X		X		X		X		X			X		
Symptom-directed physical exam	X		X		X		X		X			X		
12-lead ECG[5]	X								X (Odd cycles only)					
ECOG	X								X					
Rheumatology consultation and testing[23]	As clinically indicated													
Hematology consultation, testing, and biopsy[24]	As clinically indicated													
Clinical Labs														
Urinalysis	X								X					
CBC with differential	X		X		X		X		X			X		
TSH[9]	X		X		X		X		X			X		
Complete serum chemistry	X		X		X		X		X			X		
Amylase and lipase[9]	X								X					
Coagulation tests	X													
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[25]	As clinically indicated													
NHL Only Procedures														
PET-CT or CT scan[12]									X (±7 days; odd cycles only)					

	Cycle 2								Cycle 3 and Beyond					
	Week 1		Week 2		Week 3		Week 4		Week 1		Week 2	Week 3		Week 4
	D1	D4 ±1 day	D8	D11 ±1 day	D15	D18 ±1 day	D22	D25 ±1 day	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day
Visit Type	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit	Phone Call	Phone Call
Lymph node core biopsy[2]									X (±7 days; C6 only)					
EORTC QLQ-C30 and FACT-Lym questionnaires[14]	X								X					
Advanced Solid Malignancy Only Procedures														
CT or MRI or PET-CT[15]									X (±7 days; odd cycles only)					
Tumor biopsy[2]									X (±7 days; C6 only)					
EORTC QLQ-C30[14]	X								X					
Study treatment dosing in-clinic[20]	X		X		X		X		X			X		
PK/CCI														
Blood draws for PK analysis[16]					X				X (Odd cycles only)					
CCI														
Adverse events	Continuous													
Concomitant medications	Continuous													
Telephone contact[18]		X		X		X		X		X	X		X	X

Table 3: Schedule of Assessments: End-of-Treatment and Beyond (Parts A and B)

Activity/Assessment	End-of-Treatment (EoT) Visit	Safety Follow-up Call[22]	Durability of Response and Survival Follow-up[19]
	≤ 14 Days Post Last Dose	30 Days Post-Last Dose + 7 days	Every 3 months for 1 year after the safety follow-up call ± 7 days
Clinical Assessments			
Patient weight	X		
Vital Signs (BP, pulse, temp)[4]	X		
Complete physical exam	X		
12-lead ECG[5]	X		
Echocardiogram or MUGA[6]	X		
Ophthalmic exam[7]	X		
ECOG	X		
Rheumatology consultation and testing[23]	As clinically indicated		
Hematology consultation, testing, and biopsy[24]	As clinically indicated		
Clinical Labs			
Urinalysis	X		
CBC with differential	X		
TSH[9]	X		
Complete serum chemistry	X		
Amylase and lipase[9]	X		
Coagulation tests	X		
Serum hCG pregnancy test[10]	X		
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[25]	X		
NHL Only Procedures			
PET-CT or CT scan[12]	X		X
EORTC QLQ-C30 and FACT-Lym questionnaires[14]	X		
Advanced Solid Malignancy Only Procedures			
CT or MRI or PET-CT[15]	X		X
EORTC QLQ-C30[14]	X		
PK CCI			
Blood draws for PK analysis[16]	X		
CCI			
Adverse events	X	X	

Activity/Assessment	End-of-Treatment (EoT) Visit	Safety Follow-up Call[22]	Durability of Response and Survival Follow-up[19]
	≤ 14 Days Post Last Dose	30 Days Post-Last Dose + 7 days	Every 3 months for 1 year after the safety follow-up call ± 7 days
Concomitant medications	X	X	
Telephone contact[18]		X	X (If in person visit is not performed)
Antineoplastic therapy after EoT		X	X

Sites should adhere to the 28-day cycle.

Procedures to be performed during clinic visits will be done prior to the administration of study treatment on those days.

Abbreviations: AE = adverse event; BSA = body surface area; CBC = complete blood count; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EoT = End of Treatment; FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma; MRI = magnetic resonance imaging; PET = positron emission tomography; CCI [redacted]; PK = Pharmacokinetic; TSH = thyroid stimulating hormone

1 Prior to any study-specific measure.

2 For explorative analysis research procedure, tumor tissue (lymph node core biopsy for NHL patients or tumor biopsy for patients with advanced solid malignancy) will be obtained pre- treatment (Day -30 to Day 7), C1D26 (±7 days), and at C6D1 (±7 days) and/or at the time of progression. Each biopsy will be divided into 3 portions, resulting in two fresh biopsies and one formalin fixed biopsy. Dose Escalation Phase: 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. NAPRT1 and IDH1 tumor status must be determined for all patients prior to enrollment in the KPT-9274 ± niacin ER expansion cohort. Prescreening to determine NAPRT1 and IDH1 tumor status will be performed on archival biopsy material obtained ≤6 months prior to screening, followed by confirmation of NAPRT1 and IDH1 tumor status during screening period. ***For the biopsies on C1D26 and C6D1 only, patients will be allowed to continue treatment if: 1) a patient refuses the biopsy, 2) in the opinion of the treating physician or physician performing the biopsy that the biopsy will pose significant risk to the patient, or 3) if the biopsy sample obtained on the first attempt is not adequate.***

3 A complete medical history will be obtained from each patient. Medical history will include baseline symptoms of the disease under study as well as a detailed history of prior procedures for the patient's NHL or advanced solid malignancy and other prior cancer therapies (i.e., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability, toxicity, or any other serious illness; Tumor Nodes Metastasis (TNM) staging will be collected on for patients with advanced solid malignancies. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will also be collected.

4 Vital signs: blood pressure, pulse and body temperature; see Section 7.5.1.2 for a detailed description of vital sign assessments.

5 12-Lead ECG to be completed 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. See Section 9.6.1.3 for a detailed description of electrocardiography.

6 Echocardiogram or MUGA scan at Screening (Day -30 to Day -1), EoT and as clinically indicated at the discretion of the Investigator during the study. See Section 7.5.1.3 for a detailed description of echocardiography.

7 A full ophthalmic examination at Screening (Day -30 to Day -1) and EoT will include, prior to dilation, best corrected visual acuity, slit lamp examination including tonometry, following dilation; fundoscopy and slit lamp to document lens clarity. See Section 7.5.1.4 for a detailed description of ophthalmic examination.

8 The following procedures must be performed at Screening (Day -30 to Day -1) and pre-dose on C1D1 (and as shown in Table 1 , Table 2 , and Table 3 during the study): ECOG performance assessment, echocardiogram or MUGA scan (Screening only), 12-lead ECG, and ophthalmic exam (Screening only). The following procedures must be performed at Screening (Day -14 to Day -1) and pre-dose on C1D1 (and as shown in Table 1, Table 2, and Table 3 during the study): urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests (Screening only), amylase, and lipase.

9 TSH, amylase and lipase do not need to be repeated separately if included in serum chemistry.

[10] For females of childbearing potential, negative serum hCG pregnancy test must be performed ≤ 3 days of C1D1 and the EoT Visit. Repeat testing during the study as clinically appropriate. Test sensitivity for hCG must be ≥ 25 mIU/mL.

[11] Disease risk assessment: See Section 7.2.3 for additional details.

[12] NHL disease assessment is preferably based on PET/CT for FDG-avid lymphomas, or CT for non-FDG-avid lymphomas. PET/MRI or MRI may be substituted if CT is contraindicated. Scans are performed at Screening and after every 8 weeks ± 7 days (e.g., Day 1 of odd numbered cycles) until disease progression or the EoT visit and Durability of Response and Survival Follow-up. EoT scan is only required for patients who end treatment for reasons other than disease progression. The same scan modality should be used for all assessments. Durability of Response and Survival Follow-up scan is only for patients who have not progressed.

[13] Bone marrow biopsies and/or aspirates will be taken within 30 days prior to first dose (baseline) to assess NHL involvement in bone marrow. The bone marrow biopsy will be repeated whenever clinically indicated, at the discretion of the Investigator, to confirm CR/PR in only those patients who had NHL with known bone marrow involvement prior to dosing (see Section 7.3.2.2).

[14] Patient will complete QoL questionnaires before they have any study procedures (including discussions with medical personnel and administration of study treatment) at these visits (see Section 7.3.1.1).

[15] Advanced solid malignancies: CT, MRI, or PET-CT scans will be performed at screening (Day -30 to Day -1), then every 8 weeks ± 7 days (e.g., Day 1 of odd numbered cycles), until disease progression or the EoT visit and Durability of Response and Survival Follow-up. EoT scan is only required for patients who end treatment for reasons other than disease progression. The same scan modality should be used for all assessments. Durability of Response and Survival Follow-up scan is only for patients who have not progressed.

[16] See Section 7.4 for timing of blood samples to be collected for PK analysis. Please note that if a patient's dose is changed, blood sampling for PK (as requested for C1D1) should be repeated on the first day of dose change at the same times as described for C1D1, C1D2, and C1D3. If the dose is missed, PK blood draws will not be collected on that day.

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[18] Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications, adverse events, and serious adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place Cycle 1 Days 4 +1day, 11 and 18±1 day; Cycle 2 and beyond – Days 4, 11, 18, and 25±1 day; Safety Follow-up phone call +7 days; and durability of response ±7days if the in person visit is not performed.

[19] If feasible and clinically indicated, the following assessments should be performed every 3 months for 1 year after the Safety Follow-up Visit/Call for patients who have not progressed to assess durability of response: PET/CT for FDG-avid lymphomas, or CT for non-FDG-avid lymphomas (or PET/MRI or MRI, respectively, if CT is contraindicated) scans for NHL patients and CT, MRI, or PET-CT scans for solid malignancy patients. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for 1 year to inquire about the patient's survival, disease status, and overall medical condition, and information on any antineoplastic therapies utilized since discontinuation of KPT-9274 study treatment.

[20] See Table 4 for at home versus in-clinic visit dosing.

[21] These assessments are to be completed pre-dose on C1D1 and are to be used to establish baseline values, not to reconfirm eligibility. However, if a safety concern is noted, contact Karyopharm.

[22] Safety follow-up telephone call [30 days post-last dose (+ 7 days)] with patient after their last dose of study treatment to evaluate their overall medical condition and status of disease, AEs, including follow-up on any AEs that were not resolved at the EoT Visit, and collection of information on any antineoplastic therapies used after discontinuation of study treatment.

[23] At the Investigator's discretion, in consultation with the Karyopharm Medical Monitor, patients with clinically significant joint or muscle-related AEs may have a rheumatology consultation. Rheumatology testing may be completed as clinically indicated per institutional standards (e.g., antinuclear antibodies, rheumatoid factor, C-reactive protein, erythrocyte sedimentation rate, uric acid [if not already available], or other autoantibodies based on symptoms).

[24] At the Investigator's discretion, in consultation with the Karyopharm Medical Monitor, patients with clinically significant hematological AEs, including any grade of treatment-emergent anemia or abnormal reticulocyte counts, may have a hematology consultation. Hematological testing (including but not limited to standard hematological evaluations and erythropoietin level) ± bone marrow biopsy may be performed as clinically indicated per institutional standards.

[25] Patients with treatment-emergent anemia should have blood levels of vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin and reticulocyte counts assessed as soon as possible after onset. Patients with ≤ Grade 1 anemia should have their levels/counts assessed no less than once a month and patients with ≥ Grade 2 anemia should have their levels/counts assessed every 2 weeks.

Table 4: Dosing Schedule (Parts A and B)

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
KPT-9274	X		X		X			X		X		X			X		X		X			X		X		X		
Niacin ER[1]	X		X		X			X		X		X			X		X		X			X		X		X		

[1] Patients in the Dose Escalation Phase or in the potential Dose Expansion Phase of KPT-9274 + niacin ER cohort will receive niacin ER (500 mg – 2,000 mg co-administered with each dose of KPT-9274).

Niacin ER=Niacin (vitamin B3/nicotinic acid) extended release.

Note: Study treatment dosing will occur in the clinic during Cycle 1 on Days 1, 3, 8, 15, 22, 24, and 26, during Cycle 2 on Days 1, 8, 15, and 22, and during > Cycle 3 on Days 1 and 15. Study treatment dosing will occur at home during Cycle 1 on Days 5, 10, 12, 17, and 19, during Cycle 2 on Days 3, 5, 10, 12, 17, 19, 24, and 26 and during Cycles ≥3 on Days 3, 5, 8, 10, 12, 17, 19, 22, 24, and 26.

Table 5: Schedule of Assessments for Screening and Cycle 1 (Part C)

If an in-clinic visit is missed during Cycle 1 due to a national or local holiday, the patient should come to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic.

	Screening		Cycle 1								
			Week 1				Week 2		Week 3		Week 4
	Day -30 to Day -1	Day -14 to Day -1	Day 1	Day 2	Day 3	D4 +1 day	D8	D11 ±1 day	D15	D18 ±1 day	D22
Visit Type	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Clinic Visit**
Activity/Assessment											
Informed consent[1]	X										
Determination of Melanoma that Has Progressed on Prior Anti-PD-1 or Anti-PD-L1 Treatment[2]	X										
Inclusion/exclusion criteria	X	X									
Patient History											
Demographics	X										
Medical history[3]	X										
Clinical Assessments											
Patient height	X										
Patient weight	X		X				X		X		X
Vital Signs (BP, pulse, temp)[4]	X		X				X		X		X
Complete physical exam	X										
Symptom-directed physical exam			X				X		X		X
12-lead ECG[5,7]			X[5] (Pre-dose and 4 hours post-dose)								
Echocardiogram or MUGA[6,7]	X										
ECOG[7]	X		X								
Hematology consultation and testing[17]			As clinically indicated								
Clinical Labs											
CBC with differential[7]		X	X[15]				X		X		X
TSH[7,8]		X	X[15]				X		X		
Complete serum chemistry[7]		X	X[15]				X		X		X
Amylase and lipase[7,8]		X	X[15]								

Serum hCG pregnancy test[9]		X									
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[18]	X		As clinically indicated								
PK CCI											
Blood draws for PK analysis[10]			X	X	X						
CCI											
Adverse events	Continuous (starting at C1D1)										
Concomitant medications	Continuous (starting at Screening)										
Telephone contact[12]						X		X		X	
Tumor biopsy[19]	X										
Disease Assessment											
CT, MRI, PET-CT or imaging methodology per investigator discretion[20]	X										
Study treatment dosing in-clinic[14]			See Table 8								

Table 6: Schedule of Assessments for Cycles 2 and Beyond (Part C)

If an in-clinic visit is missed during Cycle 2 and beyond, the patient should come to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic.

	Cycle 2						Cycle 3 and Beyond					
	Week 1		Week 2	Week 3		Week 4	Week 1	Week 2		Week 3		Week 4
	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day
Visit Type	Clinic Visit	Phone Call	Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit	Phone Call	Phone Call
Activity/Assessment												
Clinical Assessments												
Patient weight	X			X			X			X		
Vital Signs (BP, pulse, temp)[4]	X			X			X			X		
Symptom-directed physical exam	X			X			X			X		
ECOG	X						X					
Hematology consultation, testing, and biopsy[17]	As clinically indicated											
Clinical Labs												
CBC with differential	X			X			X			X		
TSH[8]	X						X					
Complete serum chemistry	X			X			X			X		
Amylase and lipase[8]	X						X					
Coagulation tests	X											
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[18]	As clinically indicated											
PK CCI												
Blood draws for PK analysis – KPT-9274 + nivolumab[10]	X											
CCI												
Adverse events	Continuous											
Concomitant medications	Continuous											
Telephone contact[12]		X	X		X	X		X	X		X	X

	Cycle 2						Cycle 3 and Beyond					
	Week 1		Week 2	Week 3		Week 4	Week 1	Week 2		Week 3		Week 4
	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day	D1	D4 ±1 day	D11 ±1 day	D15	D18 ±1 day	D25 ±1 day
Visit Type	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Phone Call**	**Phone Call**
Tumor biopsy[19]							X ±7 days					
CT, MRI, PET-CT, imaging methodology per investigator discretion[20]							X (±7 days; odd cycles only)					
Study treatment dosing in-clinic[14]	See Table 8											

Table 7: Schedule of Assessments for End-of-Treatment and Beyond (Part C)

Activity/Assessment	**End-of-Treatment (EoT) Visit** **≤ 14 Days Post Last Dose**	**Safety Follow-up Call[16]** **30 Days Post-Last Dose + 7 days**	**Durability of Response and Survival Follow-up[13]** **Every 3 months for 1 year after the safety follow-up call ± 7 days**
Clinical Assessments			
Patient weight	X		
Vital Signs (BP, pulse, temp)[4]	X		
Complete physical exam	X		
12-lead ECG[5]	X		
ECOG	X		
Hematology consultation, testing, and biopsy[17]	As clinically indicated		
Clinical Labs			
CBC with differential	X		
TSH[9]	X		
Complete serum chemistry	X		
Amylase and lipase[8]	X		
Coagulation tests	X		
Serum hCG pregnancy test[9]	X		
Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte count[18]	X (Optional)[18]		

Activity/Assessment	End-of-Treatment (EoT) Visit ≤ 14 Days Post Last Dose	Safety Follow-up Call[16] 30 Days Post-Last Dose + 7 days	Durability of Response and Survival Follow-up[13] Every 3 months for 1 year after the safety follow-up call ± 7 days
Adverse events	X	X	
Concomitant medications	X	X	
Telephone contact[12]		X	X (If in person visit is not performed)
Antineoplastic therapy after EoT		X	X
Tumor biopsy[19]	X		
CT, MRI, PET-CT, imaging methodology per investigator discretion[20]	X		X

Sites should adhere to the 28-day cycle.

Procedures to be performed during clinic visits will be done prior to the administration of study treatment on those days.

Abbreviations: AE = adverse event; BSA = body surface area; CBC = complete blood count; CT = computed tomography; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EoT = End of Treatment; FACT-Lym = Functional Assessment of Cancer Therapy-Lymphoma; MRI = magnetic resonance imaging; PET = positron emission tomography; CCI; PK = Pharmacokinetic; TSH = thyroid stimulating hormone

1 Prior to any study-specific measure.

2 Confirmation patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1 treatment.

3 A complete medical history will be obtained from each patient. Medical history will include baseline symptoms of the disease under study as well as a detailed history of prior procedures for the patient's melanoma and other prior cancer therapies (i.e., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability, toxicity, or any other serious illness; Tumor Nodes Metastasis (TNM) staging will be collected on for patients. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will also be collected.

4 Vital signs: blood pressure, pulse and body temperature; see Section 7.5.1.2 for a detailed description of vital sign assessments.

5 12-Lead ECG (in triplicate) to be completed at C1D1 (pre-dose and 4 hours post-dose), at the EoT visit, and as clinically indicated at the discretion of the Investigator. See Section 9.6.1.3 for a detailed description of electrocardiography.

6 Echocardiogram or MUGA scan at Screening (Day -30 to Day -1), and as clinically indicated at the discretion of the Investigator during the study. See Section 7.5.1.3 for a detailed description of echocardiography.

7 The following procedures must be performed at Screening (Day -30 to Day -1) and/or pre-dose on C1D1 (and as shown in Table 5 , Table 6 , and Table 7) during the study: ECOG performance assessment, echocardiogram or MUGA scan (Screening only), 12-lead ECG. The following procedures must be performed at Screening (Day -14 to Day -1) and pre-dose on C1D1 (and as shown in Table 5, Table 6, and Table 7 during the study): urinalysis, CBC with differential, TSH, complete serum chemistry, coagulations tests (Screening only), amylase, and lipase per Table 19.

8 TSH, amylase and lipase do not need to be repeated separately if included in serum chemistry.

9 For females of childbearing potential, negative serum hCG pregnancy test must be performed ≤ 3 days of C1D1 and the EoT Visit. Repeat testing during the study as clinically appropriate. Test sensitivity for hCG must be ≥ 25 mIU/mL.

10 See Section 7.4 for timing of blood samples to be collected for PK analysis.

CCI

12 Telephone call (or visit) with patient to evaluate supportive care medications, concomitant medications, adverse events, and serious adverse events, and to adjust supportive care as appropriate. The telephone contact with the patient must take place Cycle 1 Days 4 +1day, 11 and 18±1 day; Cycle 2 and beyond – Days 4, 11, 18, and 25±1 day; Safety Follow-up phone call +7 days; and durability of response ±7days if the in person visit is not performed.

13 If feasible and clinically indicated, the following assessments should be performed every 3 months for 1 year after the Safety Follow-up Visit/Call for patients who have not progressed to assess durability of response: CT, MRI, or PET-CT scans for solid malignancy patients. If these assessments cannot be performed, and for patients with PD, a telephone call will be made to the patient (or the patient's family) every 3 months for 1 year to inquire about the patient's survival, disease status, and overall medical condition, and information on any antineoplastic therapies utilized since discontinuation of KPT-9274 study treatment.

14 See Table 8 for at home versus in-clinic visit dosing.

15 These assessments are to be completed pre-dose on C1D1 and are to be used to establish baseline values, not to reconfirm eligibility. However, if a safety concern is noted, contact Karyopharm.

16 Safety follow-up telephone call [30 days post-last dose (+ 7 days)] with patient after their last dose of study treatment to evaluate their overall medical condition and status of disease, AEs, including follow-up on any AEs that were not resolved at the EoT Visit, and collection of information on any antineoplastic therapies used after discontinuation of study treatment.

17 At the Investigator's discretion, in consultation with the Karyopharm Medical Monitor, patients with clinically significant hematological AEs, including any grade of treatment-emergent anemia or abnormal reticulocyte counts, may have a hematology consultation. Hematological testing (including but not limited to standard hematological evaluations and erythropoietin level) ± bone marrow biopsy may be performed as clinically indicated per institutional standards.

[18] Patients with treatment-emergent anemia should have blood levels of vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin and reticulocyte counts assessed as soon as possible after onset. Patients with ≤ Grade 1 anemia should have their levels/counts assessed no less than once a month and patients with ≥ Grade 2 anemia should have their levels/counts assessed every 2 weeks.

[19] For explorative analysis research procedure, tumor tissue will be obtained pre- treatment (Day -30 to Day 1) , C3D1 (±7 days), and at the time of progression. Each biopsy will be divided into 3 portions, resulting in two fresh biopsies and one formalin fixed biopsy. ***For the biopsies on C3D1 and EoT, patients will be allowed to continue treatment if: 1) a patient refuses the biopsy, 2) in the opinion of the treating physician or physician performing the biopsy that the biopsy will pose significant risk to the patient, or 3) if the biopsy sample obtained on the first attempt is not adequate.***

[20] Advanced solid malignancies: CT, MRI, or PET-CT scans will be performed at screening (Day -30 to Day -1), then every 8 weeks ± 7 days (e.g., Day 1 of odd numbered cycles), until disease progression or the EoT visit and Durability of Response and Survival Follow-up. EoT scan is only required for patients who end treatment for reasons other than disease progression. The same scan modality should be used for all assessments. Durability of Response and Survival Follow-up scan is only for patients who have not progressed.

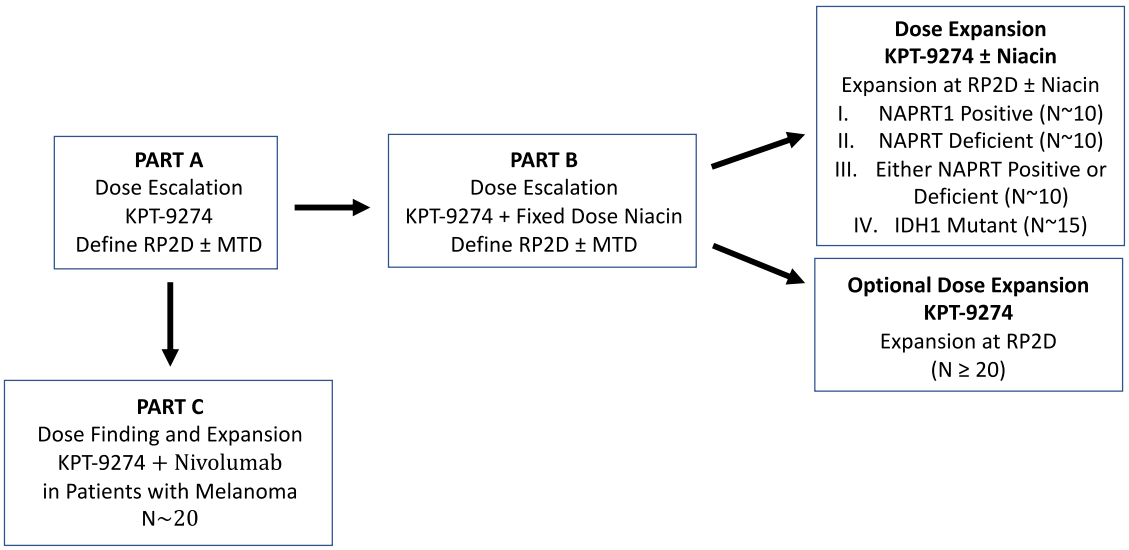
Table 8: Dosing Schedule for Patients with Melanoma Who Progressed on Prior Anti-PD-1 or Anti-PD-L1 Treatment (Part C)

Treatment	Week 1							Week 2							Week 3							Week 4						
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27	D28
KPT-9274	X		X		X			X		X		X			X		X		X			X		X		X		
Nivolumab[1]	X																											

[1]Every 4 weeks

Note: KPT-9274 dosing will occur in the clinic during Cycle 1 on Days 1, 3, 8, 15, 22, 24, and 26, during Cycle 2 on Days 1, 8, 15, and 22, and during > Cycle 3 on Days 1 and 15. KPT-9274 dosing will occur at home during Cycle 1 on Days 5, 10, 12, 17, and 19, during Cycle 2 on Days 3, 5, 10, 12, 17, 19, 24, and 26 and during Cycles ≥3 on Days 3, 5, 8, 10, 12, 17, 19, 22, 24, and 26. Nivolumab treatment will occur in the clinic on Day 1 of each cycle.

Figure 1: Study Flow Chart



The starting dose of KPT-9274 for Part B will be a dose and schedule that has cleared DLT assessment during Part A.

Dose Expansion Phase may be completed; patients 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.

If Dose Expansion patients are to be treated with KPT-9274 + niacin ER, then an optional Dose Expansion of KPT-9274 single agent at RP2D ($n \leq 20$) may also be conducted. Note that preliminary clinical results may define the patient population (i.e., specific indications) selected for enrollment in the Dose Expansion Phase.

In Part C, a starting dose of KPT-9274 will be a dose and schedule that has cleared DLT assessment in Part A.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 9: Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Explanation
°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
B-ALL	B-cell acute lymphoblastic leukemia
BP	blood pressure
BSA	body surface area
CBC	complete blood count
CBR	clinical benefit rate
CI	confidence interval
CL/F	plasma clearance
C_{max}	maximum plasma concentration
cm	centimeter
CNS	central nervous system
COX-2	cyclooxygenase-2
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXDX (e.g., C1D1)	Cycle X Day X (e.g., Cycle 1 Day 1)
DAP	Data Analysis Plan
DCR	disease control rate
DDA	deoxyribonucleic acid damaging agent
DLT	dose-limiting toxicity

Abbreviation or Specialist Term	Explanation
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EoT	end of treatment
ER	extended release
FACT-G	Functional Assessment of Cancer Therapy
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
HAT	hormone ablation therapy
Hb	hemoglobin
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPLC/MS-MS	high performance liquid chromatography/tandem mass spectrometry
hr	hour
IB	Investigator's Brochure

Abbreviation or Specialist Term	Explanation
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IDH1	isocitrate dehydrogenase 1 (NADP+), soluble
IHC	immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
Karyopharm	Karyopharm Therapeutics Inc.
kg	kilogram
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MDR	multiple drug resistance
mIU	milli-international units
mL	milliliter
MM	multiple myeloma
MRI	magnetic resonance imaging
CCI [redacted]	
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
N	number of patients
NAD	nicotinamide adenine dinucleotide
NAMPT	nicotinamide phosphoribosyltransferase/PBEF/visfatin
NAPRT1	nicotinate phosphoribosyltransferase
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
Niacin	vitamin B3/nicotinic acid
NSAID	non-steroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
OTC	over the counter

Abbreviation or Specialist Term	Explanation
PAK4	p21 protein (Cdc42/Rac)-activated kinase 4
CCI	
PD	progressive disease
CCI	
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per protocol
PPI	proton pump inhibitor
PR	partial response
CCI	
QOD	every other day
QoL	quality of life
CCI	
RAS	rat sarcoma viral oncogene homolog
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal plasma half-life
TEAE	treatment-emergent adverse event
t_{max}	time to peak plasma concentration
TNM	tumor nodes metastasis
TOI	trial outcomes index
TSH	thyroid stimulating hormone
TTP	time to progression
ULN	upper limit of normal
V_d/F	volume of distribution

Abbreviation or Specialist Term	Explanation
WBC	white blood cell

1. INTRODUCTION

1.1. Indication

This study will enroll patients with advanced solid malignancies (including sarcoma, colon, lung, etc.) or non-Hodgkin's lymphoma for which all standard therapeutic options considered useful by the investigator have been exhausted and with progressive disease on study entry.

1.2. KPT-9274

KPT-9274 is a first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of p21 protein (Cdc42/Rac)-activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase/PBEF/visfatin (NAMPT). Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of deoxyribonucleic acid (DNA) repair, cell cycle arrest, inhibition of proliferation, and ultimately apoptosis. Normal cells are more resistant to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic rates.

KPT-9274 demonstrated potent anti-proliferative activity against cancer cell lines (solid tumor cells MTT median IC_{50}: 135 nM, range 0.007 to >10 μM; hematological cancer cells MTT median IC_{50}: 40 nM, range 0.003 to >10 μM) with minimal toxicity to normal cells (median MTT IC_{50}: ~0.9 μM, range 0.033 to >10 μM). In mouse xenograft studies, KPT-9274 (oral 50-200 mg/kg twice daily for 5 days/week) was well tolerated and resulted in a marked reduction in tumor size across a variety of tumors, including colon, pancreatic, lung, multiple myeloma, leukemia, and lymphoma. In approximately half of the tumor types studied, complete elimination of tumors in as short as 3 weeks was observed with no regrowth after cessation of treatment (up to 3 weeks). In other cell types tumor growth inhibition was observed. KPT-9274 was able to control systemic acute B lymphoblastic leukemia (B-ALL) and acute myeloid leukemia (AML) tumor growth and significantly extended overall survival. Moreover, KPT-9274 has shown preliminary efficacy in companion dogs with spontaneous advanced lymphomas and multiple myeloma (MM).

Unlike the Pan-PAK inhibitor (PF-3758309), or the NAMPT inhibitors (APO866 and GMX1777/GMX1778) that advanced to human clinical trials, the dual NAMPT/PAK inhibitor KPT-9274 demonstrates consistent pharmacokinetic (PK) properties (e.g., oral absorption), exhibits minimal brain penetration, and does not inhibit any of the cytochrome P450 (CYP450) enzymes. The nonclinical toxicity profile of KPT-9274 recapitulates the expected class level gastrointestinal (GI) and hematopoietic toxicities but not the retinal and cardiac effects observed preclinically with some NAMPT inhibitors. The lack of retinal and cardiac effects of KPT-9274 may be attributed to its minimal permeability and decreased potency compared to other NAMPT inhibitors. Furthermore, no orally available PAK4 selective inhibitors have been developed to date. Thus, KPT-9274 captures many of the favorable therapeutic aspects of targeting both NAMPT and PAK4 with the potential for reduced adverse effects.

Preliminary two-week non-good laboratory practices (GLP) toxicology studies in rats and dogs suggest that KPT-9274 has an acceptable tolerability profile. The dog has been identified as the most sensitive species for KPT-9274 GI toxicity, with rats also showing GI toxicity at significantly higher doses. The primary KPT-9274 toxicity that has been observed in dogs is gastrointestinal

hemorrhages in the small intestine, colon, and rectum. Other target organ effects include hypocellularity in the bone marrow and lymphoid depletion in the lymphoid tissues.

Nicotinamide adenine dinucleotide (NAD) regeneration pathways can bypass NAMPT inhibition by utilizing niacin (vitamin B3/nicotinic acid) through nicotinate phosphoribosyltransferase (NAPRT1). Supplemented niacin can alleviate adverse events due to NAMPT inhibition when tissues express NAPRT1. However, NAPRT1 is frequently repressed in tumors (through epigenetic modulation or isocitrate dehydrogenase 1 (NADP+), soluble [IDH1] mutation) while remaining intact in surrounding normal tissue potentially increasing therapeutic index in the presence of niacin. Additional exploratory studies and data from 4-week GLP studies indicate that co-administration of niacin can increase tolerability of KPT-9274 in dogs. These data demonstrate that a dose of KPT-9274 previously shown to have an adverse toxicologic profile was tolerable and had minimal GI macroscopic findings. For this reason, co-administration of KPT-9274 with niacin in patients with or without NAPRT1 or IDH1 mutation in their tumors is planned.

KPT-9274 demonstrated anti-tumor activity in dogs with spontaneous advanced lymphomas and multiple myeloma. Patient dog #1 was given 4 doses of 2 mg/kg KPT-9274 and had progressive disease after 1 week. This patient dog was given 25 mg/kg doxorubicin (Adriamycin) on Day 8 (~24 hours post-final KPT-9274 dose). The bulk disease responded shortly thereafter with a partial response (PR) at the end of week 2 that transitioned into a complete response (CR). As of October 2015, the patient dog remains in complete remission for >4 months off all therapy with no AEs reported to date. A T-cell lymphoma dog experienced a ~1 week PR at 2 mg/kg of KPT-9274 every other day (QOD) × 3 but subsequently progressed. A patient dog with refractory multiple myeloma (4 lines of previous therapy) treated with 3 mg/kg of KPT-9274 QOD x 3 plus prednisone had a PR with decreases in globulins and resolution of anemia and thrombocytopenia for ~5 weeks, but progressed during Week 6. Two additional B-cell lymphoma dogs did not respond to 2 mg/kg or 3 mg/kg of KPT-9274 QOD × 3 in which one dog (2 mg/kg dose) had low drug levels in the plasma. These preliminary results suggest that KPT-9274 show anti-tumor activity both as a single agent and in combination with DNA damaging agents (DDA) with minimal or no side effects observed. Dose escalation evaluation in patient dogs with lymphoma and solid tumors is on-going.

KPT-9274 has clear preclinical anti-tumor activity (*in vitro* and *in vivo*) as well as an encouraging safety profile (compared to previously described Pan-PAK and NAMPT inhibitors) making it an attractive novel drug candidate. Since both solid tumor and hematologic malignancies were seen to be susceptible to single-agent cytotoxicity with KPT-9274, development is planned in both areas.

1.2.1. Potential Risks

As of 02 March 2019, 47 patients had received KPT-9274 alone or with niacin ER in Parts A and B of this study. Dose levels and schedules are outlined in Table 10, along with the number of patients enrolled in each cohort. The most common AEs occurring across all patients in Parts A and B, were anemia (68%), nausea (34%), arthralgia (32%), fatigue (32%), and myalgia (23%) (Table 11; Table 12). AEs were largely dose dependent and increased with higher doses of KPT-9274. There were 2 DLTs reported among the first 47 patients. These included one case of grade 4 anemia, which occurred in the 40 mg KPT-9274 qodX3 cohort, and one case of grade 3 fatigue which occurred in the 80 mg KPT-9274 qodX3 + niacin cohort. Both dose levels enrolled

additional patients per the 3+3 study design, and both dose levels ultimately cleared DLT evaluation. To date, a MTD has not been reached.

Table 10: Dose Levels and Schedules Tested as of 02 March 2019

Cohort	Dose / Schedule	Patients Enrolled
1	10 mg / qodx3	3
2	20 mg / qodx3	3
3	30 mg / qodx3	5
4	40 mg / qodx3	7
5	40 mg / qodx2	5
3B	30 mg / qodx3 + 500 mg niacin ER	3
4B	40 mg / qodx3 + 500 mg niacin ER	4
5B	60 mg / qodx3 + 500 mg niacin ER	10
6B	80 mg / qodx3 + 500 mg niacin ER	6
7B	100 mg / qodx3 + 500 mg niacin ER	1

Table 11: Treatment Related Adverse Events Occuring in ≥ 10% of All Patients

Adverse Events	All Dose Levels (N=47)				
	G1	G2	G3	G4	Total
Anemia	2	7	22	1	32 (68%)
Nausea	13	3			16 (34%)
Arthralgia	11	4			15 (32%)
Fatigue	7	6	2		15 (32%)
Myalgia	7	4			11 (23%)
Diarrhea	6	3	1		10 (21%)

Vomiting	7	1	1		9 (19%)
Dyspnea	4	2	2		8 (17%)
AST increase	2	3			5 (11%)
Peripheral edema	3	2			5 (11%)

Table 12: Treatment Related Adverse Events Occuring in ≥ 10% of Patients by Dose Level and Schedule

10 mg (N=3)	**20 mg (N=3)**		**30 mg (N=5)**		**30 mg + Niacin (N=3)**		**40 mg (N=7)**		**40 mg + Niacin (N=4)**		**40 mg BIW (N=5)**		**60 mg + Niacin (N=11)**		**80 mg + Niacin (N=5)**		**100 mg + Niacin (N=1)**	
All	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**	**G1/2**	**G3+**
No Events	1	1	1	2	1			6		2	3	2	2	5	1	4		1
							3		3		1		5		3		1	
			2		2		5		1		1		2		1		1	
			1	1	1		2		1		2		4		2	1		
	1		2		1		1		1		2		2				1	
			1		1		2				1	1	1		2		1	
							1		2				2	1	2		1	
					1		1	1					1	1	3			
			1		1				1		1		1					
	1		1				1						1		1			
			2		1								1					
					1		1						1		1			
							2							1			1	

1.2.2. Reproductive Risks of KPT-9274

It is unknown whether KPT-9274 might have reproductive toxicity in humans; therefore, all patients in this study must agree to use effective contraception (see Prevention of Pregnancy, Section 6.9.2.2) during the study, and for 3 months after their last dose of KPT-9274.

1.3. Study Rationale

KPT-9274 is a first-in-class orally bioavailable, non-competitive, small molecule, dual modulator of PAK4 and NAMPT. PAK4 is a key downstream effector for RAS and forms a critical link between RAS-driven oncogenic transformation and activation of the WNT/β-catenin signaling pathway. NAMPT is the rate-limiting enzyme in the metabolic scavenging pathway that utilizes nicotinamide to replenish nicotinamide adenine dinucleotide (NAD), an essential metabolic cofactor and second messenger.

Hematologic and solid tumor cells are susceptible to single-agent cytotoxicity by KPT-9274 as they become dependent on both the PAK4 and NAMPT pathways. KPT-9274 demonstrated potent anti-proliferative activity against cancer cell lines with minimal toxicity to normal cells. In mouse xenograft studies, KPT-9274 was well tolerated and resulted in a marked reduction/elimination of tumors, tumor growth inhibition or disease control across a variety of tumors, including colon, pancreatic, lung, sarcoma, multiple myeloma, leukemia, and lymphoma. In approximately half of the tumor types studied, complete elimination of tumors in as short as 3 weeks was observed with no regrowth after cessation of treatment (for up to 3 additional weeks). Moreover, KPT-9274 has shown preliminary efficacy in companion dogs with spontaneous advanced lymphomas and multiple myeloma.

1.3.1. Rationale for the KPT-9274 Dose

The first-in-human starting dose was calculated based on a pivotal GLP 4-week repeat-dose toxicology study in male and female dogs, the most sensitive species, where the highest non-severely toxic dose (HNSTD) is 2 mg/kg/dose (40 mg/m^2) for KPT-9274 when administered orally on a QODx3 weekly schedule. Using a conservative estimate of average human body surface area (BSA) of 1.7 m^2, this is equivalent to an oral dose of 68 mg, and application of a 6-fold safety factor results in a 10 mg starting dose for humans. Additionally, Karyopharm Therapeutics has conducted a pivotal GLP 4-week repeat-dose toxicology study in rats where the severely toxic dose in 10% of the animals (STD_{10}) is 80 mg/kg/dose (460 mg/m^2). Similarly, using the same flat dose calculation as above, a 460 mg/m^2 (~782 mg) dose and a safety factor of 10, results in a starting dose of 80 mg for humans. Based on these data, the dog is the more sensitive species, and therefore the appropriate starting dose for humans is 10 mg orally.

1.3.2. Rationale for Adding Niacin

NAD can be generated by catabolism of tryptophan, salvage of nicotinamide through NAMPT or salvage of exogenous niacin through NAPRT1. Some cancers lack the enzyme(s) necessary for the *de novo* synthesis of NAD from tryptophan, while NAPRT1 (a niacin utilizing enzyme) activity is frequently down-regulated by epigenetic modulation or IDH1 mutation leaving these cancers dependent on NAMPT activity. If tumors have reduced or absent NAPRT1 function, then this tissue may not be able to utilize niacin to make NAD. Therefore, patients with NAPRT1 in normal tissue, but not in their tumors, might benefit from a niacin co-dosing strategy in order to reduce

side effects. Pivotal GLP and exploratory non-GLP studies have demonstrated that co-dosing niacin with KPT-9274 can increase tolerability; therefore, KPT-9274 co-administered with orally administered niacin extended release (ER) will be evaluated in the current study. In addition, lack of NAPRT1 or IDH1 mutation in the tumor may be used as a prognostic marker of KPT-9274 response and therefore may be used to characterize patient populations. CCI

1.3.3. Rationale for Combining KPT-9274 with Nivolumab in Melanoma

KPT-9274 binds to and reduces the steady state level of the PAK4 protein kinase as well as blocking the activity of NAMPT. In addition, through PAK4 inhibition, KPT-9274 reduces the stability, nuclear transportation and function of β-catenin by inhibiting its phosphorylation on S675. This is consistent with β-catenin being a target of PAK4. Nivolumab is a monoclonal antibody directed against the programmed cell death 1 receptor (PD-1) on lymphocytes. Anti-PD-1 treatment increases the immune response, allowing T cell killing of tumor cells. Nivolumab has been FDA-approved for use in patients with advanced melanoma. There is evidence suggesting that patients most likely to respond to anti-PD-1 treatment are those who have an elevated baseline of CD8+ T cell infiltration within the tumor microenvironment (TME) (Abril-Rodriguez, 2020). Those who lack a T cell infiltrate respond poorly. A correlation was reported between hyperactivation of the WNT/β-catenin signaling pathway and T cell exclusion in melanoma patient tumor samples (Spranger 2015). Recently, this correlation has been extended to PAK4 overexpression (Abril-Rodriguez, 2020). These data suggest that combination therapies in which activated β-catenin is inhibited through PAK4 inhibition simultaneously with targeting PD-1, may be particularly effective therapy. Indeed, in vivo models of mice engrafted with melanoma cells that were treated with KPT-9274 + an anti-PD-1 antibody showed marked tumor growth inhibition compared to either agent alone (Abril-Rodriguez, 2020). Therefore, combinatorial treatment with KPT-9274, which blocks β-catenin, with nivolumab may be beneficial to patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. 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 (RECIST 1.1 - Appendix 4])) or Lugano Classification (Appendix 3), respectively.

Part C

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

2.1.2. 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.

2.1.3. Exploratory Objectives

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2.2. Endpoints

2.2.1. 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.

2.2.2. Efficacy Endpoints

Disease response will be evaluated according to RECIST 1.1 (advanced solid malignancies and melanoma (Appendix 4)) or Lugano Classification (NHL) (Appendix 3) and will include the following:

- **Overall 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) ≥ 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.

2.2.3. PK Endpoints

KPT-9274 PK parameters may include, but are not limited to, maximum plasma concentration (C_{max}), area under the curve (AUC), time-to-peak plasma concentration (t_{max}), terminal plasma half-life ($t_{½}$), apparent volume of distribution (V_d/F), and apparent plasma clearance (CL/F).

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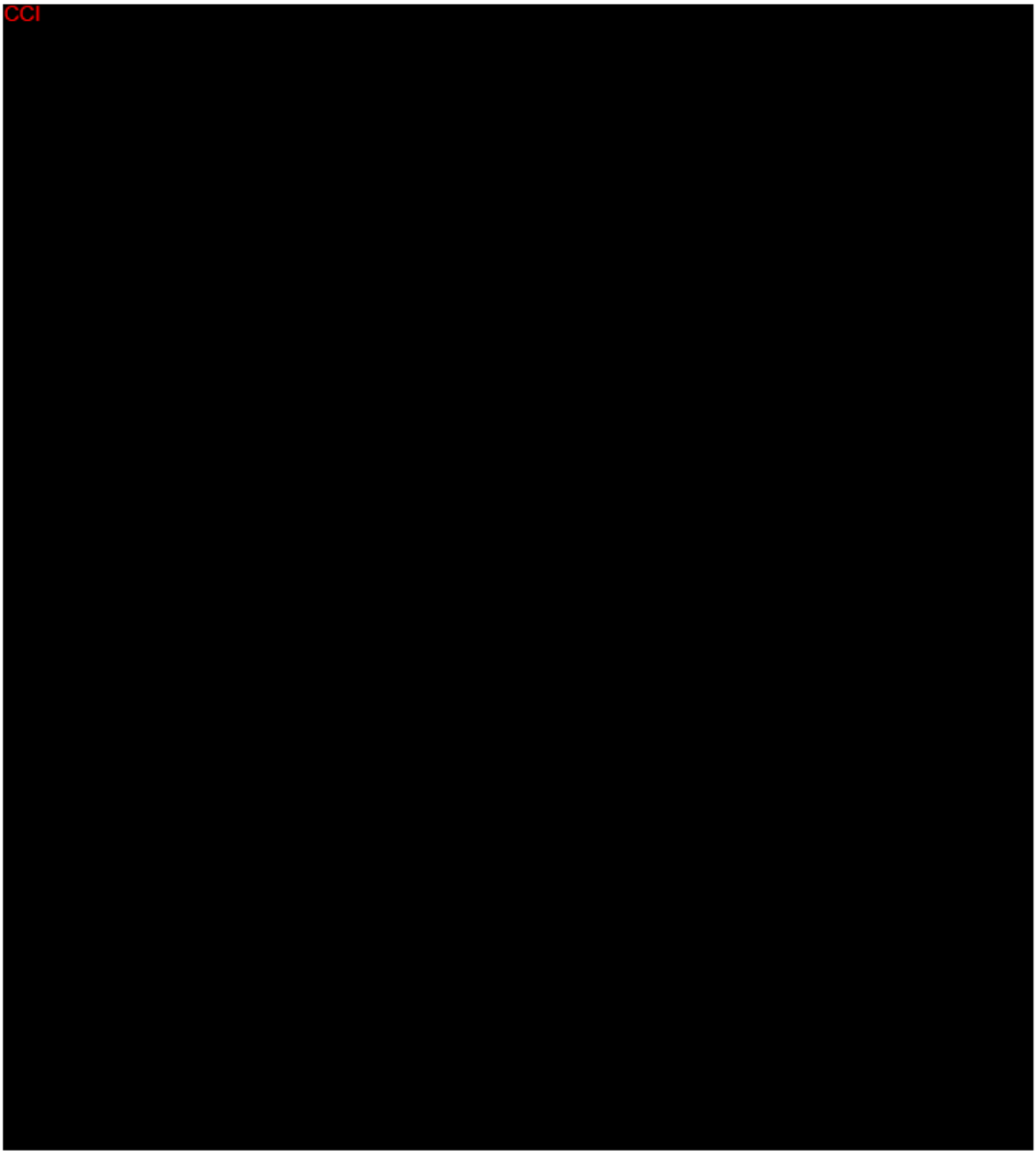

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3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 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. 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. For the purposes of dose escalation decisions, a standard 3+3 dose escalation design will be used during both 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 500 mg up to 2,000 mg niacin ER; the starting dose of KPT-9274 for Part B will be a dose and schedule that has cleared DLT assessment during Part A.

A Dose Expansion Phase may be completed; this phase will determine the safety, tolerability, and preliminary evidence of anti-tumor activity of KPT-9274 at the RP2D ± niacin ER in patients with advanced solid malignancies or NHL according to RECIST 1.1 (advanced solid malignancies [Appendix 4]) or the Lugano Classification for response assessment of NHL (Appendix 3) and described in terms of best overall response, ORR, DOR, DCR, duration of disease control, PFS, OS, and TTP. 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, 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 additional, optional expansion with < 20 patients at the RP2D of KPT-9274 single agent may also be initiated.

In Part C, a cohort of patients with melanoma that have progressed on an anti-PD1 or anti-PD-L1 antibody will be treated with KPT-9274 (at a dose that cleared DLT evaluation in Part A) + nivolumab. 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 (Appendix 4).

All phases of the study will be comprised of Screening, Treatment, and Follow-up periods.

Screening will be performed 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), as summarized in Table 1 and Table 5. During the Treatment period, procedures are to be performed during clinic visits prior to the administration of study treatment on those days as presented in Table 1, Table 2, Table 5 and Table 6. The Follow-up period includes the EOT visit, the Safety Follow-up visit, and Durability of Response and Survival Follow-up; see Table 3 and Table 7 for assessments to be completed during the Follow-up period.

Enrollment is estimated at 175 patients. However, the number of patients required for completion of study enrollment cannot be defined *a priori* since this depends on the number of patients needed for the dose escalations in Parts A and B. Assuming that 9 dose levels of KPT-9274 are evaluated during both Part A (KPT-9274 single agent) and Part B (KPT-9274 + niacin ER) 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. Each cohort in Parts A and B of the Escalation Phase will consist of 3 or 6 patients per cohort. The Dose Expansion Phase may include up to 65 additional patients (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).

The KPT-9274 ± niacin ER expansion cohort will consist of 4 groups of approximately 45 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) including the following:

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

An additional, optional KPT-9274 single agent expansion cohort will consist of < 20 patients with any tumor mutational status.

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 500 mg up to 2,000 mg niacin ER co-administered with each dose of KPT-9274.

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.

Further details on the Dose Escalation phase are provided in Section 6.2.5 and Section 6.2.6 and additional details on the Dose Expansion phase are provided in Section 6.2.7.

3.2. Replacement Policy

Patients who complete the first cycle of therapy will not be replaced during the Escalation Phase of the study. However, if a patient is considered as non-evaluable for DLT (i.e., did not complete the first cycle of therapy and did not experience a DLT), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients.

During the Dose Expansion Phase, patients who have not completed 1 cycle will be replaced unless they were discontinued from the study due to a drug-related toxicity, PD, or death.

3.3. Treatment Duration

Treatment cycles are 28 days long. A patient may continue to receive KPT-9274 until that patient experiences 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 Investigator or the Karyopharm Medical Monitor.

4. STUDY POPULATION SELECTION

4.1. Study Population

This study will enroll adult patients with advanced solid malignancies (including sarcoma, colon, lung, etc.) or non-Hodgkin's lymphoma for which standard therapeutic options considered useful by the investigator have been exhausted and with progressive disease on study entry, and meet all of the inclusion criteria and none of the exclusion criteria.

4.2. Inclusion Criteria (Parts A and B)

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
2. Age ≥ 18 years.
3. Patients with advanced solid malignancies or NHL for which all standard therapeutic options considered useful by the investigator have been exhausted.
4. Patients must have objective evidence of progressive disease on study entry:
   a. Advanced solid malignancies: Measurable disease as defined by RECIST 1.1 (Appendix 4).
   b. NHL: Measurable disease including target lesion(s) as defined by the Lugano Classification for initial evaluation and staging (Appendix 3).
5. Patients must have a site of disease amenable to biopsy and be a candidate for biopsy according to the treating institution's guidelines.
6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
7. Adequate hepatic function:
   a. Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3 times ULN),
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their advanced solid malignancy or NHL who must have their AST and ALT ≤ 5.0 times ULN).
8. Adequate renal function: estimated creatinine clearance of ≥ 60 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female.
9. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception [as defined in Section 6.9.2.2]) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.

10. Adequate hematopoietic function: total white blood cell (WBC) count ≥ 1500/mm^3, absolute neutrophil count (ANC) ≥ 1000/mm^3, hemoglobin (Hb) ≥ 10.0 g/dL, and platelet count ≥ 75,000/mm^3.
11. Dose Escalation Phase: 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.
12. Dose Expansion Phase (KPT-9274 ± niacin ER cohort only): Patient tumors NAPRT1 and IDH1 status must be determined at the central laboratory prior to enrollment.
    a. Confirmation of NAPRT1 expression and IDH1 mutation based on evaluation of a fresh tumor biopsy or archival tumor biopsy taken ≤ 6 months of screening tests as follows:
        i. NAPRT1 positive for expansion cohort I or III
        ii NAPRT1 negative for expansion cohort II or III
        iii. IDH1 mutation status for expansion cohort IV
13. Life expectancy of ≥ 3 months.

4.3. Exclusion Criteria (Parts A and B)

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Female patients who are pregnant or lactating.
2. Time since the last prior therapy for treatment of advanced solid malignancies or NHL**:
    a. Radiation, chemotherapy, immunotherapy or any other anticancer therapy, including investigational anti-cancer therapy ≤ 2 weeks prior to C1D1.
    b. Palliative steroids for disease related symptoms < 7 days prior to C1D1.

**Patients must have recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤ Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor.

3. Patients with known central nervous system (CNS) disease or leptomeningeal involvement, regardless of response to prior therapy, are excluded.
4. Major surgery within four weeks before C1D1.
5. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    a. Unstable angina or acute myocardial infarction ≤ 3 months prior to C1D1;
    b. Clinically significant heart disease (e.g., symptomatic congestive heart failure; uncontrolled arrhythmia, or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen).

6. Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted.
7. Patients with a known history of Human Immunodeficiency Virus (HIV); HIV testing is not required as part of this study.
8. Known, active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen). Testing is not required.
9. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.
10. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent.
11. Active peptic ulcer disease or other active gastrointestinal bleeds.

4.4. Inclusion Criteria (Part C)

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines.
2. Age ≥18 years.
3. Patients must have objective and measurable melanoma by RECIST 1.1 after disease progression on a prior anti-PD-1 or anti-PD-L1 therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
5. Adequate hepatic function:
    a. Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3 times ULN),
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their advanced solid malignancy who must have their AST and ALT ≤ 5.0 times ULN).
6. Adequate renal function: Estimated creatinine clearance of ≥ 60 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female.
7. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.

8. Adequate hematopoietic function: total white blood cell (WBC) count ≥ 1500/mm^3, absolute neutrophil count (ANC) ≥ 1000/mm^3, hemoglobin (Hb) ≥ 10.0 g/dL, and platelet count ≥ 100,000/mm^3.
9. Life expectancy of ≥ 3 months.

4.5. Exclusion Criteria (Part C)

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Female patients who are pregnant or lactating.
2. ≤ 2 weeks since the last prior therapeutic regimen for melanoma. Palliative steroids for disease related symptoms < 7 days prior to C1D1, unless physiologic doses of steroids are used.
3. Patients who have not recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤ Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor.
4. Patients with untreated central nervous system (CNS) disease or leptomeningeal involvement are excluded. Patients without active brain or leptomeningeal metastases after prior treatment with local therapies are eligible provided that the treatment had been done ≥ 2 weeks prior to enrollment.
5. Major surgery within four weeks before C1D1.
6. Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted.
7. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.
8. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent.
9. Active peptic ulcer disease or other active gastrointestinal bleeds.
10. Patients requiring treatment with corticosteroids at doses higher than substitute therapy (> 10 mg prednisone), are unstable with substitute hormonal therapy, or are deemed to be likely to re-occur by the treating physician when administered nivolumab.

4.6. Screening and Registration

The Screening period starts once a patient has provided written informed consent to participate in the study and ends on the day of study entry (C1D1).

Patient eligibility (inclusion/exclusion criteria) will be reviewed for each patient participating in the study by the Karyopharm Medical Monitor before the patient receives study treatment on C1D1. The procedure used to check eligibility and registration of patients is the same in the Dose Escalation Phase and the Dose Expansion Phase of the study, as follows:

The eligibility check form/Patient Registration Form will be sent from the site to Karyopharm for evaluation either by fax or email. Upon confirmation of eligibility, Karyopharm will return the signed eligibility check form/Patient Registration Form via fax or email to the site. The Patient Registration Form will indicate the dose group to which the patient has been assigned (see Section 4.6.1).

4.6.1. Study Patient Number

Upon screening, each patient will be assigned a unique patient number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients will be identified to Karyopharm by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient master log.

4.6.2. Rescreening

Rescreening is permitted in this study following discussion with the Karyopharm Medical Monitor. If a patient fails any of the inclusion or exclusion criteria, that patient may be rescreened after a suitable period of time (the exact length is dependent upon the reason for the screen failure) at the agreement of the Karyopharm Medical Monitor and the Investigator. Any patient who is rescreened must be re-consented. A patient may only be re-screened once.

4.6.3. Screen Failures

Patients who sign an informed consent but fail to start on treatment for any reason will be considered a screen failure. Date of consent and reason for ineligibility will be entered into the clinical database. No other data will be entered into the clinical database for patients who are screen failures, unless those patients experience serious adverse event (SAE) during the Screening Phase.

5. DISCONTINUATION CRITERIA

5.1. Early Termination of the Study

This study may be discontinued at the sole discretion of Karyopharm for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. If this occurs, Karyopharm will notify ethics committees, Investigators, and regulatory authorities, as applicable.

5.2. Discontinuation of Study Treatment and/or Withdrawal of Patients from the Study

The Investigator may remove a patient from study treatment after consultation with the Karyopharm Medical Monitor for any of the following reasons:

- Unacceptable AEs or toxicity that cannot be managed by supportive care
- Any medically appropriate reason (e.g., clinical progression) or significant protocol violation, in the opinion of the Investigator

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

- Disease progression per response criteria
- Patient withdraws consent to continue study treatment
- Pregnancy

Patients who are removed from study treatment by the Investigator are not permitted to restart study treatment.

Patients may discontinue study treatment for any reason. Patients who choose to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. Patients may elect to withdraw consent and decline further participation in the study at any time. If a patient withdraws consent after completing Cycle 1, he/she may request to re-enter the study, if it occurs within 28 days since the last dose, by re-signing consent. This is permitted based on the Investigator's discretion and after consultation with the Karyopharm Medical Monitor.

The reason for the patient’s discontinuation of study treatment/withdrawal from the study must be recorded on the eCRF.

All patients will be followed until PD, withdrawal of consent, occurrence of any withdrawal criteria, intolerable toxicity precluding further treatment with study treatment, death or loss to follow up.

6. STUDY TREATMENTS

6.1. Treatments Administered

6.1.1. KPT-9274

KPT-9274 is an orally bioavailable small molecule prepared in a tablet solid dosage form for oral administration.

KPT-9274 tablets are designed for immediate-release oral administration and will be supplied in high-density polyethylene (HDPE) bottles with induction seals and polypropylene caps.

KPT-9274 tablets will be film coated for ease of handling and provided in tablet strengths of 5 mg and 20 mg. KPT-9274 will be supplied by Karyopharm. Additional details on KPT-9274 are provided in the IB. The investigational treatments will be administered as a flat dose and not by body weight or body surface area.

6.1.2. Niacin ER (Part B)

Patients enrolled in Part B of the Dose Escalation Phase or in the Dose Expansion cohort with co-administration of niacin will also receive 500 mg of any FDA approved prescription, generic niacin ER for oral use co-administered with each dose of KPT-9274. The starting dose of 500 mg niacin ER may be titrated up to 2,000 mg of daily dose, per label. A list of approved generic niacin ER will be provided in the Pharmacy Manual. The niacin ER study treatment will be obtained by the site pharmacy.

6.1.3. Nivolumab (Part C)

Nivolumab will begin on the first day (C1D1) and will be administered through an intravenous (IV) line on Day 1 of each cycle (once every 4-week cycle] at 480 mg according to the current prescribing information. Nivolumab will be given per standard of care.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the eCRF.

6.1.4. Placebo or Control

Not applicable. This is not a placebo-controlled study and the active treatment will not be compared to a control treatment.

6.2. Study Treatment Dose Schedules and Administration

6.2.1. Labeling

All labels will include conditions for storage, lot number, and other pertinent information such as Sponsor and a caution statement. Medication labels for KPT-9274 will be in the local language of the site and comply with the legal requirements of each country.

6.2.2. Dispensing Directions

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment(s) as per protocol. Study treatment(s) will be dispensed to the patient by authorized site personnel only.

6.2.3. Dosing Information

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.

Study treatment will be administered in the clinic and at home as indicated in Table 4. Study treatment dosing will occur in the clinic during Cycle 1 on Days 1, 3, 8, 15, 22, 24, and 26, during Cycle 2 on Days 1, 8, 15, and 22, and during ≥ Cycle 3 on Days 1 and 15. Study treatment dosing will occur at home during Cycle 1 on Days 5, 10, 12, 17, and 19, during Cycle 2 on Days 3, 5, 10, 12, 17, 19, 24, and 26 and during Cycles ≥ 3 on Days 3, 5, 8, 10, 12, 17, 19, 22, 24, and 26.

During Part B of the Dose Escalation Phase, patients will receive 500 mg niacin ER co-administered with each dose of KPT-9274. The starting dose of 500 mg niacin ER may be titrated to 2,000 mg of daily dose, per label. The starting dose for KPT-9274 in Part B will be a dose and schedule that cleared DLT assessment during Part A. For the purposes of dose escalation decisions, a standard 3+3 dose escalation design will be used during both Part A and Part B.

A total of ~65 patients with advanced solid malignancies and NHL may be enrolled to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274 ± niacin ER. After declaring the RP2D ± niacin ER (see Section 6.2.6), 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 be initiated. Futility analyses based on clinical efficacy will be conducted in a maximum of 10 patients dosed at the RP2D ± niacin ER (see Section 6.2.7 for additional details).

Dose escalation will occur according to the Dose Escalation Guidelines provided in Section 6.2.6.

Patients with melanoma enrolled in Part C, KPT-9274 + nivolumab, cohort will receive nivolumab (480 mg once per 28 day cycle) according to the current prescribing information.

6.2.4. Dosing Instructions for Patients

Study medications will be dosed according to the schedules provided in Table 4. For doses of oral medication to be taken on non-clinic days, patients will be provided with an adequate supply of study treatment for self-administration at home until at least their next scheduled study visit. Patients will be provided with a take home diary to complete on home dosing days; the patient diary will be reviewed at each clinic visit.

Oral KPT-9274 should be given with food, or within 30 minutes after the patient has eaten, together with 240-355 mL (8-12 ounces) of fluids.

KPT-9274 tablets should be swallowed whole (not crushed).

Nivolumab (anti-PD-1) will be administered at the site based on the product label.

6.2.5. Dose Schedules for Evaluation During the Dose Escalation Phase

The dose schedule for evaluation during the Dose Escalation Phase in Part A is presented in Table 13. A similar dose escalation plan will be used in Part B; however, the starting dose of KPT-9274 will be a dose and schedule that has cleared DLT assessment during Part A.

To better evaluate the safety, tolerability, and PK of KPT-9274, additional cohorts of patients may be enrolled on alternate dosing schedules (e.g. dosing on 2 days per week), at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation. Assessments at clinic visits may need to be adjusted based on the dosing schedule.

Table 13: 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)	10 mg
2	20 mg
3	30 mg
4	40 mg
5+	Increases at 20 mg per cohort

Three patients will be enrolled in each cohort, if 1 of 3 patients in a cohort experiences a DLT, the number of patients in that cohort will be expanded to 6 patients. A maximum of 6 patients will be enrolled per cohort. If ≥ 2 patients in a cohort experience a DLT, the MTD will be defined as 1 dose level lower.

6.2.6. Dose Escalation Guidelines

6.2.6.1. Dose Escalation Procedures

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 a starting dose of 500 mg niacin ER (and may be titrated up to 2,000 mg 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.

For the purposes of dose escalation decisions for both Part A and Part B, a standard 3+3 dose escalation design will be used. 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 single agent):

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 13 and as further described for both parts 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 (and may be titrated to 2,000 mg daily dose, per label) with each dose of KPT-9274.

Part A and Part B:

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

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.

Dose escalation decisions will be made by enrolling Investigators and Karyopharm study personnel. Decisions will be based on an evaluation of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE (Version 4.03) toxicity data during Cycle 1 and PK data (if available) from evaluable patients (see Section 6.2.6.3)

Table 13 describes the starting dose and the dose cohorts that may be evaluated in Part A. A similar dose escalation plan will be used in Part B. 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.

Dose escalation for Part A and Part B will be conducted as follows:

- If 0 of 3 patients experiences a DLT, escalate to next higher dose cohort.
- If 1 of 3 patients experiences a DLT, that cohort will be expanded to 6 patients. If 1 of 6 patients experiences a DLT, escalate to the next higher dose cohort;
- If ≥ 2 of 3 or ≥ 2 of 6 patients experience a DLT, MTD is exceeded. If the MTD is exceeded, the patients will be de-escalated to the next lower dose level (the MTD).

Part C (KPT-9274 + nivolumab):

The initial cohort will consist of 3 enrolled patients who will be treated at a dose of 30 mg KPT-9274, co-administered with a dose of 480 mg nivolumab. If these patients do not experience a DLT during Cycle 1, the KPT-9274 dose will be escalated to 40 mg for another cohort of 3 patients upon approval during a dose decision meeting. A maximum of 10 patients may be enrolled at each dose level.

Additional KPT-9274 dose levels (e.g., 20 mg or 60 mg) may be evaluated if an optimal dose is not identified and the safety review committee is in agreement.

6.2.6.2. Dose-Limiting Toxicity

A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria included in Table 14. The CTCAE, Version 4.03 will be used for grading. In addition, > 3 missed (consecutive or non-consecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

Other events may occur which do not meet the definition of a DLT, but are of concern to the Investigators and Karyopharm, and may then be considered to be DLTs.

Table 14: Criteria for Defining Dose-Limiting Toxicities

Toxicity	**Any of the following criteria (based on CTCAE [Version 4.03]):**
Non-Hematologic	Grade ≥ 3 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications.
	Any other Grade ≥ 3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy.
Hematologic	Grade 4 neutropenia lasting more than 5 days.
	Febrile neutropenia of any duration (ANC < 1.0×10^9 with single temperature >38.3°C or a sustained temperature ≥ 38°C for more than 1 hour).
	Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion.
	Grade 4 anemia, unexplained by underlying disease.
CTCAE Version 4.03 will be used for grading AEs and laboratory abnormalities. Patients may receive supportive care as per local institutional guidelines.	

6.2.6.3. Dose Decision Meeting or Teleconference

To implement dose escalation decisions, available toxicity information (including all AEs and all laboratory abnormalities regardless of DLT assessment) will be evaluated by the enrolling Investigators and Karyopharm study personnel during a dose decision meeting or teleconference. Decisions will be based on an evaluation of all relevant data available from all dose cohorts evaluated in the ongoing study including safety information, DLTs, all NCI CTCAE (Version 4.03), toxicity data during Cycle 1 and PK data (if available) from evaluable patients.

Drug administration at the next higher dose cohort may not proceed until the Investigator receives written confirmation from Karyopharm indicating that the results of the previous dose cohort were evaluated and that it is permissible to proceed to the next higher dose cohort.

Interim safety data will be examined on an ongoing basis to ensure patient safety and to comply with the clinical study dose escalation rules (see Section 9.8). In addition, Karyopharm will conduct regular safety meetings with investigators and other site staff where all AEs are shared across the study, and appropriate management of toxicities fully reviewed and, as needed, implemented.

6.2.7. Dose Schedule for Evaluation During the Dose Expansion Phase (Parts A and B)

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 ~8 weeks) must be seen in any of the first ten 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 KPT-9274.

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:

- NAPRT1 deficient tumor group, approximately 10 patients
- NAPRT1 positive tumor group, approximately 10 patients
- Either NAPRT1 deficient or positive tumor group, approximately 10 patients
- 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.

6.2.8. KPT-9274 Dose Reduction Guidelines for Toxicity

For Grade 2 toxicities present at baseline, the drug will not be held and the treating investigator will closely monitor and support the patient.

Patients are expected to be aggressively treated to minimize the likelihood and/or severity of side effects at the discretion of the Investigator (consultation with the Karyopharm Medical Monitor is strongly encouraged), particularly GI symptoms and hematopoietic toxicities as observed in KPT-9274 animal toxicology studies. See Section 6.9.1 for supportive care details.

For patients who do not tolerate the protocol-specified dosing schedule, KPT-9247 dose adjustments are permitted in order to allow the patient to continue the study treatment. The criteria for dose modifications of KPT-9274 for toxicities are outlined in Table 15. These changes must be recorded on the eCRF. If a patient requires a dose delay of more than 28 days (> 28 days) from the intended day of the next scheduled dose, then the patient should be discontinued from the study (in exceptional situations, if the patient is clearly benefiting from the study treatment, and in the opinion of the Investigator no safety concerns are present, after discussion with the Karyopharm Medical Monitor, the patient may remain in the study).

If, after interruption of treatment and resolution of the event, treatment is resumed at the same dose and the same toxicity reoccurs with the same severity, the next treatment re-initiation must resume at the next lower dose level, irrespective of duration. Patients who do not recover (i.e., ≤ Grade 1 or baseline) within 28 days (≤ 28 days) of discontinuation of study treatment will not be permitted to re-start study treatment and will be discontinued from the study.

In the event of a DLT (Cycle 1) during the Dose Escalation Phase the patient must discontinue KPT-9274.

In the event of any other toxicity (< Grade 3) during the Dose Escalation Phase, one of the following actions may be taken at the Investigator's discretion after consulting with the Karyopharm Medical Monitor:

- Patients can continue treatment with KPT-9274 without a dose delay or reduction.
- If the decision is made to hold KPT-9274:
    - Patients may be re-started on KPT-9274 either at the original dose OR at one dose level lower upon recovery to Grade ≤ 1 or baseline (see Table 15 for pre-specified dose modifications for AEs and Table 16 for dose modification guidelines for KPT-9274).

For the Dose Expansion Phase, if an event meeting the definition of a DLT, but without necessarily occurring within the first 28 days, is observed in > 33% of patients at any time, or if > 33% of treated patients have withdrawn consent due to toxicity, enrollment will be held and a meeting with all investigators and Karyopharm/Medical Monitor will take place to review the

events and discuss their clinical significance. Based on this review, the sponsor may elect to reduce the dose for enrolled patients and to resume enrollment of the expansion cohort at this lower dose, or the enrollment into the expansion cohort will may be stopped.

Table 15 summarizes the pre-specified dose modifications (i.e., Dose Levels 1 through 5+) for AEs listed in Table 16.

Table 15: Pre-specified Dose Modifications for Adverse Events

Dose Level	KPT-9274 Dose (mg) (Dose Escalation, Part A and Part B)*
5+	Increase in 20 mg increments
4	40 mg
3	30 mg
2	20 mg
1	10 mg

*From the RP2D, patients will be dose reduced by 1 dose level increments as needed as in Table 16.

For dose reduction, find the current dose in Table 15 and reduce as indicated in Table 16.

Table 16: KPT-9274 Dose Modification and Supportive Care Guidelines

Toxicity and Intensity	Dose Modification
Non-hematologic Toxicity	
Grade 1	Maintain dose. Consider instituting supportive care medications per institutional guidelines. For additional options, see NCCN Clinical Practice Guidelines in Oncology for Fatigue, Palliative Care, and Antiemesis, also refer to Benson guidelines).
Grade 2	Institute supportive care medications per institutional guidelines. For additional options, see NCCN Clinical Practice Guidelines in Oncology for Fatigue, Palliative Care, and Antiemesis, (also refer to Benson Guidelines). For Grade 2 toxicities, the Investigator should consult with the Karyopharm Medical Monitor when deciding on treatment delays or modifications. If modifications are desired, guidelines for AEs ≥ Grade 3 should be followed. At the Investigator's discretion after consulting with the Karyopharm Medical Monitor, patients may continue on KPT-9274 uninterrupted at their current dose.

≥ Grade 3	Optimal supportive care medications according to institutional guidelines or NCCN Clinical Practice Guidelines in Oncology should already be instituted. Also refer to Benson Guidlines.
	
	Hold KPT-9274 until the event resolves to ≤ Grade1 or baseline (as appropriate):
	• First occurrence of ≥ Grade 3:
	  ○ If supportive care results in the AE improving to Grade ≤1 or baseline within 3 days (≤ 3 days), restart KPT-9274 at the current dose.
	  ○ If the improvement to Grade ≤ 1 or baseline takes longer than 3 days (> 3 days), KPT-9274 should be resumed at one dose level lower (see Table 15).
	• Second or greater occurrence of ≥ Grade 3, restart KPT-9274 at one dose level lower (see Table 15) upon improvement to Grade ≤ 1 or baseline irrespective of duration.
	**If the toxicity does not resolve to ≤ Grade 1 or baseline within 28 day (≤ 28 days), study treatment will be discontinued permanently.
	**If, after interruption of treatment and resolution, treatment is resumed at the same dose and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next lower dose level, irrespective of duration.

Toxicity and Intensity	Dose Modification
Hematological Toxicity	
Thrombocytopenia	
Grade 2	Maintain dose
≥ Grade 3 *without bleeding*	Follow institutional guidelines for Grade 3 or 4 thrombocytopenia without bleeding. Transfusions are allowed per institutional guidelines. Hold KPT-9274 until resolves to ≤ Grade 1 or baseline (maximum of 28 days, ≤ 28 days): • First occurrence of ≥ Grade 3: o If improves within 7 days (≤ 7 days), restart KPT-9274 at the current dose. o If the improvement takes longer than 7 days (> 7 days), KPT-9274 should be resumed at one dose level lower. (see Table 15). • Second or greater occurrence of ≥ Grade 3, restart KPT-9274 at one dose level lower (see Table 15) upon improvement to Grade ≤1 or baseline irrespective of duration. **If the toxicity does not resolve to ≤ Grade 1 or baseline within 28 days (≤ 28 days), study treatment will be discontinued permanently. **If, after interruption of treatment and resolution, treatment is resumed at the same dose and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next lower dose level (see Table 15), irrespective of duration.
≥ Grade 3 *with bleeding*	Follow institutional guidelines for Grade 3 or 4 thrombocytopenia with bleeding. Transfusions are allowed per institutional guidelines. Hold KPT-9274 until resolves to Grade ≤ 1 or baseline and restart at one dose level lower (see Table 15).
Neutropenia	
≥ Grade 3 neutropenia without fever	Implement growth factors per institutional guidelines. Hold KPT-9274 until resolves to Grade ≤ 1 or baseline and restart at one dose level lower (see Table 15).
≥ Grade 3 neutropenia with fever (febrile neutropenia)	Implement growth factors and broad anti-microbial coverage per institutional guidelines. Hold KPT-9274 until the event resolves to Grade ≤ 1 or baseline and restart at one dose level lower (see Table 15).
All other hematologic Toxicity	
Grade 1 or 2	Maintain dose
≥ Grade 3	Implement growth factors and broad anti-microbial coverage per institutional guidelines. Transfusions (e.g., RBCs for anemia) are allowed per institutional guidelines. Consider holding KPT-9274 until the event resolves to Grade ≤ 1 or baseline and restart at one dose level lower (see Table 15). At the discretion of the Investigator after consulting with the Karyopharm Medical Monitor, patient may be treated with KPT-9274 without dose delays or modifications while receiving transfusions and/or growth factor support per institutional guidelines.
All dose modifications should be based on the worst preceding toxicity. *Isolated values of ≥ Grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of gamma-glutamyl transferase (GGT), 5'-nucleotidase (5'NT), or other liver enzymes should be performed. Note: for combinations of Grade 1 or 2 adverse events (e.g., nausea, fatigue, anorexia) that significantly impair the patient's quality of life, 1-2 doses of study treatment may be skipped after consultation with the Karyopharm Medical Monitor and supportive care per institutional guidelines has been implemented. Study treatment may then be restarted after consultation with the Karyopharm Medical Monitor.	
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6.2.8.1.1. Conditions Not Requiring KPT-9274 Dose Reduction

The following conditions are exceptions to the dose-modification guidelines. KPT-9274 does not need to be held in the following cases:

- Alopecia of any grade.
- Electrolyte or serum analyte (e.g., urate) abnormalities that are reversible with standard interventions.

6.2.8.1.2. Dose Holds or Reductions for Nivolumab (Part C)

- Dose reductions are not allowed for nivolumab. Consult the product label for dose holds.

6.2.9. Missed or Vomited Doses

6.2.9.1. Missed Doses of Study Treatments

If a dose must be skipped (e.g., due to recommendation of Investigator), the next dose will be taken as per schedule; all missed doses should be documented.

6.2.9.2. Vomited Doses of Study Treatments

If a dose is vomited within 1 hour of ingestion, it will be replaced. If vomiting occurs more than 1 hour after dosing, it will be considered a complete dose.

6.3. Study Treatment Storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, KPT-9274 and niacin ER should be stored according to the instructions specified on the drug labels and in the IB for KPT-9274. Nivolumab should be stored according to the package label.

6.4. Study Treatment Accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Study treatment accountability will be noted by the clinical research associate during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

KPT-9274 should not be used for any purpose outside the scope of this protocol, nor may KPT-9274 be transferred or licensed to any party not participating in the clinical study.

6.5. Selection and Timing of Dose for Each Patient

The rationale for the dose to be used is provided in Section 1.3.1. Guidelines for modifying the dose of KPT-9274, if needed due to AEs, are given in Table 16.

6.6. Method of Assigning Patients to Treatment Groups

During the Dose Escalation Phase, assignment of a patient to a particular cohort will be coordinated by Karyopharm. Patients will be enrolled in the Dose Expansion Phase based on Investigator judgment and availability within the cohort. Patients may be enrolled in any actively enrolling cohort.

6.7. Blinding

Not applicable, this is an open-label study.

6.8. Compliance

The Investigator or other study staff will either directly administer or supervise study treatment given in the clinic and instruct the patient on study medication self-administration, as appropriate. Patients will be provided with a take home diary to complete on home dosing days; the patient diary will be reviewed at each clinic visit.

Patients will be asked to bring their study medication containers with them at each visit and compliance with protocol-defined study treatment intake will be checked by tablet count.

Compliance to study medication will be assessed by the Investigator at each visit and recorded in source documents after discussion with the patient and performing drug accountability. Dates will be recorded as per study treatment schedule. The Investigator will account for the number of tablets dispensed against those returned by the patient. Any deviations and missed doses will be recorded in the eCRF.

The Investigator will try to ensure complete compliance with the dosing schedule by providing timely instructions to the patients. In case of non-compliance, the patients will be instructed again.

6.9. Supportive Care, Contraception Requirements, and Concomitant Medications

6.9.1. Supportive Care

Patients are expected to be aggressively treated to minimize the likelihood and/or severity of side effects at the discretion of the Investigator (consultation with the Karyopharm Medical Monitor is strongly encouraged), including hematologic and musculoskeletal (arthralgias and myalgias) symptoms observed in humans.

Supportive care including anti-nausea/anti-emetic therapy, acid suppression (e.g., PPIs ± H2 blockers), anti-diarrheal therapy, and other standard treatments may be administered as per institutional guidelines for symptomatic patients. For additional options, please see NCCN Supportive Care Clinical Practice Guidelines in Oncology. Note: the use of PPIs is allowed in all patients but the Investigator must consult with the Karyopharm Medical Monitor prior to their use in patients receiving niacin ER. If any deficiencies in vitamin B12, folate, iron, erythropoietin, or transferrin are observed, then standard medical practice for their replacement should be instituted.

Anemia appears to be dose dependent and should be treated with dose interruption, dose reduction, use of growth factors (i.e., erythropoietins), and/or transfusions. The addition of niacin ER (up to 2,000 mg daily dose, per label) willwill be allowed after completion of the DLT period in cycle 1 (first 28 days) in an attempt to offset potential side effect (i.e. anemia, arthralgias, myalgias, etc.) of KPT-9274. After Week 8, niacin may be titrated, as per label, to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.

Arthralgia should be treated with non-steroidal anti-inflammatory drug (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, tramadol, and/or low-dose steroids. Myalgia and flu-like illness should be treated with KPT-9274 dosing at night, acetaminophen (including pre-treatment with acetaminophen), NSAIDs, COX-2 inhibitors, and/or low-dose steroids. Consultation with the Karyopharm Medical Monitor is recommended for questions regarding these recommendations.

For additional information on supportive care recommendations for events such as anemia, arthralgias, and myalgias see the current version of the IB as well as Section 7.5.2 and Section 7.5.3).

6.9.2. Non-study Related Concomitant Medication and Treatment

No significant inhibition of any of the CYP450 enzymes were observed after KPT-9274 treatment. Weak induction of CYPs 1A2, 2B6, and 3A4 were observed in an exploratory pre-clinical study after KPT-9274 treatment; however, it is unlikely that a potential drug-drug interaction will occur in a clinical setting. Therefore, the use of any concomitant medication/therapy (except medications listed in the prohibited medications section, see Section 6.9.3), including over-the-counter (OTC) medications (excluding herbal supplements, dietary supplements), deemed necessary for the care of the patient is permitted during the study.

6.9.2.1. Permitted Concomitant Medication

Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases and supportive care agents (e.g., blood product transfusions [see Section 6.9.2.6], antibiotics with [if appropriate] granulocyte-colony stimulating factors [G-CSF] for neutropenic infection), pain medications, anti-emetics, and anti-diarrheals are allowed. Concurrent therapy with growth factors is allowed. The use of any immunosuppressive agents must be discussed between the Investigator and the Karyopharm Medical Monitor on a case-by-case basis. The addition of niacin ER (up to 2,000 mg daily dose, per label) is allowed after completion of the DLT period in cycle 1 (first 28 days) in an attempt to offset potential side effect (i.e. anemia, arthralgias, myalgias, etc.) of KPT-9274.

Note: the use of PPIs is allowed in all patients, but the Investigator must consult with the Karyopharm Medical Monitor prior to their use in patients receiving niacin ER.

Hormonal contraceptives are permitted in women of child-bearing potential. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a

progestational agent. Since the effect of KPT-9274 on oral contraceptives is unknown at this time, it is recommended that patients use at least 2 forms of contraceptives while on study.

Additionally, the nivolumab product label will be consulted to obtain the permitted concomitant medications for patients in Part C (the KPT-9274 + nivolumab).

6.9.2.2. Prevention of Pregnancy

Patients should not become pregnant or father a child while on this study because it is unknown whether KPT-9274 can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important that patients understand the need to use birth control while on this study. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at Screening; male patients must use an effective barrier method of contraception if sexually active with a female of child bearing potential.

The use of two forms of contraception are required, including one highly effective and one effective method of contraception, from the following lists.

- Highly effective methods include:
  - Hormonal contraceptives (e.g., combined oral contraceptives, patch, vaginal ring, injectables, and implants)
  - Intrauterine device (IUD) or intrauterine system (IUS)
  - Vasectomy and tubal ligation
- Effective methods include:
  - Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)

    Notes:
    - *No barrier method by itself achieves a highly effective standard of contraception*
    - *The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method.*
    - *The cervical cap and contraceptive sponge are less effective in parous women.*
    - *The use of spermicide alone is not considered a suitable barrier method for contraception.*
    - *When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above.*
    - *Male and female condoms should not be used together as they can tear or become damaged.*

Acceptable methods of contraception also include:

- A sexual partner who is surgically sterilized or post-menopausal.
- Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar,

ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For both male and female patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose.

See Section 1.2.2 for additional safety information related to pregnancy.

6.9.2.3. Radiation Therapy

Palliative radiation therapy to non-target lesions is permitted but study treatment should be held for ≥1 day before the start of palliative radiation therapy and ≥1 day following each dose of palliative radiation therapy. Treatment with KPT-9274 shall not be discontinued solely due to palliative radiation.

6.9.2.4. Hormone Ablation Therapy to Treat Advanced Prostate Cancer

Conventional hormone ablation therapy (HAT) is permitted while on study; however, patients receiving HAT prior to the start of the study must not terminate HAT within 6 weeks prior to C1D1; termination of HAT during this study must be discussed with the sponsor.

6.9.2.5. Glucocorticoid Therapy

Glucocorticoids ≥10 mg oral prednisone (or equivalent) per day are not permitted at baseline; however physiological doses ≤10 mg oral prednisone (or equivalent) for non-malignant conditions (e.g., asthma, IBD, etc.) are permitted as needed.

As part of supportive care (e.g., for nausea or anorexia), oral dexamethasone, up to 40 mg/week, may be given to patients.

6.9.2.6. Use of Blood Products

During treatment, patients may receive RBC or platelet transfusions per institutional guidelines. Patients who require repeated transfusion support should be discussed with the Karyopharm Medical Monitor.

Appropriate anti-coagulation is allowed during the study (e.g., low molecular weight heparin, direct factor Xa inhibitors, etc.). Warfarin is allowed during the study provided patients are monitored for international normalized ratio (INR) twice a week during the first 2 cycles of therapy, then weekly to biweekly thereafter.

Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or granulocyte macrophage-colony stimulating factor (GM-CSF), pegylated growth factors, and platelet stimulatory factors, in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

6.9.3. Prohibited Concomitant Medications

The use of niacin or niacin-containing supplements (e.g., multivitamins and energy drinks) is not allowed in cycle 1 of the Part A KPT-9274 only cohorts in the Dose Escalation or Expansion Phases. However, for patients in these cohorts that have cleared DLT in cycle 1, niacin ER (up to 2,000 mg co-administered with KPT-9274) may be used as supportive care in an attempt to

offset potential side effects (e.g. anemia, arthralgias, myalgias, etc.) of KPT-9274. Prior to initiating niacin ER, patient symptoms and laboratory values should be reviewed and discussed with the Medical Monitor for this study.

Investigational or commercial anticancer agents other than KPT-9274 are not allowed during the study. The initiation of any non-protocol specific anti-tumor treatment is considered an indication of disease relapse/progression and should be recorded appropriately in the eCRFs.

There are exceptions including localized palliative radiation (see Section 6.9.2.3), hormonal contraception for the prevention of pregnancy (see Section 6.9.2.2), hormonal therapy for patients with prostate cancer (see Section 6.9.2.4), and blood products/growth factors (see Section 6.9.2.6). For other possible cases, please consult the Karyopharm Medical Monitor.

7. ASSESSMENTS

7.1. Informed Consent

Study-specific assessments may not be performed until the patient provides written informed consent (see Section 10.4).

7.2. Demographic and Baseline Characteristics Assessments

7.2.1. Demographics

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

7.2.2. Medical History

A complete medical history will be obtained from each patient. Medical history will include baseline symptoms of the disease under study as well as a detailed history of prior procedures for the patient's NHL or advanced solid malignancy and other prior cancer therapies (i.e., chemotherapy, hormonal therapy, immunotherapy, biotherapy, radiotherapy, and surgery), including start and end dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability, toxicity, or any other serious illness; Tumor Nodes Metastasis (TMN) staging will be collected on for patients with advanced solid malignancies. Smoking history will be recorded. A detailed history of disease-specific diagnostic and prognostic testing and test results (such as phenotypic and cytogenetic profiles) will also be collected.

7.2.3. Disease Risk Assessment (NHL patients only)

Disease risk assessment will be performed according to the Revised International Prognostic Index (R-IPI; Sehn, 2007) for NHL patients only.

7.2.4. Baseline Characteristics and Determination of Eligibility

Baseline characteristics will include ECOG performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight.

Inclusion/exclusion criteria will be reviewed to determine eligibility.

Patients with known active HAV, HBV, HBC, or HIV infection will be excluded from this study. However, testing for these viruses is not required as part of this study.

7.2.5. Determination of NAPRT1 and IDH1 Tumor Status

NAPRT1 and IDH1 tumor status for Parts A and B must be determined prior to enrollment in the KPT-9274 ± niacin ER escalation and expansion cohorts. Archival biopsy material obtained ≤ 6 months prior to screening may be used to prescreen patients for NAPRT1 and IDH1 tumor status. A fresh biopsy will be collected during screening to determine or confirm that NAPRT1 and IDH1 tumor status. Screening period includes Day -30 to Day 7 prior to C1D1. Additional details are provided in Section 7.4.3.3.

7.2.6. Determination of Patients with Melanoma Who Progressed on Prior Anti-PD-1 or Anti-PD-L1 Treatment

Patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1 treatment must be determined prior to enrollment in Part C - KPT-9274 + nivolumab. Screening period includes Day -30 to Day -1 prior to C1D1.

7.3. Efficacy Assessments

7.3.1. Non-Hodgkin's Lymphoma and Advanced Solid Malignancy Assessments

7.3.1.1. Quality of Life

QoL will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Questionnaire for all patients and the Functional Assessment of Cancer Therapy and Lymphoma (FACT-Lym) Questionnaire (Webster, 2005) for patients with NHL.

The QoL assessments will be performed at Screening before undergoing any study procedures (including discussions with medical personnel and administration of study treatment) on Day 1 of each cycle and at the EoT Visit.

The EORTC QLQ-C30 is a validated, patient self-administered instrument for assessing the health-related QoL of cancer patients participating in international clinical trials. It is a questionnaire containing both multi-item and single scales, including five functional scales (physical, role, emotional, social and cognitive), three symptom scales (fatigue, nausea & vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

NHL patients only: The FACT-Lym combines the General version of the Functional Assessment of Cancer Therapy (FACT-G) with a lymphoma-specific subscale (15 items). The subscales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). The trial outcomes index (TOI; total of 29 items) will be the primary measurement of interest, comprised of the Physical and Functional subscales plus the lymphoma-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (="Not at all") to 4 (="Very much"), therefore the TOI has a score ranging from 0 to 116.

7.3.2. Non-Hodgkin's Lymphoma Only Assessments

Patient response will be assessed by the procedures described in the following subsections and graded according to the Lugano Classification (NHL) summarized in Appendix 3.

7.3.2.1. PET-CT (or CT) Scan

Disease response will be preferably based on tumor measurement using PET/CT for FDG-avid lymphomas, or CT for non-FDG-avid lymphomas (or PET/MRI or MRI if CT is contraindicated) scans. Scans will be conducted at Screening (Day -30 to Day -1) and after every 8 weeks ±

7 days (e.g., Day 1 of odd numbered cycles) until disease progression or the EoT visit. EoT scan is only required for patients who end treatment for reasons other than disease progression. The same scan modality should be used for all assessments. PET/CT for FDG-avid lymphomas or CT for non-FDG-avid lymphomas (or PET/MRI or MRI if CT is contraindicated) is strongly preferred.

7.3.2.2. Bone Marrow Aspirate and/or Biopsy

Bone marrow biopsies and/or aspirates will be taken within 30 days prior to first dose (baseline) to assess NHL involvement in bone marrow. The bone marrow biopsy will be repeated whenever clinically indicated, at the discretion of the Investigator, to confirm CR/PR only in those patients who had NHL with known bone marrow involvement prior to dosing.

7.3.3. Advanced Solid Malignancy Only Assessments

Patient response will be assessed by the procedures described in the following subsections and graded according to RECIST 1.1 (Appendix 4).

7.3.3.1. CT, MRI, PET-CT, or Imaging Methodology Per Investigator Discretion

Disease response is based on tumor measurement using computed tomography (CT) scans or, magnetic resonance imaging (MRI) scans, or PET-CT, or imaging methodology per Investigator discretion. Scans will be performed at Screening (Day -30 to Day -1), then every 8 weeks ± 7 days (e.g., Day 1 of odd numbered cycles) until disease progression or the EoT visit. EoT scan is only required for patients who end treatment for reasons other than disease progression.

The same scan modality should be used for all assessments.

7.4. Pharmacokinetic Assessments

7.4.1. PK Sampling for KPT-9274

Parts A and B

PK sampling will be performed in all patients receiving KPT-9274.

- PK samples will be collected for all patients at PK time points listed in Table 17 except on C1D24 at 4, 12, 18, and 32 hours post-dose; PK samples on C1D24 at 4, 12, 18, and 32 hours post-dose will only be collected for the first 18 patients enrolled in the expansion phase (see Section 3.1).

Blood draws (using 2 mL/K_2EDTA purple top tubes) for PK analysis will be performed as described in Table 17.

Details of PK sample collection and processing can be found in the *Laboratory Manual*.

Plasma samples will be analyzed via validated high performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) methods for plasma KPT-9274 concentrations.

PK parameters may include, but are not limited to, estimations of C_{max}, AUC, t_{max}, $t_{½}$, V_d/F, and CL/F.

Patients must attend the clinic for PK sampling that occurs on non-dosing days.

If the dose is missed, PK blood draws will not be collected on that day.

If a patient's dose is changed, blood sampling for PK (as requested for C1D1) should be repeated on the first day of dose change at the same time points as described for C1D1, C1D2, and C1D3.

If a patient experiences an AE that fits the criteria of a DLT as determined by the Investigator in either the Dose Escalation or Dose Expansion Phase, an unscheduled PK blood sample should be collected for measurement of drug concentrations. If a patient experiences a study treatment-related AE that fits the criteria of a SAE or discontinues from the study treatment due to study treatment related toxicities, an unscheduled PK blood sample must be obtained as soon as possible after the last dose of KPT-9274 and the date and time of last dose recorded. Additionally, if at any time during the study a QTc >500 msec has been demonstrated by 12-lead ECG, then an unscheduled PK draw should be obtained as close to the time of the repeat ECG as possible.

Part C

Starting from Cycle 1 Day 1 (C1D1), blood will be drawn at 0 h (< 15 mins prior to dosing), 3 h ± 15 mins, 6 h ± 30 mins, 8 h ± 30 mins, 24 h ± 60 mins, and 48 h ± 60 mins. Cycle 2 Day 1 (C2D1), blood will be drawn at 0 h (< 15mins prior dosing), 3 h ± 15 mins, , 6 h ± 30 mins, 8 h ± 30 mins, 24 h ± 60 mins, and 48 h ± 60 mins after C2D1 dose. Time since last meal and a description of the meal contents will be reported by the patient to the treating physician prior to each PK blood draw. PK assessments are outlined in Table 18.

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Table 17: Collection Time Points and Sample Volumes for PK and [redacted] for Parts A and B

Time Point	Total Volume of Blood (mL)	Number of Tubes by Volume of Blood		Biopsy
		PK	[redacted]	Lymph Node Biopsy and/or Tumor Biopsy
		1 tube x 2.0 mL		
Screening				
Between D -30 and D 7	--	--		2 fresh biopsies and 1 formalin fixed biopsy
C1D1 (repeat if patient dose changes)				
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
0.5 hr (± 5 min) post-dose	2	X		--
1 hr (± 10 min) post-dose	2	X		--
2 hr (± 10 min) post-dose	2	X		--
4 hr (± 20 min) post-dose	13	X		
8 hr (± 30 min) post-dose	13	X		--
C1D2 (repeat if patient dose changes)				
24 hr (± 2 hours) after intake of first dose on C1D1	13	X		--
C1D3 (repeat if patient dose changes)				
48 hr (± 2 hours) after intake of first dose on C1D1, prior to C1D3 dose	13	X		--
C1D8				
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
2 hr (± 10 min) post-dose	2	X		--
C1D15				

Time Point	Total Volume of Blood (mL)	Number of Tubes by Volume of Blood		Biopsy
		PK	CCI	Lymph Node Biopsy and/or Tumor Biopsy
		1 tube x 2.0 mL		
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
2 hr (± 10 min) post-dose	2	X		--

Time Point	Total Volume of Blood (mL)	Number of Tubes by Volume of Blood		Biopsy
		PK	CCI	Lymph Node Biopsy and/or Tumor Biopsy
		1 tube x 2.0 mL		
C1D24				
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
2 hr (± 10 min) post-dose	2	X		--
4 hr (± 20 min) post-dose (Expansion Phase only) [2]	2	X		
8 hr (± 30 min) post-dose	13	X		--
12 hr (± 60 min) post-dose (Expansion Phase only) [2]	2	X		
18 hr (± 60 min) post-dose (Expansion Phase only) [2]	2	X		
C1D25				
24 hr (± 2 hours) after intake of dose on C1D24	13	X		--
32 hr (± 2 hours) after intake of dose on C1D24 (Expansion Phase only)[2]	2	X		
C1D26				
48 hr (± 2 hours) after intake of dose on C1D24, prior to C1D26 dose	13	X		2 fresh biopsies and 1 formalin fixed biopsy[1]
1 hr (± 10 min) post-dose	2	X		--
2 hr (± 10 min) post-dose	2	X		--
4 hr (± 20 min) post-dose	13	X		--
8 hr (± 30 min) post-dose	13	X		--

Time Point	Total Volume of Blood (mL)	Number of Tubes by Volume of Blood		Biopsy
		PK	CCI	Lymph Node Biopsy and/or Tumor Biopsy
		1 tube x 2.0 mL		
C2D15				
Pre-dose (< 10 min before KPT-9274 dosing)	2	X		--
2 hr (± 10 min) post-dose	2	X		--
C3D1				
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
2 hr (± 10 min) post-dose	2	X		--
24 hr (± 2 hours) after intake of first dose on D1	13	X		--
Day 1 of Cycle 5 and Beyond Odd Cycles Only				
Pre-dose (< 10 min before KPT-9274 dosing)	13	X		--
24 hr (± 2 hours) after intake of first dose on D1	13	X		--
Cycle 6 Day 1 and/or at the time of progression				
± 7 days	--			2 fresh biopsies and 1 formalin fixed biopsy[1]
End-of-therapy				
± 7 days	13	X		--

[1] For the biopsies on C1D26 (± 7 days) and C6D1 (± 7 days), patients will be allowed to continue treatment if: 1) a patient refuses the biopsy, 2) in the opinion of the treating physician or physician performing the biopsy that the biopsy will pose significant risk to the patient, or 3) if the biopsy sample obtained on first attempt is not adequate.
[2] PK samples at these time points will only be collected for the first 18 patients enrolled in the expansion phase (see Section 3.1).

Table 18: Collection Time Points and Sample Volumes for PK and [redacted] for for Part C

Time Point	Total Volume of Blood (mL)	Number of Tubes by Volume of Blood	[redacted]	Biopsy
		PK		Tumor Biopsy
		1 tube x 2.0 mL		
Screening				
Between D -30 and D -1	--	--		2 fresh biopsies and 1 formalin fixed biopsy
C1D1				
Pre-dose (< 15 min before KPT-9274 dosing)	4.5	X		--
3 hr (± 15 min) post-dose	2	X		--
6 hr (± 30 min) post-dose	2	X		--
8 hr (± 30 min) post-dose	2	X		--
C1D2				
24 hr (± 60 min) after intake of first dose on C1D1	2	X		--
C1D3				
48 hr (± 60 min) after intake of first dose on C1D1, prior to C1D3 dose	2	X		--
C2D1				
Pre-dose (< 15 min before KPT-9274 dosing)	4.5	X		2 fresh biopsies and 1 formalin fixed biopsy[1]
3hr (± 15 min) post-dose	2	X		--
6 hr (± 30 min) post-dose	2	X		--
8 hr (± 30 min) post-dose	2	X		--
24 hr (± 60 min) after intake of first dose on D1	2	X		--
48 hr (± 60 min) after intake of first dose on D1	2	X		--
End-of-therapy				2 fresh biopsies and 1 formalin fixed biopsy[1]

1. For the biopsies on C2D1 (± 7 days) and EoT (± 7 days), patients will be allowed to continue treatment if: 1) a patient refuses the biopsy, 2) in the opinion of the treating physician or physician performing the biopsy that the biopsy will pose significant risk to the patient, or 3) if the biopsy sample obtained on first attempt is not adequate.

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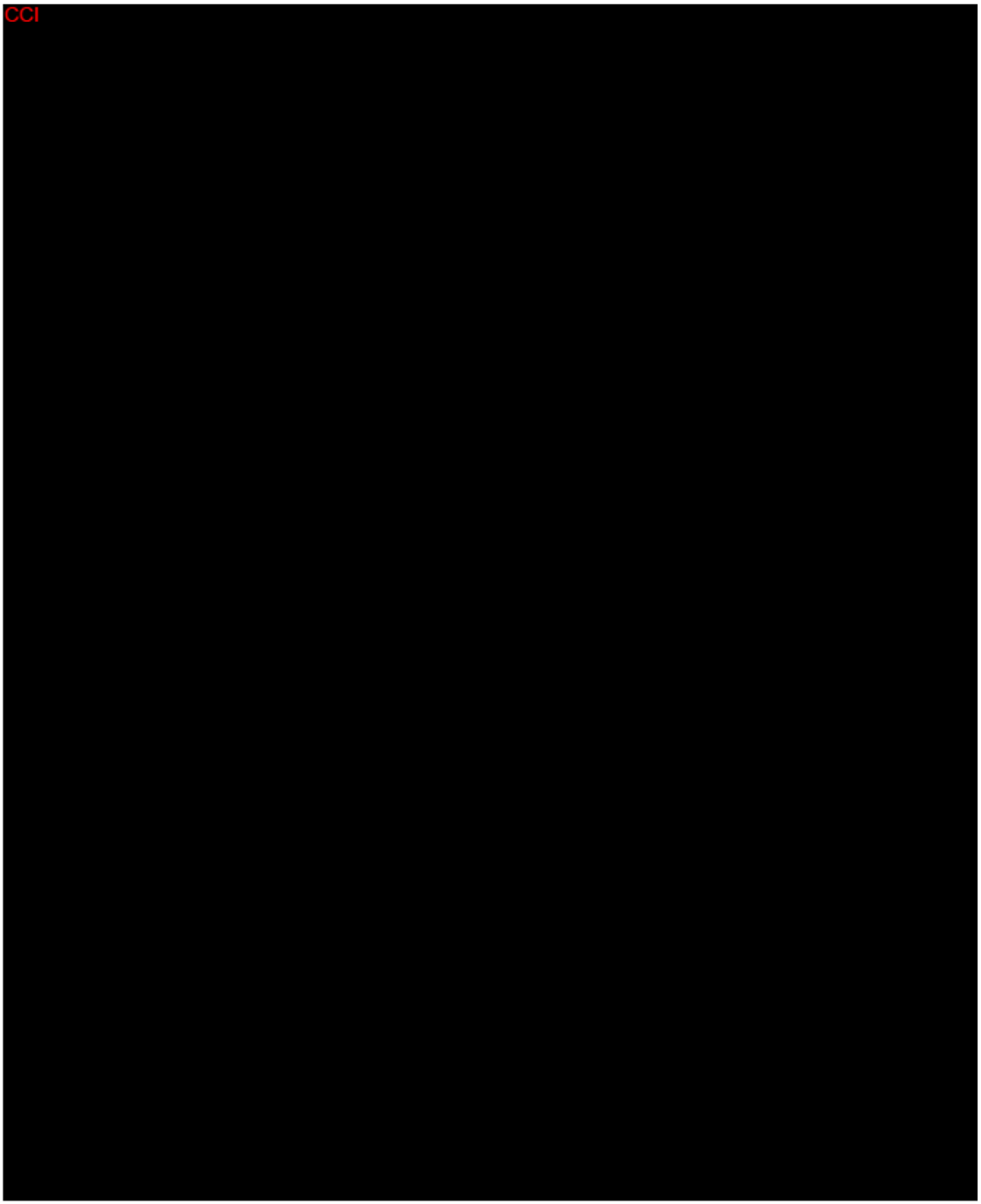

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[redacted]

7.5. Safety Assessments

Safety evaluations will be conducted as described below. Refer to Table 1, Table 2, and Table 3 for the timing of all safety assessments.

7.5.1. Clinical Safety Assessments

7.5.1.1. Weight and Height

Height (without shoes) in centimeters (cm) and weight (indoor clothing without shoes) in kilograms (kg) will be measured.

7.5.1.2. Physical Examination, Vital Signs, and ECOG Performance Status

Physical examination must be performed for Parts A and B as indicated in Table 1, Table 2, and Table 3 and for Part C as indicated in Table 5, Table 6, and Table 7.

These examinations will be performed according to the standards at each institution. The physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator and if medically indicated. If baseline/screening examinations are performed within 3 calendar days prior to the first dose of study treatment, they need not be repeated on C1D1 (except vital signs, which must be conducted on C1D1).

Complete physical examinations should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations.

Symptom-directed physical examinations should include body systems as appropriate. These examinations will be performed according to the standards at each institution.

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

Vital signs include systolic and diastolic BP, pulse measurements, and body temperature (°C or °F). Vital signs should be assessed pre-dose on the scheduled visit day, if possible. BP and pulse rate should be measured after the patient has been in a supine or sitting position for 5 minutes. BP should be assessed on the same arm throughout the study.

ECOG performance status assessments (Oken 1982) will be performed during the study to assess how the disease affects the daily living abilities of the patients (Appendix 1).

7.5.1.3. Echocardiography and Electrocardiography

An echocardiogram or multiple gated acquisition (MUGA) scan to assess cardiac function and risk of cardiac dysfunction, including cardiomyopathy is required at Screening (Day -30 to Day -1) and at the EoT Visit. Additional echocardiogram or MUGA scans may be performed

throughout the study if clinically indicated at the discretion of the Investigator. The same procedure (either MUGA or echocardiogram) should be performed at screening/baseline and subsequent visits. Preferably the same cardiologist/radiologist should read and report the outcome to minimize variability in results. Copies of all transthoracic echocardiograms and/or MUGA scans performed on subjects who experience a greater than or equal to 20% decrease in left ventricular ejection fraction (LVEF) from baseline and whose cardiac ejection fraction is below the institution's lower limit of the normal range (LLN) will be required by Karyopharm for review.

A single standard 12-lead ECG will be performed for patients in Part A and B. Patients must rest for at least 5 minutes prior to the ECG recording. The Investigator will interpret the ECG using one of the following categories: normal, abnormal but not clinically significant, or abnormal and clinically significant. The date and time the ECG is performed and the following parameters will be recorded in the eCRF: heart rate, PR interval, QT interval, QRS interval, and QT corrected using Bazett's formula.

7.5.1.4. Ophthalmic Examination

For Parts A and B, an ophthalmic examination by an optometrist or ophthalmologist is required at Screening and the EoT Visit, and if clinically indicated (at the discretion of the Investigator) during the study (e.g., monitoring of pre-existing cataracts, visual disturbances).

Patient reporting *de novo* or worsening of visual symptoms should immediately be referred for further examination.

The ophthalmic examination is to include the following:

- Prior to dilation:
  - best corrected visual acuity
  - slit lamp examination (for cataracts or other abnormalities)
  - tonometry
- Following dilation:
  - fundoscopy
  - slit lamp examination to document lens clarity

If a cataract/lens opacity is seen during the examination, the cataract/lens opacity will be graded according to a Grade 1-4 system.

An ophthalamic examination is not required for patients enrolled in Part C, but may be performed at any time during the study if clinically indicated (at the discretion of the Investigator).

7.5.1.5. Concomitant Medications

Concomitant medications will be documented for each patient at each scheduled visit during the treatment phase. A detailed history of medications will be documented during Screening and C1D1. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study treatment (from Screening through the EoT Visit). All

concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded on the eCRFs.

Necessary supportive care such as appetite stimulants, anti-emetics, and anti-diarrheals, etc., are allowed (see Table 16 and Section 6.9.1).

7.5.2. Rheumatology Consultation and Testing

At the Investigator's discretion, in consultation with the Karyopharm Medical Monitor, a rheumatological consultation is recommended for patients with clinically significant joint or muscle-related AEs. Rheumatology testing is recommended as clinically indicated and may be completed as clinically indicated per institutional standards (e.g., antinuclear antibodies, rheumatoid factor, C-reactive protein, erythrocyte sedimentation rate, uric acid [if not already available], or other autoantibodies based on symptoms).

7.5.3. Hematology Consultation, Testing, and Biopsy

At the Investigator's discretion (after the screening assessment), in consultation with the Karyopharm Medical Monitor, a hematology consultation is recommended for patients with clinically significant hematological AEs, including any grade of treatment-emergent anemia or abnormal reticulocyte counts. Hematological testing (including but not limited to standard hematological evaluations and erythropoietin level) ± bone marrow biopsy may be performed as clinically indicated per institutional standards. In addition, assessments for vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte counts will be completed as described in Section 7.5.4.2.

7.5.3.1. Adverse Events

Information regarding AEs and SAEs will be collected. See Section 8.

It is the responsibility of the Investigator to record and document all SAEs (occurring from the signing of the informed consent form [ICF]) and all AEs (occurring from the first dose of study treatment on C1D1) throughout the study and for 30 days after the last dose of study treatment.

Each AE will be graded according to the CTCAE v4.03 at every visit (Section 8.1.3).

7.5.4. Laboratory Safety Assessments

7.5.4.1. Clinical Laboratory Tests

Table 19 presents the clinical laboratory tests that will be performed during the study.

Table 19: Clinical Laboratory Tests (Parts A, B, and C Unless Indicated)

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	Band neutrophils (Parts A and B Only)	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[3]	Lipase[3]	Creatinine kinase
Urate	Thyroid-stimulating hormone[3]			
Coagulation				
Prothrombin time (Parts A and B Only)	International normalization ratio (Parts A and B Only)	Activated thromboplastin time (Parts A and B Only)		
Urinalysis[4]				
Appearance (Parts A and B Only)	Color (Parts A and B Only)	Urine bilirubin (Parts A and B Only)	Glucose (Parts A and B Only)	Hemoglobin (Parts A and B Only)
Ketones (Parts A and B Only)	pH (Parts A and B Only)	Protein (Parts A and B Only)	Specific gravity (Parts A and B Only)	Urobilinogen (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.

[3] If not included in the complete serum chemistry panel at the site, amylase, lipase, and TSH must be performed at the time points indicated in Table 1, Table 2, and Table 3 for Parts A and B and Table 5, Table 6, and Table 7 for Part C.

[4] Microscopy will only be performed if clinically indicated at the discretion of the Investigator. Urinalysis is only required for Parts A and B.

All laboratory safety assessments will be performed and analyzed at each site by a certified local laboratory. The Investigator or designee will review the laboratory results and assess the clinical significance of all abnormal values. Appropriate action will be taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study treatment) or baseline.

In addition, laboratory safety assessments will be collected and analyzed on the scheduled day, even if study treatment is being withheld. More frequent assessments may be performed if clinically indicated, or at the Investigator's discretion and these should be recorded on the Unscheduled Visit eCRFs.

Any laboratory value that remains abnormal at the EoT Visit and that is considered clinically meaningful will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline. Toxicity will be graded using CTCAE Version 4.03.

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

7.5.4.2. Vitamin B12, Folate, Iron, Erythropoietin, Haptoglobin, and Transferrin Levels and Reticulocyte Counts

Vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin levels and reticulocyte counts will be assessed at Screening and the EoT Visit. Additionally, patients with treatment-emergent anemia should have these analyte levels/counts assessed as soon as possible after onset. Patients with ≤ Grade 1 anemia should have their levels/counts assessed no less than once a month from and patients with ≥ Grade 2 anemia should have their levels/counts assessed every 2 weeks from onset. A hematology consultation is recommended as appropriate (see Section 7.5.3). Supportive care recommendations for deficiencies in these analytes are noted in Section 6.9.1.

7.5.4.3. Pregnancy Testing

For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained < 3 days prior to Cycle 1 Day 1 and at the EoT Visit. Test sensitivity for hCG must be ≥ 25 mIU/mL. Pregnancy testing is to be performed as clinically indicated at the discretion of the Investigator during the study.

7.6. Other Assessments

7.6.1. Collection of Information on Antineoplastic Therapy

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

8. SAFETY DEFINITIONS, RECORDING, AND REPORTING

Note: For urgent medical issues in which the Karyopharm Medical Monitor should be contacted, please refer to the *Study Manual* for complete contact information.

8.1. Adverse Events

8.1.1. Definitions

- *Adverse event (AE)*: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- *Treatment-emergent adverse event (TEAE)*: Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.
- *Serious adverse event (SAE):* Any untoward medical occurrence that, at any dose, results in death; is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. (See Section 8.2.2 for additional information about SAE reporting.)

8.1.2. Recording of Adverse Events

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

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

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

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

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

8.1.2.1. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for an AE should be followed until they have returned to normal or an adequate explanation of the abnormality is identified. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

A laboratory abnormality that does not meet the definition of an AE should not be reported as an AE. A Grade 3 or 4 event (severe per NCI CTCAE v4.03) does not automatically indicate an SAE unless it meets the definition of serious as defined in Section 8.1.1 and/or as per Investigator's discretion. A laboratory abnormality that results in a dose being held or modified would, by definition, be an AE and must be recorded as such in the eCRFs.

8.1.3. Adverse Event Severity

The severity of the AE will be graded by the Investigator according to the NCI CTCAE Grading Scale, v. 4.03 (the NCI CTCAE files can be accessed online at the following URL: http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

If NCI CTCAE grading does not exist for an AE, the severity will be characterized as "mild," "moderate," "severe," or "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.

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

8.1.4. Adverse Event Causality

The Investigator will make a judgment regarding the relationship of the AE to study treatment, as outlined in Table 20.

Table 20: Classification of Adverse Events by Causality

Not related	The lack of a temporal relationship of the event to the study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation.
Related	The temporal relationship of the event to the study treatment makes a definitive relationship, and the event is more likely explained by exposure to the study treatment than by any other drugs, therapeutic interventions, or underlying conditions.

8.2. Serious Adverse Events

See Section 8.1.1 for the definition of an SAE. Please note that 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).

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not due to an AE are not considered SAEs. A hospitalization meeting the regulatory definition for ‘serious’ is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. An emergency room visit is not considered a hospitalization unless it results in an official admission to the hospital.

Progression of the malignancy (including fatal outcomes) should not be reported as an SAE during the study or within the safety reporting period (see Section 8.2.2). Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of malignancy, the finding should be reported as an AE or SAE, as appropriate.

8.2.1. Recording of Serious Adverse Events

It is the responsibility of the Investigator to record and document all SAEs occurring from the signing of the ICF until at least 30 days after the patient has stopped study treatment. All SAEs must be reported on an SAE report form, in addition to being recorded in the eCRF. The original SAE report form must be retained in the Investigator’s site file.

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

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

8.2.2. Reporting of Serious Adverse Events

Every SAE, regardless of the causal relationship to the study treatment, occurring after the patient has signed informed consent, until at least 30 days after the patient has stopped study treatment, must be reported to the Karyopharm Pharmacovigilance Department within *24 hours* of learning of its occurrence. The investigational site personnel must use the SAE Report Form provided by Karyopharm for reporting any SAE to the Karyopharm Pharmacovigilance Department.

Upon completion, the SAE Report Form must be immediately emailed or faxed to:

Pharmacovigilance Department

Karyopharm Therapeutics Inc.

Email: pharmacovigilance@karyopharm.com

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

Any SAE observed after the 30-day follow-up period should only be reported to Karyopharm if the Investigator suspects that the SAE has a causal relationship to study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

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

8.2.3. Suspected Unexpected Serious Adverse Reactions

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

In addition, Karyopharm will communicate all cases of cerebellar toxicity, Grade 3 or higher, to regulatory authorities, central ethics committees (e.g., IRBs), and Investigators, in the format of an expedited Safety Report, within 7 days of awareness of the event.

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

8.3. Procedures for Handling Special Situations

8.3.1. Pregnancy

Note: Pregnancy *per se* is not considered to be an AE; however, it is discussed here because of the importance of reporting pregnancies that occur during studies and because a medical occurrence observed in the mother or fetus/newborn would be classified as an AE.

To ensure patient safety, a pregnancy occurring while the patient is on study treatment must be reported to Karyopharm Pharmacovigilance by email or fax within 24 hours of first knowledge of its occurrence. A pregnancy report form is provided by Karyopharm.

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

Pregnancies must be reported to Karyopharm, regardless of whether the patient withdraws from the study or the study is completed, for 3 months after the patient receives his/her last dose of study treatment. Patients should be instructed to inform the Investigator regarding any pregnancies.

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

A pregnancy in a female partner of a male patient must be reported to Karyopharm within 24 hours of learning of its occurrence. Pregnancies in female partners should only be followed if the male patient is being treated with a KPT-9274-containing regimen.

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

All incidences of abuse, misuse, medication errors, overdose, and occupational exposure are required to be reported to Karyopharm Pharmacovigilance on an SAE report form, faxed to pharmacovigilance@karyopharm.com, regardless of whether or not there is an associated AE or SAE.

8.3.2.1. Overdose

An overdose is a deliberate or accidental administration of any study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study protocol. If an overdose occurs, the Investigator and Karyopharm should be notified immediately, and the patient should be observed closely for AEs. Resulting symptoms should be treated, as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record and in the eCRF. Overdose is to be reported on an SAE report form to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the overdose. If the overdose is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible.

8.3.2.2. Abuse, Misuse, or Medication Error

Abuse is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.

A medication error is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the

following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

All occurrences of abuse, misuse, or medication error with any study treatment are to be reported on an SAE report form to Karyopharm Pharmacovigilance regardless of whether or not an AE or SAE has occurred due to the abuse, misuse, or medication error. If the abuse, misuse, or medication error is associated with an SAE, the SAE report form must be submitted to Karyopharm Pharmacovigilance within 24 hours of awareness. If there is no AE or SAE, the report must be submitted as soon as possible.

8.3.2.3. Occupational Exposure

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

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

9. STATISTICAL METHODS

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

9.1. General Considerations

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology with median event time and associated 2 sided 95% confidence intervals, as well as number and percentage of patients with events and censored patients.

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 assessment of the Dose Expansion Phase.

Efficacy and safety endpoints will be presented separately for Part A, B and two dose levels of Part C.

9.2. Determination of Sample Size

9.2.1. 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.

9.2.2. 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.

9.3. Analysis Populations

9.3.1. Intent-to-Treat Population

The intent to treat (ITT) population for Part A and Part B will consist of all patients who receive at least one dose of the RP2D ± niacin ER chosen for expansion. Note that patients who are in the Dose Escalation Phase being treated at the RP2D ± niacin ER dose will be included.

The ITT population for Part C will consist of all patients who receive at least one dose of study treatment.

ITT population will be used for primary analyses of efficacy.

9.3.2. Per Protocol Population

The per-protocol (PP) population will consist of all ITT 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 medication, 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.

9.3.3. Safety Population

All patients who receive any amount of the study treatment will be included in the safety population for analysis. All safety analyses will be performed on the safety population.

9.3.4. Pharmacokinetic Population

All subjects who received at least 1 dose of study medication and had adequate sampling will be included in the PK population. All PK analyses will be performed on the PK population.

9.3.5. 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.

9.4. Data Analysis and Presentation

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

9.4.1. Disposition of Patients

A tabulation of patient disposition will be presented including the number in each analysis population, the number lost to follow-up, the number that withdrew, and reason(s) for withdrawal.

9.4.2. Demographic Characteristics

Demographic characteristics will be summarized by dose cohort, as well as overall, and will include date of birth, sex, race, ethnicity, and age at time of consent. For sex, race, and ethnicity, the summary statistics will be the number and percentage of patients within each category. The categories for race will be those recorded in the database. For age at time of consent, the mean, median, minimum, maximum, and standard deviation will be provided for each arm and the total sample. No formal hypothesis testing of differences among dose cohorts will be performed.

9.4.3. Baseline Characteristics and Medical History

Baseline characteristics include ECOG performance status, duration from initial diagnosis, response to previous therapy, types of prior therapy, and height/weight/BSA. Baseline data will be tabulated for the same categories as used for demographics, using summary statistics; no formal hypothesis testing of dose cohort differences will be performed. Medical history and physical examination results at baseline will be tabulated by treatment cohort.

9.5. Efficacy Analysis

Disease response will be evaluated according to RECIST 1.1 (advanced solid malignancies) Appendix 4]) or Lugano Classification (NHL) (Appendix 3) 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.

- Overall response rate (ORR): The analysis of ORR will be performed by calculating the point estimate of the percentage of patients who have either CR or PR, presented as the number and percentage of patients, including a two-sided 95% CI.
- Duration of response (DOR): the duration of time from first meeting CR or PR measurement criteria (whichever occurs first) until the first date that Progressive Disease (PD) recurrence is objectively documented. Patients without documented PD will be censored on the date of last disease assessment.
- Disease control rate (DCR): The analysis of DCR will be similar to that described for ORR, for patients who achieve CR, PR, or SD for ≥ 16 weeks.
- Duration of disease control: the duration of time from date of first study treatment until the first date the PD is objectively documented. Patients without documented disease progression will be censored on the date of last disease assessment.
- Progression-free survival (PFS): the duration of time from date of first dose of study treatment until the first date that PD is objectively documented or death due to any cause. Patients without documented PD will be censored on the date of last disease assessment.
- Overall survival (OS): the duration of time from date of first dose of study treatment until death from any cause. Patients who withdraw from the study or are alive at the time of data analysis will be censored on the date of last contact.

- TTP: The duration of time from date of first dose of study treatment to date of PD. Patients who withdraw from the study or are alive at the time of data analysis per Section 2.2.2 without documented DD will be censored on the date of last contact.

9.5.1. Futility Testing

For Part A or Part B, at least one clinical response (minimum of stable disease ~16 weeks) must be seen in any of the first ten 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 escalation will not be dependent upon demonstration of clinical benefit of the single agent, but futility at the KPT-9274 + niacin RP2D will be assessed prior to full expansion using the same criterion as described above for the single agent KPT-9274.

9.6. Pharmacokinetic Analysis

PK Parameters for KPT-9274 will be determined following administration of KPT-9274 (Section 7.4).

KPT-9274 PK parameters may include, but are not limited to, C_{max}, AUC, t_{max}, $t_{½}$, V_d/F, and CL/F. Interim PK analyses may be performed throughout the study on draft, unaudited plasma KPT-9274 concentration data.

The PK properties of KPT-9274 will be evaluated and data collected over time will be summarized. PK endpoints will be computed using non-compartmental methods. Summary statistics such as mean, standard deviation, median, range, etc., will be compiled and reported. A separate Data Analysis Plan (DAP) might be prepared prior to initiation of the final PK analysis.

9.8. Safety Analysis

All safety analyses will be made on the Safety Population. Details of the analyses will be described in the SAP.

The safety and tolerability of KPT-9274 ± niacin ER will be evaluated by means of DLTs, AE reports, physical examination results, electrocardiogram results and laboratory safety evaluations. NCI CTCAE, Version 4.03 will be used for grading of AEs.

The MTD will be based on the assessment of DLTs during the first cycle of therapy and will be defined as the highest dose at which ≤1 patient experiences DLTs within Cycle 1. If the true DLT rate is 33% for each dose cohort, the probability of halting dose escalation at a given dose cohort is 0.57.

9.8.1. Adverse Events

Adverse Events (AEs) will be coded using the MedDRA dictionary and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term. Analyses of AEs will be performed for those events that are considered to be treatment-emergent AEs (TEAEs), defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the Investigator through the end of the study. Adverse events with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

Adverse events will be summarized by frequency counts at patient level . Tabulations will be provided for all TEAEs, for TEAEs assessed by the Investigator as at least possibly related to treatment, for ≥ Grade 3 TEAEs, and for serious AEs (SAEs).

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment-emergent and post-treatment) will be listed in patient data listings. Separate by-patient listings will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

9.8.2. Clinical Laboratory Data

Clinical laboratory values will be expressed using conventional SI units.

The actual value and change from Baseline for each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry.

Severity of select clinical lab measures will be determined using CTCAE criteria (i.e. those measures that have a corresponding CTCAE grade classification). Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

9.8.3. Vital Signs and Examinations

The actual value and change from baseline to each on-study evaluation will be summarized.

Physical examination results at Screening will be summarized; all other abnormal physical examination data are to be recorded on the AE eCRF. All examination findings will be presented in a data listing.

ECOG performance status scores, 12-lead ECG results, and ophthalmic examination results will be summarized.

9.8.4. Concomitant Medications

Concomitant medications will be coded and tabulated based on the current version of the World Health Organization (WHO) Drug Dictionary.

10. ADMINISTRATIVE AND REGULATORY REQUIREMENTS

10.1. Good Clinical Practice (GCP)

The study will be conducted in accordance with the ICH Guideline for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and IB. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.2. Institutional Review Board

The protocol, ICF(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

10.3. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at a site where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

10.4. Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the patient, guardian or legal representative prior to study participation, on the appropriate IRB/EC approved consent form. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

10.5. Patient Confidentiality

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients.

In order to maintain patient privacy, all eCRFs, study treatment accountability records, study reports, and communications will identify the patient only by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from Karyopharm or its designee and regulatory authorities access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations.

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

Karyopharm may request medical records in order to obtain additional details on subject safety. Any medical records must be de-identified to remove all PHI.

If a site indicates that country rules or ethics committee standards do not permit collection of key sensitive personally identifiable information (e.g., patient initials and exact Date of Birth), Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

10.6. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Karyopharm, and given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and Karyopharm. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB. Karyopharm will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact Karyopharm, if circumstances permit, to discuss the planned course of action. Any deviation from the protocol must be fully documented in the eCRF and source documentation.

10.7. Direct Access to Source Data

Monitoring and auditing procedures will be followed in compliance with ICH-GCP guidelines. The study will be monitored by Karyopharm or its designee. Monitoring will be done by personal visits from a representative of Karyopharm (site monitor) and will include on-site review of the eCRFs for completeness and clarity, verification with source documents, and confirmation of compliance with the study protocol and applicable regulations. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, e-mail, telephone, and fax).

Regulatory authorities, the IEC/IRB, and/or Karyopharm’s clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

10.8. Electronic Case Report Form Completion

Required study data will be captured on eCRFs via electronic data capture (EDC) unless otherwise specified in this document.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

10.9. Record Retention

The Investigator will maintain all study records according to ICH GCPs and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Karyopharm must be notified in writing if a custodial change occurs.

Karyopharm has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

11. LIST OF REFERENCES

Abril-Rodriguez G, Torrejon DY, Liu W et al. PAK4 inhibition improves PD-1 blockade immunotherapy. *Nature Cancer*; 2020; 1:46-58.

Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Onc 2004; 22:2918.

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.

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

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

National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Fatigue, version 2.2015. Available at http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Published 22 January 2015.

National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, version 1.2015. Available at http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Published 01 April 2015.

National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Palliative Care, version 2.2015. Available at http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf. Published 18 May 2015.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007;109:1857-1861.

Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signaling prevents anti-tumour immunity. *Nature*. 2015 Jul 9;523(7559):231-5.

Webster K, Cashy J, Cella D, et al. Measuring quality of life (QoL) in patients with non-Hodgkin's lymphoma (NHL): The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). *Qual Life Res*. 2005; 14:1650.

12. APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS CRITERIA

Table 21: ECOG Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655).

APPENDIX 2. THE LUGANO CLASSIFICATION FOR INITIAL EVALUATION AND STAGING OF NHL

Table 22: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Nonavid disease	CT	> 13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (e.g., skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

[a] PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table 23: Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

•NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

[a] Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

APPENDIX 3. THE LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT OF NHL (CHESON, 2014)

Table 24: Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

a. A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any

site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

b. PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX 4. RECIST VERSION 1.1

(Modified from Eisenhauer 2009)

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

Complete Response (CR)

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

Partial Response (PR)

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

Stable Disease (SD)

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

Progressive Disease (PD)

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

Response Duration

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

Stable Disease Duration

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

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

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

Target lesions	Non-Target lesions	New Lesions	Overall response
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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

Method of Measurement

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

Clinical Lesions

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

Chest X-ray

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

CT, MRI.

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

Ultrasound

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

Cytology, Histology

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

APPENDIX 5. EORTC-QLQ-C30

The EORTC-QLQ-C30 contains 30 questions and includes 5 functional scales (Physical, Role, Emotional, Social, and Cognitive Functioning), 3 symptom scales (Fatigue, Nausea/Vomiting and Pain) and a Global Health Status/QoL scale at the following uniform resource locator (URL) http://groups.eortc.be/qol/.

APPENDIX 6. PROTOCOL AMENDMENTS: RATIONALES AND SUMMARIES OF CHANGES

Clinical Study Protocol

Summary of Changes

This primary reason for amending this protocol is to add an additional arm administering KPT-9274 + nivolumab to patients with melanoma and assessing the following parameters:

- Safety, tolerability, and RP2D
- Antitumor activity
- PK
- CCI [redacted]

The revised protocol Version 5.0 dated 11 March 2020 will be submitted to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the key changes that were made to Version 4.1 of the protocol, including the rationale for these changes in Version 5.0 is provided in the table below. Global changes or modification of large amounts of texts are not described in detail, rather, a general description of the change is provided. When appropriate, exact changes to the text are provided. In these instances, ~~red font~~ indicates text that was deleted. Text that was added is provided in blue font.

Changes that were primarily editorial or administrative in nature or were made for readability and clarity are not detailed in the table.

Section(s)	Description of Change	Rationale for the Change
Global	Revised text referring to Version 4.1 to include any Version 5.0.	Administrative
Global	Minor wording changes to improve clarity and conciseness	Administrative
Synopsis	A new table was added to clearly and concisely present the objectives and endpoints of the study.	Administrative
Protocol Synopsis Figure 1: Study Flow Chart Section 2.1 Objectives Section 3.1 Overall Study Design and Plan Section 6.1.1. Study Treatments Section 9.2 Determination of Sample Size	Addition of a new arm (Part C) to include patients with melanoma. Study Flow Chart has been updated to reflect the addition of Part C including patients with melanoma that will receive KPT-9274 + nivolumab. The following details were added throughout. Patients enrolled in Part C (KPT-9274 + nivolumab) will receive nivolumab (480 mg) intravenously on Day 1 of each 28 day cycle per the FDA approved package insert. Nivolumab (anti-PD-1) will be administered at the site based on the product label. Patients with melanoma (up to 20) who progressed on prior anti-PD-1 or anti-PD-L1 treatment starting at the RP2D or a DLT-cleared dose of KPT-9274 in combination with nivolumab (anti-PD-1) will be enrolled for dose finding (Part C). --- Primary **Part C** To evaluate the safety, tolerability, and RP2D of KPT-9274 + nivolumab in patients with melanoma. Secondary **Part C** • To determine the preliminary evidence of anti-tumor activity of KPT-9274 + nivolumab in patients with melanoma • To characterize PK of KPT-9274 + nivolumab in patients with melanoma Exploratory	Changes in trial arms relative to tested doses and their administration were undertaken based on promising published data demonstrating marked tumor growth inhibition by KPT-9274 + an anti-PD-1 antibody compared to either agent alone.

Section(s)	Description of Change	Rationale for the Change
	CCI --- **Section 3.1 Overall Study Design and Plan** In Part C, a cohort of patients with melanoma that have progressed on an anti-PD1 or anti-PD-L1 antibody will be treated with KPT-9274 (at a dose that cleared DLT evaluation in Part A) + nivolumab. 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 (Appendix 4). ---	

Section(s)	Description of Change	Rationale for the Change
	Section 9.2 Determination of Sample Size Section 9.2.1 Sample size for Part A and B: 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. Section 9.2.2 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. ~~For the Dose Expansion Phase, up to 65 additional patients may be enrolled at the RP2D for KPT-9274 single agent and 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) to further explore safety, tolerability, and efficacy of the RP2D of KPT-9274 ± niacin ER. Patients with melanoma (up to 20) who progressed on prior anti-PD-1 or anti-PD-L1 treatment starting at the RP2D or a DLT-cleared dose of KPT-9274 in combination with nivolumab (anti-PD-1) will be enrolled for dose dose finding (Part C). Safety will be continuously monitored. No formal statistical calculations were performed for the number of patients to be included.~~	
Protocol Synopsis Section 1.3.3: Rationale for Combining KPT-9274 with	Rationale has been provided for combining KPT-9273 with nivolumab: **Rationale for combining KPT-9274 with Nivolumab:** KPT-9274 binds to and reduces the steady state level of the PAK4 protein kinase as well as blocking the activity of NAMPT. In addition, through PAK4 inhibition, KPT-9274 reduces the stability, nuclear transportation and function of β-catenin by inhibiting its phosphorylation on S675. This is consistent with β-catenin being a target of PAK4.	Rationale was provided as justification for the addition of an additional arm of the study.

Section(s)	Description of Change	Rationale for the Change
Nivolumab in Melanoma	Nivolumab is a monoclonal antibody directed against the programmed cell death 1 receptor (PD-1) on lymphocytes. Anti-PD-1 treatment increases the immune response, allowing T cell killing of tumor cells. Nivolumab has been FDA-approved for use in patients with advanced melanoma. There is evidence suggesting that patients most likely to respond to anti-PD-1 treatment are those who have an elevated baseline of CD8+ T cell infiltration within the tumor microenvironment (TME) (Abril-Rodriguez 2020). Those who lack a T cell infiltrate respond poorly. A correlation was reported between hyperactivation of the WNT/β-catenin signaling pathway and T cell exclusion in melanoma patient tumor samples (Spranger et al 2015). Recently, this correlation has been extended to PAK4 overexpression (Abril-Rodriguez 2020). These data suggest that combination therapies in which activated β-catenin is inhibited through PAK4 inhibition simultaneously with targeting PD-1, may be particularly effective therapy. Indeed, in vivo models of mice engrafted with melanoma cells that were treated with KPT-9274 + an anti-PD-1 antibody showed marked tumor growth inhibition compared to either agent alone (Abril-Rodriguez 2020). Therefore, combinatorial treatment with KPT-9274, which blocks β-catenin, with nivolumab may be beneficial to patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1 treatment.	
Protocol Synopsis Section 6.2.6.2 Dose-Limiting Toxicity Table 14: Criteria for Defining Dose Limiting Toxicities	Clarification of fever has been adjusted in the DLT table. Febrile neutropenia of any duration (ANC < 1.0 $\times 10^9$ with single temperature >38.3°C, ~~fever >38.5°C~~ or a sustained temperature ≥ 38°C for more than 1 hour).	Corrected typo to be consistent with CTCAE v4.03 guidelines for febrile neutropenia.
Protocol Synopsis	Explanation of Dose Escalation Phase for Part C is included. **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,	With the addition of a new arm (Part C), dosing information has been provided.

<table>
<tr><th>Section(s)</th><th>Description of Change</th><th>Rationale for the Change</th></tr>
<tr><td></td><td>tolerability and preliminary evidence of anti-tumor activity of the RP2D (or any DLT-cleared dose) of KPT-9274 + nivolumab.

DOSE ESCALATION 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. 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.
1.
KPT-9274 Dose Finding (Part C)
<table>
<tr><th rowspan="2">Cohort</th><th>KPT-9274</th><th>Nivolumab</th></tr>
<tr><td>Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 in a 28-day cycle</td><td>Day 1 in a 28-day cycle</td></tr>
<tr><td>1</td><td>30 mg</td><td>480 mg</td></tr>
<tr><td>2</td><td>40 mg</td><td>480 mg</td></tr>
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Section(s)	Description of Change	Rationale for the Change
	Dose Finding and Expansion in Part C may include approximately 20 patients with melanoma.	
Protocol Synopsis Section 4.4/4.5: Study Population, Inclusion / Exclusion Criteria (Part C)	Inclusion and exclusion criteria specific to Part C have been added. **Inclusion/Exclusion Criteria (Part C):** **Inclusion Criteria** Patients must meet all of the following inclusion criteria to be eligible to enroll in this study. 1. Written informed consent obtained prior to any screening procedures and in accordance with federal, local, and institutional guidelines. 2. Age ≥18 years. 3. Patients must have objective and measurable melanoma by RECIST 1.1 after disease progression on a prior anti-PD-1 or anti-PD-L1 therapy. 4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 5. Adequate hepatic function: a. Total bilirubin < 1.5 times the upper limit of normal (ULN) (except patients with Gilbert's syndrome [hereditary indirect hyperbilirubinemia] who must have a total bilirubin of ≤ 3 times ULN), b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times ULN (except patients with known liver involvement of their advanced solid malignancy who must have their AST and ALT ≤ 5.0 times ULN). 6. Adequate renal function: Estimated creatinine clearance of ≥ 60 mL/min, calculated using the formula of Cockroft and Gault (140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female. 7. Female patients of child-bearing potential must agree to use dual methods of contraception (including one highly effective and one effective method of contraception) and have a negative serum pregnancy test at Screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. For both male and female	Separate inclusion and exclusion criteria were developed and included for the additional arm to administer KPT-9274 + nivolumab to patients with melanoma.

Section(s)	Description of Change	Rationale for the Change
	patients, effective methods of contraception must be used throughout the study and for 3 months following the last dose. 8. Adequate hematopoietic function: total white blood cell (WBC) count ≥ 1500/mm^3, absolute neutrophil count (ANC) ≥ 1000/mm^3, hemoglobin (Hb) ≥ 10.0 g/dL, and platelet count ≥ 100,000/mm^3. 9. Life expectancy of ≥ 3 months. **Exclusion Criteria** Patients meeting any of the following exclusion criteria are not eligible to enroll in this study: 1. Female patients who are pregnant or lactating. 2. ≤ 2 weeks since the last prior therapeutic regimen for melanoma. Palliative steroids for disease related symptoms < 7 days prior to C1D1, unless physiologic doses of steroids are used. 3. Patients who have not recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤ Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor. 4. Patients with untreated central nervous system (CNS) disease or leptomeningeal involvement are excluded. Patients without active brain or leptomeningeal metastases after prior treatment with local therapies are eligible provided that the treatment had been done ≥ 2 weeks prior to enrollment. 5. Major surgery within four weeks before C1D1. 6. Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted. 7. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea that could interfere with the absorption of KPT-9274.	

Section(s)	Description of Change	Rationale for the Change
	8. Serious psychiatric or medical conditions that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give consent. 9. Active peptic ulcer disease or other active gastrointestinal bleeds. 10. Patients requiring treatment with corticosteroids at doses higher than substitute therapy (> 10 mg prednisone), are unstable with substitute hormonal therapy, or are deemed to be likely to re-occur by the treating physician when administered nivolumab.	
Protocol Synopsis	DLT has been more stringently defined: A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities as described in the table below.	Definitions for DLTs have been updated and clarified.
Protocol Synopsis Section 2.2.2 Efficacy Endpoints Section 9.5 Efficacy Analysis	Definitions of efficacy endpoints have been updated. ***Efficacy Endpoints:*** The secondary endpoint of disease response will be evaluated according to RECIST 1.1[1] (advanced solid malignancies) or Lugano Classification[2] (NHL) and will include the following: • **Overall response rate (ORR):** ORR = ~~Complete response (CR) + Partial Response (PR)~~ 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. Patients without documented PD will be censored on the date of last disease assessment.~~ the duration of time	Definitions for efficacy endpoints have been updated and clarified.

Section(s)	Description of Change	Rationale for the Change
	from first meeting CR or PR measurement criteria (whichever occurs first) until the first date that PD recurrence is objectively documented. • **Disease control rate (DCR):** DCR = proportion of patients who have a response of CR, PR, and Stable Disease (SD) ≥ 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. Patients without documented PD will be censored on the date of last disease assessment.~~ 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 dose of study treatment until the first date that PD is objectively documented or death due to any cause. Patients without documented PD will be censored on the date of last disease assessment~~ 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. ~~Patients who withdraw from the study or are alive at the time of data analysis will be censored on the date of last contact.~~ • **Time to Progression (TTP):** ~~The duration of time from date of first dose of study treatment to date of PD. Patients without documented PD will be censored on the date of last disease assessment.~~ the duration of time from date of first study treatment until the first date that PD is objectively documented or death due to PD. Patients without documented PD will be censored on the date of last disease assessment.	
Protocol Synopsis Section 2.2.4: CCI	CCI Table 18: Collection Time Points and Sample Volumes for PK and CCI for Part C was added.	CCI

Section(s)	Description of Change	Rationale for the Change
Table 18: Collection Time Points and Sample Volumes for PK and CCI for Part C CCI		
Table 5: Schedule of Assessments for Screening and Cycle 1 (Part C) Table 6: Schedule of Assessments for Cycles 2 and Beyond (Part C)	Table of Assessments has been included for Part C and includes relevant activities, timepoints, and footnotes.	A separate Schedule of Assessments was developed and included for the additional arm to administer KPT-9274 + nivolumab to patients with melanoma.
Section 1.2.1 Potential Risks Table 10: Dose Levels and Schedules Tested as of 02 March 2019 Table 11: Treatment Related Adverse Events Occurring in ≥ 10% of All Patients	Section has been updated to include the most recent information available on enrolled patients to date. As of 02 March 2019, 47 patients had received KPT-9274 alone or with niacin ER in Parts A and B of this study. Dose levels and schedules are outlined in Table 10, long with the number of patients enrolled in each cohort. The most common AEs occurring across all patients in Parts A and B, were anemia (68%), nausea (34%), arthralgia (32%), fatigue (32%), and myalgia (23%) (Table 11; Table 12). AEs were largely dose dependent and increased with higher doses of KPT-9274. There were 2 DLTs reported among the first 47 patients. These included one case of grade 4 anemia, which occurred in the 40 mg KPT-9274 qodX3 cohort, and one case of grade 3 fatigue which occurred in the 80 mg KPT-9274 qodX3 + niacin cohort. Both dose levels enrolled additional patients per the 3+3 study design, and both dose levels ultimately cleared DLT evaluation. To date, a MTD has not been reached.	Updated information was available and therefore included.

Section(s)	Description of Change	Rationale for the Change
Table 12: Treatment Related Adverse Events Occurring in ≥ 10% of Patients by Dose Level and Schedule		
Section 6.2.6.1 Section 6.2.8.1.2 Dose Holds or Reductions for Nivolumab (Part C) Section 6.3 Study Treatment Storage	Instructions for dose levels, dose holds, reductions and storage for nivolumab were added. **Part C (KPT-9274 + nivolumab):** The initial cohort will consist of 3 enrolled patients who will be treated at a dose of 30 mg KPT-9274, co-administered with a dose of 480 mg nivolumab. If these patients do not experience a DLT during Cycle 1, the KPT-9274 dose will be escalated to 40 mg for another cohort of 3 patients upon approval during a dose decision meeting. A maximum of 10 patients may be enrolled at each dose level. Additional KPT-9274 dose levels (e.g., 20 mg or 60 mg) may be evaluated if an optimal dose is not identified and the safety review committee is in agreement. Section 6.2.8.1.2 Dose reductions are not allowed for nivolumab. Consult the product label for dose holds. Section 6.3 Nivolumab should be stored according to the package label.	Separate instructions were developed and included for the additional arm to administer KPT-9274 + nivolumab to patients with melanoma.
Section 6.9.1 Supportive Care	Instructions for increasing the dose of niacin were clarified. After Week 8, niacin may be titrated, as per label, to patient response and tolerance. If response to 1000 mg daily is inadequate, increase dose to 1500 mg daily; may subsequently increase dose to 2000 mg daily. Daily dose should not be	Updated information to clarify potential changes in niacin dosing.

Section(s)	Description of Change	Rationale for the Change
	increased more than 500 mg in a 4-week period, and doses above 2000 mg daily are not recommended. Women may respond at lower doses than men.	
Section 6.9.2.1 Permitted Concomitant Medication Section 9.8.4 Concomitant Medications	Additional clarification on contraceptives was added, in addition to details to obtain information on nivolumab concomitant medication. Since the effect of KPT-9274 on oral contraceptives is unknown at this time, it is recommended that patients use at least 2 forms of contraceptives while on study. Additionally, the nivolumab product label will be consulted to obtain the permitted concomitant medications for patients in Part C (the KPT-9274 + nivolumab).	Separate instructions were developed and included for the additional arm to administer KPT-9274 + nivolumab to patients with melanoma.
Section 6.9.2.5 Glucocorticoid Therapy	Updates were made to administration of glucocorticoids. **6.9.2.5 Glucocorticoid Therapy** Glucocorticoids ≥≤10 mg oral prednisone (or equivalent) per day are not permitted at baseline; however physiological doses ≤10 mg oral prednisone (or equivalent) for non-malignant conditions (e.g., asthma, IBD, etc.) are permitted as needed.	Corrected typo, however allowed for physiological doses ≤10 mg oral prednisone (or equivalent) in Part C as this may be common in the treatment population.
Section 7.2.6 Determination of Patients with Melanoma Who Progressed on Prior Anti-PD-1 or Anti-PD-L1 Treatment	An additional section on assessments of patients in Part C has been added. Section 7.2.6 Determination of Patients with Melanoma Who Progressed on Prior Anti-PD-1 or Anti-PD-L1 Treatment Patients with melanoma who progressed on prior anti-PD-1 or anti-PD-L1 treatment must be determined prior to enrollment in Part C - KPT-9274 + nivolumab. Screening period includes Day -30 to Day -1 prior to C1D1.	Separate information was developed and included for the additional arm to administer KPT-9274 + nivolumab to patients with melanoma.
Section 8.1.2 Recording of Adverse Events	Updated section on recording of adverse events was included. Section 8.1.2 Recording of Adverse Events Adverse Events will be reported and recorded in the eCRF from the time of the first dose of study drug through 30 days after the last dose of study drug or until the	Instructions for recording of adverse events have been updated and clarified.

Section(s)	Description of Change	Rationale for the Change
	start of subsequent antineoplastic therapy, whichever occurs first. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE. The Investigator should ask the patient non-leading questions to determine if any AEs have occurred during the study, since the last study visit. Adverse events may also be recorded when they are volunteered by the patient, or through physical examination, laboratory tests, or other clinical assessments. An AE should be followed, and an assessment should be made at each visit (or more frequently, if necessary) for any changes in severity of the event, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized.	
Section 9.1 General Considerations	Clarification to statistical section Section 9.1 General Considerations ~~Descriptive statistics will be provided to summarize safety and efficacy endpoints by study phase, dose cohort, and niacin ER use. In the Dose Expansion Phase, data will also be presented by NAPRT1 and IDH1 status (positive vs. deficient) and test methodology. For categorical variables, summary tabulations of frequency and percentage of patients within each category will be presented along with two-sided 95% exact confidence intervals where appropriate. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values~~	Clarification to the considerations for the method and manner of application of statistical analysis for the study

Section(s)	Description of Change	Rationale for the Change
	~~will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology with associated 2-sided 95% confidence intervals (if estimable), as well as percentage of censored observations at dose cohort of interest (e.g., RP2D) as appropriate.~~ Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology with median event time and associated 2 sided 95% confidence intervals, as well as number and percentage of patients with events and censored patients.	
Section 9.8.2 Clinical Laboratory Values	Changes made to data tabulation Section 9.8.2 Clinical Laboratory Values Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced. ~~Labs with CTCAE ≥ Grade 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.~~	Clarification of analysis of selected clinical laboratory values to enhance understanding of changes in lab values.

Amendment 4.0, Version 4.1

Version 4.1 incorporates changes to 4.0

Amendment Rationale

The primary purpose for this amendment is to clarify dosing of niacin ER as a starting level of 500 mg which may be titrated up to a daily dose of 2,000 mg, per label.

The revised protocol Version 4.1 dated 13 December 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the changes that were made to Version 4.0 of the protocol in Version 4.1 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 4.1 and 13 December 2017 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Made internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections:** Global).

Protocol Approver Signature Page

- PPD to replace PPD, MD, PhD, PPD

Study Rationale

- CCI
    - **Modified Sections:** Synopsis, Section 3.1

Methodology Section

- Revised the text for patients in Part B to read, "..starting dose of 500 mg niacin ER (may be titrated to 2,000 mg of daily dose, per label)
    - **Rationale**: To clarify that niacin ER may dose may increase as necessary, per the label.
    - **Modified Sections:** Synopsis, Section 3.1, Section 4.2, Section 6.1.1, and Section 6.2.6.1.
- Added the following text for enrolment of patients according to their NAPRT1 status, "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."

- **Rationale:** To clarify the enrolment of patients based on their NAPRT1 status
- **Modified Sections:** Synopsis, Section 3.1

Dose Expansion Phase

- Added a statement noting that the composition of the expansion groups may change based on the results from the escalation phase.
  - **Rationale:** To allow for the group(s) in the expansion phase to be defined by the results from the escalation phase rather than be pre-defined.
  - **Modified Sections:** Synopsis, Section 3.1

Inclusion/Exclusion Criteria

- New inclusion criteria #11 for patient enrolment according to their NAPRT1 status which is specific for the Dose Escalation Phase
  - **Rationale:** To clarify the enrolment of patients based on their NAPRT1 status
  - **Modified Sections:** Synopsis, Section 4.2
- Clarification text added to inclusion #12a for confirmation of NAPRT1 based on the evaluation of a fresh tumor biopsy in addition to an archival tumor biopsy
  - **Rationale:** To provide the investigators with an additional confirmation of NAPRT1 status in patients if they do not have an archival tumor biopsy
  - **Modified Sections:** Synopsis, Section 4.2

Supportive Care

- Added the following clarifying statement, "For Part A patients, the addition of niacin ER (up to 2,000 mg daily dose) is allowed after completion of the DLT period in cycle 1 (first 28 days) in an attempt to offset potential side effect (i.e. anemia, arthralgias, myalgias, etc.) of KPT-9274."
  - **Rationale:** To provide the investigators with dosing guidance in order to offset the potential side effects of KPT-9274
  - **Modified Sections:** Synopsis, Section 6.9.1

Prohibited Concomitant Medications

- Added the following statement, "However, for patients in these cohorts that have cleared DLT in cycle 1, niacin ER (up to 2,000 mg co-dosed with KPT-9274) may be used as supportive care in an attempt to offset potential side effects (e.g. anemia, arthralgias, myalgias, etc.) of KPT-9274. Prior to initiating niacin ER, patient symptoms and laboratory values should be reviewed and discussed with the Medical Monitor for this study."
  - **Rationale:** To provide the investigators with dosing guidance in order to offset the potential side effects of KPT-9274

- **Modified Sections:** Synopsis, Section 6.9.3

Schedule of Assessments, Table 1

- Added the following statement, "If an in-clinic visit is missed during Cycle 1 due to a national or local holiday, the patient should come to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic."
  - **Rationale:** To clarify the procedure for missed doses during Cycle 1
  - **Modified Sections:** Table 1

Schedule of Assessments, Table 1

- Revised footnote #2 to verify that pre-treament period is Day -30 to Day 7) and added the following text, "Dose Escalation Phase: 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. NAPRT1."
  - **Rationale:** To clarify the timeframe for pre-treatment and to clarify the enrolment of patients based on their NAPRT1 status
  - **Modified Sections:** Table 1, footnote #2

Introduction

- Added KPT-9274 to Section 1.3.1 to clarify this is the rationale for the KPT-9274 dose.

Amendment 3.0, Version 4.0

Version 4.0 incorporates changes to 3.0.

Amendment Rationale

The primary purpose for this amendment is to add assessments to better understand the safety profile of KPT-9274.

These changes have been made to address treatment-emergent adverse events. This includes determining the etiology of anemia, arthralgias, and myalgias and courses of treatment to alleviate the conditions that emerge. Minor changes that were addressed in memos to the sites are also incorporated in this amendment.

The revised protocol Version 4.0 dated 15 June 2017 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the changes that were made to Version 3.0 of the protocol in Version 4.0 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 4.0 and 15 June 2017 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Made internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections:** Global).
- Updated the potential risks based on the v2.0 of the KPT-9274 Investigator's Brochure, dated 25APR2017 (**Modified section:** Section 1.2.1).

Study Population Selection

- Revised inclusion criterion #10 to increase the hemoglobin level for inclusion from ≥9.0 g/dL to ≥10 g/dL.
  - **Rationale**: To reduce the potential for patients to develop life-threatening treatment-emergent anemia.
  - **Modified Sections:** Synopsis, Section 4.2.
- Removed exclusion criterion #12 (prohibition of use of proton pump inhibitors [PPIs] in patients in niacin ER cohorts).
  - **Rationale**: PPIs are not contraindicated in patients receiving niacin ER according to niacin prescribing information
  - **Modified Sections:** Synopsis, Section 4.3.

Study Activities

- Removed Section 5.0 Study Activities and added an overview of the timing for study activities and references to the schedule of assessments tables in Section 3.1. Section

numbers for Sections 6.0 through 13 of protocol version 3.0 were renumbered, accordingly (i.e., to Sections 5.0 through 12).

- **Rationale:** Reduce length and complexity of the protocol.
- **Modified Sections:** Section 3.1 and Section 5.0 (deleted section from protocol version 3.0).

Study Treatments

- Revised the starting dose for Part B from "the RP2D defined during Part A" to "a dose and schedule that has cleared DLT assessment in Part A."
  - **Rationale**: Co-administration of KPT-9274 with niacin to determine if adverse events with single agent can be mitigated will be started without having determined the MTD with single agent (Part A).
  - **Modified Sections:** Synopsis, Sections 3.1, 6.2.3, 6.2.5, and 6.2.6.1.
- Specified the minimum number of KPT-9274 doses during Cycle 1 that patients must receive to be evaluable for dose escalation decisions.
  - **Rationale**: 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.
  - **Modified Sections**: Synopsis, Sections 6.2.6.1, 9.3.3, and 9.3.5 (new section).
- Revised the volume of fluids required for dosing from at least 4 ounces to 8 to 12 ounces.
  - **Rationale**: The current volume (4 ounces) of fluids noted in protocol version 3.0 for dosing has not demonstrated linear PK with increasing doses. The current KPT-9274 formulation requires aqueous media for disintegration, dissolution, and absorption. The revised recommendation to take KPT-9274 tablets with 8 to 12 ounces of fluids may help to provide a more consistent and dose dependent PK profile.
  - **Modified Section:** Section 6.2.4.

Supportive Care

- Added supportive care recommendations for treatment-emergent anemia, arthralgia, and myalgia.
  - **Rationale**: Treatment-emergent anemia, arthralgia, and myalgia are the most common AEs reported with KPT-9274 treatment.
  - **Modified Sections:** Synopsis and Section 6.9.1.
- Clarified that the use of niacin or niacin-containing supplements includes multivitamins and energy drinks.
  - **Rationale:** To control the amount of niacin consumed by patients on the KPT-9274 + niacin cohort.
  - **Modified Sections:** Synopsis, Section 6.9.3.

- Modified to allow patients to receive proton pump inhibitors (removal of PPIs as a prohibited medication in patients receiving niacin).
  - **Rationale:** To be consistent with removal of exclusion criterion #11.
  - **Modified Sections:** Synopsis, Sections 6.9.1 and 6.9.2.1.

Assessments

- Added rheumatology consult and testing for patients with clinically significant joint or muscle-related AEs.
  - **Rationale:** To investigate the mechanism of treatment-emergent arthralgia.
  - **Modified Sections:** Schedule of Assessments (Table 1, Table 2, and Table 3) and Section 7.6.2 (new section).
- Added hematology consultation and testing for patients with clinically significant hematological AEs.
  - **Rationale:** To further assess the safety profile of KPT-9274 concerning observations of non-hemolytic anemia.
  - **Modified Sections:** Schedule of Assessments (Table 1, Table 2, and Table 3) and Section 7.6.3 (new section).
- Added testing for blood levels of vitamin B12, folate, iron, erythropoietin, haptoglobin, and transferrin and reticulocyte counts at Screening and the EoT Visit for all patients. This testing may also be performed throughout the study as clinically indicated. For patients who develop treatment-emergent anemia, this testing should be performed as soon as possible after onset. Patients with ≤ Grade 1 anemia should have their levels/counts assessed no less than once a month and patients with ≥ Grade 2 anemia should have their levels/counts assessed every 2 weeks.
  - **Rationale**: To further assess the mechanism of the treatment-emergent non-hemolytic anemia observed when patients are dosed with KPT-9274.
  - **Modified Sections:** Schedule of Assessments (Table 1, Table 2, and Table 3) and Section 7.6.4.2 (new section).
- Added PK sampling time points at C1D24 at 4, 12, 18, and 32 hours post dose for the first 18 patients enrolled in the expansion phase.
  - **Rationale:** To accurately determine the $t_{½}$ and clearance rate of KPT-9274.
  - **Modified Sections:** Section 7.4.1 and Table 10.

Safety Definitions, Recording, and Reporting

- Revised start time for recording of AEs from “from the first dose of study treatment on C1D1 “to “after the patient has provided informed consent” to ensure compliance with regulations.
  - **Rationale:** To ensure compliance with regulations.
  - **Modified Sections:** Section 8.1 and Table 1.

- Updated the safety section with the current standard Karyopharm safety definitions and recording/reporting procedures.
    - **Rationale:** To ensure compliance and consistency across Karyopharm clinical studies.
    - **Modified Section:** Section 8.

Amendment 2.0, Version 3.0

Version 3.0 incorporates changes to 2.0.

Amendment Rationale

The primary purpose for this amendment is to reduce the number of clinic visits in response to investigator feedback obtained during an Investigator Meeting dated 22 March 2016.

Additional changes have been made for consistency and clarity, including minor adjustments to the frequency of some clinical laboratory assessments, alignment of collection of PK samples with CCI samples, type of disease assessment scans for NHL tumor patients, inclusion of archival biopsy material to pre-screen patients for NAPRT1 and IDH1 tumor mutation status, and creation of an enrollment allocation in the KPT-9274 ± niacin ER dose expansion arm to allow for an "either" category and minimize the possibility of a patient not being enrolled in the trial, and clarification of the definition of a DLT.

The revised protocol Version 3.0 dated 02 May 2016 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the changes that were made to Version 2.0 of the protocol in Version 3.0 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 3.0 and 02 May 2016 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections:** Global).

Revisions to the number of Clinic Visits to Address Investigator Feedback.

- **Number of clinic visits were reduced:**
  - **Change From**: Screening assessments occurred between Days -30 to -1. Clinic visits occurred in Cycle 1 on Days 1, 2, 3, 8, 12, 15, 19, 22, 26, 27, and 28, Cycle 2 on Days 1, 5, 8, 12, 15, 19, 22, and 26, and Cycles >3 Days 1, 2, 8, 12, 15, 19, 22, and 26.
  - **Change To**: Screening assessment can occur between either Days -30 to -1, or Days -14 to -1. Clinic visits occur in Cycle 1 on Days 1, 2, 3, 8, 15, 22, 24, 25, 26, Cycle 2 Days 1, 8, 15, and 22, and Cycles >3 Days 1 and 15.
- **If dosing were to occur on a Monday, then Cycle 1 Days 27 and 28 clinic visits would occur on a weekend and was thus changed to Cycle 1 Days 24 and 25 to eliminate weekend visits.**
- **Phone call days were moved to Thursdays (if dosing occurs on a Monday dosing) and a window of ± 1 day added, except Cycle 1 Day 4 where window was +1 day to avoid conflicting with Cycle 1 Day 3 in-clinic visit.**
- **Adjusted all collection windows from ± 5 days to ± 7 days for lymph node core biopsies, tumor biopsies, and MRI, PET-CT or CT scans.**

- **Comment added to Table 2 to account for in clinic visits that fall on a holiday or missed for other reasons,** "If an in-clinic visit is missed during Cycle 2 and beyond the patient should come in to the clinic on their next dosing day to complete the visit assessments. Patient is to be instructed that dose is to be taken in the clinic."
- **Clarified in-clinic versus at home dosing in Table 4: "**Study treatment dosing will occur in the clinic during Cycle 1 on Days 1, 3, 8, 15, 22, 24, and 26, during Cycle 2 on Days 1, 8, 15, and 22, and during ≥Cycle 3 on Days 1 and 15. Study treatment dosing will occur at home during Cycle 1 on Days 5, 10, 12, 17, and 19, during Cycle 2 on Days 3, 5, 10, 12, 17, 19, 24, and 26 and during Cycles ≥3 on Days 3, 5, 8, 10, 12, 17, 19, 22, 24, and 26."
- **Added urinalysis on Cycle 1 Day 3 to be consistent with other clinical assessments.**
- **Aligned TSH timepoints with complete serum chemistry.**
- **Modified Sections**: Schedule of Assessments, Table 4, Section 6.2, Section 8.2.3, Section 8.2.4, Table 10.

Clarified the definition of a DLT with addition of underlined text, "A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274, except for those that are clearly and incontrovertibly due to underlying disease, disease progression, or extraneous causes, and meets any of the criteria for defining dose-limiting toxicities as described in the table below. The CTCAE, Version 4.03 will be used for grading. In addition, >3 missed (consecutive or nonconsecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

- **The definition of a DLT was revised after consultation with investigators and confirmation from the FDA.**
- **Modified Sections: Synopsis, Section 8.2.6.2.**

Revision to the Dose Expansion Study Flow where dose expansion of KPT-9274 will not be run in parallel with Dose Escalation of KPT-9274 + niacin ER and instead a decision will be made whether to initiate the Dose Expansion of KPT-9274 + niacin ER. If Dose Expansion of KPT-9274 + niacin ER is initiated, then an optional Dose Expansion with KPT-9274 single agent may be initiated.

- **Changed From:** After declaring the RP2D ± niacin ER, based on the safety and tolerability results of the Dose Escalation Phase, at least one clinical response (minimum of stable disease ~8 weeks) must be seen in any of the first ten patients treated at the RP2D in order to fully enroll the 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 escalation will not be dependent upon demonstration of clinical benefit of the single agent, but futility at the KPT-9274 + niacin RP2D will be assessed prior to full expansion using the same criterion as described above for the single agent KPT-9274. During the Dose Expansion Phase,

up to 65 additional patients (up to 20 patients in the KPT-9274-only cohort and up to 45 patients in the KPT-9274 + niacin ER cohort) with advanced solid malignancies and NHL may be enrolled to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274 ± niacin ER. Each cohort may be expanded at the time the RP2D for that cohort is declared. Note that preliminary clinical results may define the patient population (i.e., specific indications) selected for enrollment in the Dose Expansion Phase.

The KPT-9274 + niacin ER expansion cohort will consist of 3 groups of approximately 15 patients each including:

- NAPRT1 deficient tumor group
- NAPRT1 positive tumor group
- IDH1 mutant tumor group

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.

- **Changed To:** 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 one clinical response (minimum of stable disease ~8 weeks) must be seen in any of the first ten 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 KPT-9274.

The KPT-9274 ± niacin ER expansion cohort will consist of 4 groups of approximately 45 patients 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

An additional, optional KPT-9274 single agent expansion cohort will consist of <20 patients with any tumor mutational status.

- **Modified Sections**: Synopsis, Figure 1, Section 3.1, Section 8.2.3, Section 8.2.7, Section 11.2.

PK and CCI sample collections were aligned and adjustments were made to accommodate the reduction in number of clinic visits. PK and CCI collection time points and blood volumes were consolidated into one table.

- **Change From**: PK blood draws: Cycle (C) 1 Day (D) 1 (pre-dose; 0.5, 1, 2, 4, and 8 hours post-dose), Cycle 1 Day 2 (24 hours post first dose on C1D1), Cycle 1 Day 3 (48 hours post first dose on C1D1, prior to C1D3 dose), Cycle 1 Day 15 (pre-dose; 1, 2, 4, 8 hours post-dose), Cycle 1 Day 26 (pre-dose, 1, 2, 4, 8 hours post-dose), and Cycle 2 Day 15 (pre-dose and 2 hours post-dose).

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- **Change To**: PK blood draws: Cycle (C) 1 Day (D) 1 (pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose), Cycle 1 Day 2 (24 hours post first dose on C1D1), Cycle 1 Day 3 (48 hours post first dose on C1D1, prior to C1D3 dose), Cycle 1 Day 8 (pre-dose and 2 hours post-dose), Cycle 1 Day 15 (pre-dose and 2 hours post-dose), Cycle 1 Day 24 (pre-dose, 2 and 8 hours post-dose), Cycle 1 Day 25 (24 hours post first dose on C1D24), Cycle 1 Day 26 (pre-dose, 1, 2, 4, and 8 hours post-dose), Cycle 2 Day 15 (pre-dose and 2 hours post-dose), Cycle 3 Day 1 (pre-dose, 2 and 24 hours post-dose), Cycle 5 and beyond Day 1 of odd cycles only (pre-dose and 24 hours post-dose), and End-of-Therapy visit.

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- **Modified Section**: Synopsis, Schedule of Assessments, Section 6.2, Section 9.4.1, Section 9.5.1, Table 10.

Clarified scans for disease assessment for NHL.

- **Change From**: Disease response will be based on tumor measurement using computed tomography (CT) scans (preferably PET/CT) or, if CT is contraindicated, magnetic

resonance imaging (MRI) scans [preferably PET/MRI]. Scans will be conducted at Screening and after every 8 weeks ± 1 week (e.g., Day 1 of odd numbered cycles) until disease progression or the EoT visit. EoT scan is only required for patients who end treatment for reasons other than disease progression. The same scan modality should be used for all assessments. CT or MRI acceptable, however, PET-CT or PET MRI is strongly preferred

- **Change To:** Disease response will be preferably based on tumor measurement using PET/CT for FDG-avid lymphomas, or CT for non-FDG-avid lymphomas (or PET/MRI or MRI if CT is contraindicated) scans. Scans will be conducted at Screening (Day -30 to Day -1) and after every 8 weeks ± 7 days (e.g., Day 1 of odd numbered cycles) until disease progression or the EoT visit. EoT scan is only required for patients who end treatment for reasons other than disease progression.

Modified Sections: Schedule of Assessments Footnotes 12 and 19, Section 6.2, Section 9.3.2.1.

Additional text to Inclusion Criteria #11:

a. Confirmation of NAPRT1 expression and IDH1 mutation based on evaluation of archival tumor biopsy taken ≤6 months of screening tests as follows:

i. NAPRT1 positive for expansion cohort I or III

ii NAPRT1 negative for expansion cohort II or III

iii. IDH1 mutation status for expansion cohort IV

Modified Sections: Synopsis, Section 4.2.

Modified Exclusion Criteria #2 and #3:

- **Change From:**

2. Time since the last prior therapy for treatment of advanced solid malignancies or NHL**:

a. Radiation, chemotherapy, immunotherapy or any other anticancer therapy, including investigational anti-cancer therapy ≤2 weeks prior to C1D1.

b. Palliative steroids for disease related symptoms <7 days prior to C1D1.

**Patients must have recovered or stabilized (≤Grade 2 or to their baseline) from toxicities related to their previous treatment except for alopecia.

3. Patients with central nervous system (CNS) disease or leptomeningeal involvement, regardless of response to prior therapy, are excluded.

- **Change To:**

2. Time since the last prior therapy for treatment of advanced solid malignancies or NHL**:

a. Radiation, chemotherapy, immunotherapy or any other anticancer therapy, including investigational anti-cancer therapy ≤2 weeks prior to C1D1.

b. Palliative steroids for disease related symptoms <7 days prior to C1D1.

**Patients must have recovered or stabilized (Grade 1 or to their baseline for non-hematologic toxicities, ≤Grade 2 or to their baseline for hematologic toxicities) from toxicities related to their previous treatment except for alopecia. In specific cases, patients

with Grade 2 non-hematologic toxicities will be allowed following approval by the Karyopharm medical monitor.

3. Patients with known central nervous system (CNS) disease or leptomeningeal involvement, regardless of response to prior therapy, are excluded.

Modified Sections: Synopsis, Section 4.3.

Removed lymph node and tumor biopsies from EoT Visit

Modified Section: Section 6.2.3.1.

Clarified determination of NAPRT1 and IDH1 mutational status: Archival tumor biopsy taken ≤6 months of screening tests: 1. positive or deficient for NAPRT1 expression status for the Dose Expansion cohorts I-III; 2. positive for IDH1 mutation status for Dose Expansion cohort IV. If a patient's archival tumor biopsy is NAPRT1 positive and the NAPRT1 positive cohort is fully enrolled (10 patients) then patient is added to the NAPRT1 positive or deficient cohort (10 patients). If the NAPRT1 positive or deficient cohort is full then the patient will be excluded. If the IDH1 mutation cohort is full (15 patients) then the patient will be excluded. Under all circumstances a fresh biopsy will be taken during screening to verify NAPRT1 or IDH1 status. If a patient's tumor NAPRT1 or IDH1 status has changed and as a result no longer qualify for any cohorts, then the patient will be excluded.

- **Change**: Prescreening to determine NAPRT1 and IDH1 tumor status will be performed on archival biopsy material obtained ≤6 months prior to Screening for Dose Expansion Phase.
- **Modified Sections**: Synopsis, Schedule of Assessments, Figure 1. Study Flow Chart, Section 3.1, Section 4.3, Section 6.2, Section 8.2.7, Section 9.2.5.

Revised language to control for niacin bioequivalency: language was added to specify that niacin ER will be administered as a fixed dose of 500 mg and must be any FDA approved prescription generic extended release niacin, a list of which will be provided by Karyopharm in the Pharmacy Manual.

- **Modified Section:** Section 8.1.1.

Removed Section 8.2.8.2 because no adjustments will be made to the dose of niacin.

- **Modified Section**: Section 8.2.8.2.

Amendment 1.0, Version 2.0

Version 2.0 incorporates changes to 1.0.

Amendment Rationale

The primary purpose for this amendment is to address clinical deficiency items identified by the FDA in the Clinical Information Request dated 19 February 2016 and in the Clinical Information Request #2 dated 25 February 2016.

Additional changes have been made for consistency and clarity, including minor adjustments to the frequency of some clinical laboratory assessments and standardization of the timing of disease assessment scans for NHL and solid malignancy patients (every 8 weeks until disease progression).

The revised protocol Version 2.0 dated 26 February 2016 will be submitted by the Principal Investigator(s) to all applicable Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), or Research Ethics Boards (REBs), and by Karyopharm Therapeutics Inc. to all applicable Regulatory Authorities.

A summary of the changes that were made to Version 1.0 of the protocol in Version 2.0 is provided below.

Changes to the protocol

Administrative

- Updated the version number and date to Version 2.0 and 26 February 2016 throughout to reflect the changes made in this version (**Modified sections:** Global).
- Internal changes to improve clarity and eliminate inconsistencies between sections (**Modified sections:** Global).

Changes to Address Clinical Deficiencies identified by FDA:

1. **All patients with CNS disease or leptomeningeal involvement, regardless of response to prior therapy, should be excluded.**

- **Change**: A new exclusion criterion (#3) has been inserted: "Patients with central nervous system (CNS) disease or leptomeningeal involvement, regardless of response to prior therapy, are excluded."
- **Modified Sections**: Synopsis, Section 4.3.

2. **Regarding infection in the exclusion criteria (item #6): This item should read "Active infection with completion of therapeutic antibiotics, antivirals, or antifungals within one week prior to C1D1. Prophylactic antibiotics, antivirals or antifungals are permitted."**

- **Change**: Exclusion criteria #6 has been revised with the requested language.
- **Modified Sections**: Synopsis, Section 4.3.

3. **If an adverse event meets criteria for a DLT, it should be considered a DLT regardless of attribution or "clinical meaningfulness". Remove the following language and any reference to this language: "In rare instances, an event may fall within the definition of a DLT as defined above but the event may be considered not to be a DLT (e.g., not clinically meaningful/significant). If this occurs, a Dose Decision Meeting with all investigators and Karyopharm/Medical Monitor will take place to thoroughly review the event and supporting data and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale."**

- **Change:** The definition of a DLT has been changed in the revised protocol (Version 2.0).

  Change From:

  A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274 and meets any of the criteria included in the table below. The CTCAE, Version 4.03 will be used for grading. In addition, >3 missed (consecutive or non-consecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

  In rare instances, an event may fall within the definition of a DLT as defined above but the event may be considered not to be a DLT (e.g., not clinically meaningful/significant). If this occurs, a Dose Decision Meeting with all investigators and Karyopharm/Medical Monitor will take place to thoroughly review the event and supporting data and the reasons for not considering the event to be a DLT will be clearly documented with supporting rationale. In addition, other events may occur which do not meet the definition of a DLT, but are of concern to the Investigators and Karyopharm, and may e then be considered to be DLTs.

  Change To:

  A DLT is defined as an AE or abnormal laboratory value that occurs within the first 28 days of treatment with KPT-9274 and meets any of the criteria included in the table below. The CTCAE, Version 4.03 will be used for grading. In addition, >3 missed (consecutive or non-consecutive) doses of KPT-9274 in the first 28 days due to a drug related toxicity will be considered to be a DLT.

  Other events may occur which do not meet the definition of a DLT, but are of concern to the Investigators and Karyopharm and may be considered to be DLTs.

- **Modified Sections:** Synopsis, Section 8.2.6.2.

4. **Remove language allowing resumption of KPT-9274 following a DLT (in the first 28 days). Under no circumstances should a patient resume KPT-9274 following a DLT regardless of attribution or response to treatment.**

- **Change**: The requested change has been made and incorporated into the revised protocol (Version 2.0).

  Change From:

In the event of a DLT (Cycle 1) during the Dose Escalation Phase:

- Discontinue KPT-9274
- KPT-9274 may be re-introduced upon recovery to Grade ≤1 or baseline at one dose level lower at the discretion of the Investigator after consulting the Karyopharm Medical Monitor. (see Table 8)

Change To:

In the event of a DLT (Cycle 1) during the Dose Escalation Phase the patient must discontinue KPT-9274.

- **Modified Section**: Section 8.2.8.

5. Remove attribution from the dose reduction schema. Doses of KPT-9274 should be reduced if subjects experience AEs regardless of investigator attribution.

- **Change:** The requested change has been made to the title of Table 8 and the headings and applicable text within Table 9.

Change From:

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment (see Section 8.2.8.2 for niacin ER dose adjustments). The criteria for dose modifications of KPT-9274 for toxicities considered at least possibly related to the study medication treatment are outlined in Table 8. These changes must be recorded on the eCRF. If a patient requires a dose delay of more than 28 days (>28 days) from the intended day of the next scheduled dose, then the patient should be discontinued from the study (in exceptional situations, if the patient is clearly benefiting from the study treatment, and in the opinion of the Investigator no safety concerns are present, after discussion with the Karyopharm Medical Monitor, the patient may remain in the study).

Change To:

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment (see Section 8.2.8.2 for niacin ER dose adjustments). The criteria for dose modifications of KPT-9274 for toxicities are outlined in Table 8. These changes must be recorded on the eCRF. If a patient requires a dose delay of more than 28 days (>28 days) from the intended day of the next scheduled dose, then the patient should be discontinued from the study (in exceptional situations, if the patient is clearly benefiting from the study treatment, and in the opinion of the Investigator no safety concerns are present, after discussion with the Karyopharm Medical Monitor, the patient may remain in the study).

- **Modified Section:** Section 8.2.8.

6. **Provide formal stopping criteria in the dose expansion cohorts for safety. The following statement is inadequate: "Interim safety data will be examined on an ongoing basis to ensure patient safety and to comply with the clinical study dose escalation rules."**

- **Change:** Addition of specific guidance for safety assessment of dose expansion cohorts (KPT-9274 ± niacin ER, evaluated separately).

  Change From:

  > For the Dose Expansion Phase, if an event meeting the definition of a DLT, but without necessarily occurring within the first 28 days, is observed in >33% of patients at any time, the sponsor may elect to reduce the dose for enrolled patients and to resume enrollment of the expansion cohort at this lower dose, or the enrollment into the expansion cohort will may be stopped. Since the target patient population is patients who are not candidates for anti-tumor regimens known to provide clinical benefit, no formal futility monitoring is planned for the expansion cohort.

  Change To:

  > For the Dose Expansion Phase (KPT-9274 ± niacin ER, evaluated separately), if an event meeting the definition of a DLT, but without necessarily occurring within the first 28 days, is observed in >33% of patients at any time, **or if >33% of treated patients have withdrawn consent due to toxicity, enrollment will be held and a meeting with all investigators and Karyopharm/Medical Monitor will take place to review the events and discuss their clinical significance. Based on this review**, the sponsor may elect to reduce the dose for enrolled patients and to resume enrollment of the expansion cohort at this lower dose, or the enrollment into the expansion cohort will may be stopped. Since the target patient population is patients who are not candidates for anti-tumor regimens known to provide clinical benefit, no formal futility monitoring is planned for the expansion cohort.

- **Modified Sections:** Synopsis, Section 11.8

7. **Provide futility stopping criteria after the dose escalation phases. Subjects should not be enrolled in the dose expansion cohorts if there is no evidence of clinical benefit.**

- **Change**: The protocol has been modified to require at least one clinical response in the first 10 patients in the RP2D cohort prior to full dose expansion.

  Change From:

  > After declaring the RP2D ± niacin ER, based on the safety and tolerability results of the Dose Escalation Phase, up to 65 additional patients (up to 20 patients in the KPT-9274-only cohort and up to 45 patients in the KPT-9274 + niacin ER cohort) with advanced solid malignancies and NHL may be enrolled to further explore safety, tolerability and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274 ± niacin ER. Each cohort may be expanded at the time the RP2D for that

cohort is declared. Note that preliminary clinical results may define the patient population (i.e., specific indications) selected for enrollment in the Dose Expansion Phase.

Change To:

After declaring the RP2D ± niacin ER, based on the safety and tolerability results of the Dose Escalation Phase, **at least one clinical response (minimum of stable disease ~8 weeks) must be seen in any of the first ten patients treated at the RP2D in order to fully enroll the 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 escalation will not be dependent upon demonstration of clinical benefit of the single agent, but futility at the KPT-9274 + niacin RP2D will be assessed prior to full expansion using the same criterion as described above for the single agent KPT-9274. During the Dose Expansion Phase,** up to 65 additional patients (up to 20 patients in the KPT-9274-only cohort and up to 45 patients in the KPT-9274 + niacin ER cohort) with advanced solid malignancies or NHL may be enrolled to further explore safety, tolerability, and preliminary evidence of anti-tumor activity of the RP2D of KPT-9274 ± niacin ER. Each cohort may be expanded at the time the RP2D for that cohort is declared. Note that preliminary clinical results may define the patient population (i.e., specific indications) selected for enrollment in the Dose Expansion Phase.

- **Modified Sections:** Synopsis, Section 8.2.7**.**

8. For the biopsies on C1D26 and C6D1, include a clause that will allow patients to continue treatment if (1) a patient refused biopsy or (2) if it is the opinion of the treating physician or physician performing biopsy that the biopsy would pose significant risk to the patient or (3) if the biopsy sample obtained on first attempt was inadequate for analysis. Commensurate language should be included in the informed consent document as well.

- **Change**: The requested change has been made and incorporated into the revised protocol (Version 2.0).
- **Modified Sections:** Synopsis, Table 1-3, footnote 2, Sections 4.2, 9.5.1.

Indication

- Sarcomas have been added as an example of the advanced solid malginancy indication
  - **Rationale**: Sarcomas are an indication of interest to Karyopharm Therapeutics, as Ph1 and Ph2/3 studies in sarcoma patients treated with a different compound (selinexor) are in progress.
  - **Modified Sections:** Synopsis, Sections 1.1, 4.1.

Inclusion Criteria

- Addition of new inclusion criterion #5: "Patients must have a site of disease amenable to biopsy and be a candidate for biopsy according to the treating institution's guidelines."
    - **Rationale**: Biopsy tissue will be needed for studies to identify CCI of response, to better understand the KPT-9274 mechanisms of action and resistance, and to determine target engagement by measuring PAK4, NAMPT or changes in downstream signaling pathways. While each patient must be a candidate for biopsy at enrollment, the decision about the safety and feasibility of performing any biopsy is left to investigator and patient per guidance elsewhere in the protocol.
    - **Modified Sections:** Synopsis, Section 4.2.

- Inclusion criterion #7: decreased maximal allowable total bilirubin from ≤2 times the upper limit of normal to <1.5 times the upper limit of normal.
    - **Rationale**: Request from FDA in Study May Proceed Letter dated 03 March 2016.
    - **Modified Sections:** Synopsis, Section 4.2.

- Inclusion criterion #8: increased minimally acceptable creatinine clearance from ≥40 mL/min to ≥60 mL/min.
    - **Rationale**: Request from FDA in Study May Proceed Letter dated 03 March 2016.
    - **Modified Sections:** Synopsis, Section 4.2.

Assessments

- Modified the frequency of select clinical safety assessments (weight, symptom-directed physical exam) and clinical laboratory assessments (urinalysis, complete blood count with differential, complete serum chemistry).
    - **Rationale**: Minor adjustments to reflect appropriate frequency of assessments relative to the frequency of clinic visits, and for consistency between schedule of assessment tables and section 6.2.
    - **Modified Sections:** Schedule of Assessments (Tables 1-3), Section 6.2.

- Added a pre-dose ECG on Cycle 1 Day 26, resulting in coincident pre-dose and 4 hour post-dose (estimated KPT-9274 T_{max}) ECGs and PK blood samples.
    - **Rationale**: Address request from FDA in Study May Proceed Letter dated 03 March 2016 to include sampling to capture large cardiac safety signals. The time matched C1D26 pre- and post-dose PK samples and ECGs will allow pre- and post-dose (at estimated KPT-9274 T_{max}) assessment of cardiac changes after 4 weeks of dosing. These data will allow comparison of cardiac changes after one dose (C1D1) and after 4 weeks of dosing (C1D26).
    - **Modified Sections:** Schedule of Assessments (Table 1 and footnote #5), Section 6.2.2.5.

- Changed frequency of disease assessment scans for solid malignancy patients from every 6 weeks to every 8 weeks; indicated that EoT scans are only required for patients who end treatment for reasons other than disease progression.
    - **Rationale**: Standardize frequency of disease assessments for solid malignancy and NHL patients; eliminate EoT scan for patients who had a disease assessment scan at the time of their disease progression prior to EoT visit.
    - **Modified Sections:** Schedule of Assessments (Tables 1-3), Sections 6.2, 9.3.2, 9.3.3.

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References

- Removed two references that do not appear in the protocol.
    - **Rationale**: Correction of text errors.
    - **Modified Section:** Section 13.