Statistical Analysis Plan

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Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
V.0.1	30-Nov-2016	[redacted]	Initial Release Version
V.0.2	07-Feb-2017		2nd Draft SAP
V.1.0	25-Apr-2017		Final SAP
V1.1	07-Sep-2017		Add PK/PD parameter derivation sections
V1.2	25-Sep-2017		Address Alkermes comments and send 2nd draft revision SAP
V1.3	14-Dec-2018		Update SAP and shells per protocol amendment #9
V1.4	19-Nov-2019		Update SAP and shells per protocol amendment #10
V1.5	15-Jan-2020		Update SAP and shells per protocol amendment #11. Shared with Alkermes on 04 Feb 2020.
V1.6	22-Oct-2020		Update SAP and shells after iRECIST implementation in the database and request of additional specific outputs for publications, according to Protocol V12.2

Version #	**Date** (dd-mmm-yyyy)	**Document Owner**	**Revision Summary**
V1.7	08-Jan-2021	[redacted]	Update SAP following Sponsor's comments. PK, PD and ADA part removed on Sponsor's request.
V1.8	12-Feb-2021		Update SAP per Sponsor's review comments and discussions on V1.7 and updated shells from V1.6 accordingly
V1.9	02-Mar-2021		Update SAP per Sponsor's review comments on V1.8 and updated signature pages
V1.10	12-May-2021		Update SAP per Sponsor's review comments on V1.9
V1.11	31-May-2021		Update SAP per Sponsor's review comments on V1.10 • Added clarification about PK and PD related responsibilities. • Removed scheduled event and referred to protocol related sections. • Added deviation from protocol
V2.0	11-Jun-2021		Same as V1.11 but signed version

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
V3.0	03-Mar-2023	[redacted]	Update SAP and shells per protocol amendment #13. • Added extension phase. • Updated exposure analysis of ALKS 4230. • Removed exposure analysis of Pembrolizumab. • Changed laboratory data unit used in summary table from conventional unit to SI unit. Removed all iRECIST listings.

I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
[redacted] Supporting Biostatistician	**Date (dd-mmm-yyyy)**
Lead and Senior Reviewing Biostatistician [redacted], PhD Senior Principal Biostatistician	**Date (dd-mmm-yyyy)**

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AC	absolute counts
ADA	anti-drug antibodies
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
C1D1	cycle 1, day 1
C#D#	cycle #, day #
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CL	serum drug clearance
C_{last}	the last observed quantifiable concentration
CM	concomitant medication
C_{max}	maximum observed concentration
CR	complete response
CSR	Clinical study report
CTCAE	common terminology criteria for adverse events
C_{trough}	trough concentrations
DLT	dose-limiting toxicity
DCR	disease control rate
DOR	duration of response
ECG	standard 12-lead electrocardiogram

Abbreviation	Description
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
ECG	electrocardiogram
F	fold expansion of circulating CD8 T cells, Tregs, and NK cells (day 1 pre-infusion as baseline levels)
FCB_{max}	maximum observed fold change from baseline in serum concentration (Day 1 pre-infusion as baseline levels)
GCP	Good Clinical Practice
iORR	immune overall response rate
i-	immune-
iAE	immune adverse event
ICF	informed consent form
ICH	International Council for Harmonisation
iCR	immune complete response
iDCR	immune disease control rate
IDMC	Independent Data Monitoring Committee
iDOR	immune duration of response
IFN	interferon
IL-2	interleukin-2
IL-2R	interleukin-2 receptor
iORR	immune overall response rate
iPD	immune progressive disease
iPFS	immune progression-free survival

Abbreviation	Description
iPR	immune partial response
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
iSD	immune stable disease
IV	intravenous or intravenously
L1	Ligand-1
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
λ_z	terminal elimination rate constant
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer [cells]
N/A	not applicable
NSCLC	non-small-cell lung cancer
ORR	overall response rate
PCS	potentially clinically significant
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PDNC	protocol deviation and non-compliance
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term

Abbreviation	Description
PTT	partial thromboplastin time
QTcF	QT interval corrected by the Fridericia Correction Formula
RCC	renal cell carcinoma
R_{CD8}	ratio of CD8 cells to T_{regs} (day 1 pre-infusion as baseline levels)
$R_{CD8, max}$	maximum R_{CD8}
RECIST	Response Evaluation Criteria in Solid Tumors
R_{NK}	Ratio of NK cells to T_{regs} (day 1 pre-infusion as baseline levels)
$R_{NK, max}$	maximum R_{NK}
RP	relative percentage
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SE	standard error
SI	standard international system of units
SOC	system organ class
SOP	standard operating procedure
SRC	safety review committee
$t_{1/2}$	terminal elimination half-life
TBD	To be determined
TEAE	treatment-emergent adverse event
TIL	Density of tumor-infiltrating lymphocytes
TLF	table, listing and figure
t_{max}	time to C_{max}
TME	tumor microenvironment
TNF	tumor necrosis factor
$t_{CD8, max}$	time to maximum R_{CD8}
$t_{NK, max}$	time to maximum R_{NK}

Abbreviation	Description
TTR	time to response
T_{regs}	regulatory T cells
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
vs	versus
WHO	World Health Organization
WOCBP	Women of childbearing potential

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, data listings and figures (TLFs) which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives described in the latest study protocol.

2.1. RESPONSIBILITIES

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of tables, figures and listings (TLFs) detailed in this SAP text/Mock tables for safety and anti-tumor endpoints.

Alkermes will be responsible for pharmacokinetic (PK), blood-related pharmacodynamics and immunogenicity analyses and reporting. Syneos will be responsible for tumor-related pharmacodynamics (PD) listing.

STDM and ADaM data files for tumor-related PD datasets that contain tissue biomarker end points will be produced by Syneos Health. Only STDM data files for PC, blood-related PD, and ADA datasets will be produced by Syneos Health. All the PK, ADA and blood-related PD analyses will be specified in a separate analysis plan.

2.2. TIMINGS OF ANALYSES

The study will be conducted in 3 parts: Part A, a dose-escalation monotherapy part; Part B, a dose-expansion monotherapy part; and Part C, a combination therapy part with pembrolizumab. An Extension Phase is planned for subjects completing or who have completed 1 year of treatment in Part B or in Part C. There is one electronic data capture (EDC) database for Part A, Part B, and Part C together. All analysis specified in this SAP, including antitumor activity and safety, will be conducted.

No formal interim analysis is planned with respect to stopping the study early or for lack of antitumor activity purposes. Interim data cuts and analysis will be conducted to support abstract submissions, conference presentations, and/or manuscript(s).

The cut-off date of final analysis will be determined by the sponsor when more than 90% enrolled patients discontinued the treatment and all responders have been followed at least 6 months. A full set of SAP defined TLFs will be produced and used for preparing the clinical study report (CSR).

Responses in each N1 stage will be assessed to determine whether progression to the N2 stage is warranted.

3. STUDY DESIGN

3.1. PRIMARY OBJECTIVE

- To investigate the safety and tolerability of ALKS 4230 and to determine the MTD and the RP2D of ALKS 4230 in subjects with advanced solid tumors who are refractory or intolerant to therapies known to provide clinical benefit (Part A)
- To assess the safety profile and characterize antitumor activity by overall response rate (ORR) of ALKS 4230 at the RP2D in subjects with melanoma or renal cell carcinoma (RCC) (Part B)
- To characterize the safety profile and antitumor activity by ORR of ALKS 4230 administered IV in combination with pembrolizumab in subjects with advanced solid tumors (Part C)
- To describe the dose-limiting toxicity (DLT) of ALKS 4230 (Part A)

3.2. SECONDARY OBJECTIVES

- To characterize the clinical PK profile and immunogenicity of ALKS 4230 alone (Part A and Part B) and in combination with pembrolizumab (Part C)
- To investigate the clinical pharmacodynamic effects of ALKS 4230 alone (Part A and Part B) and in combination with pembrolizumab (Part C)
- To describe any antitumor activity and responses observed with ALKS 4230 (Part A)
- To evaluate duration of response (DOR), durable response rate (DRR), and time to response for subjects treated with ALKS 4230 in each of the expansion cohorts (Part B) and in combination with pembrolizumab (Part C)

3.3. EXPLORATORY OBJECTIVES

- To describe changes in post-treatment subject blood and/or tumor tissue samples as compared to baseline/pre-treatment samples (Part B)
- [redacted]

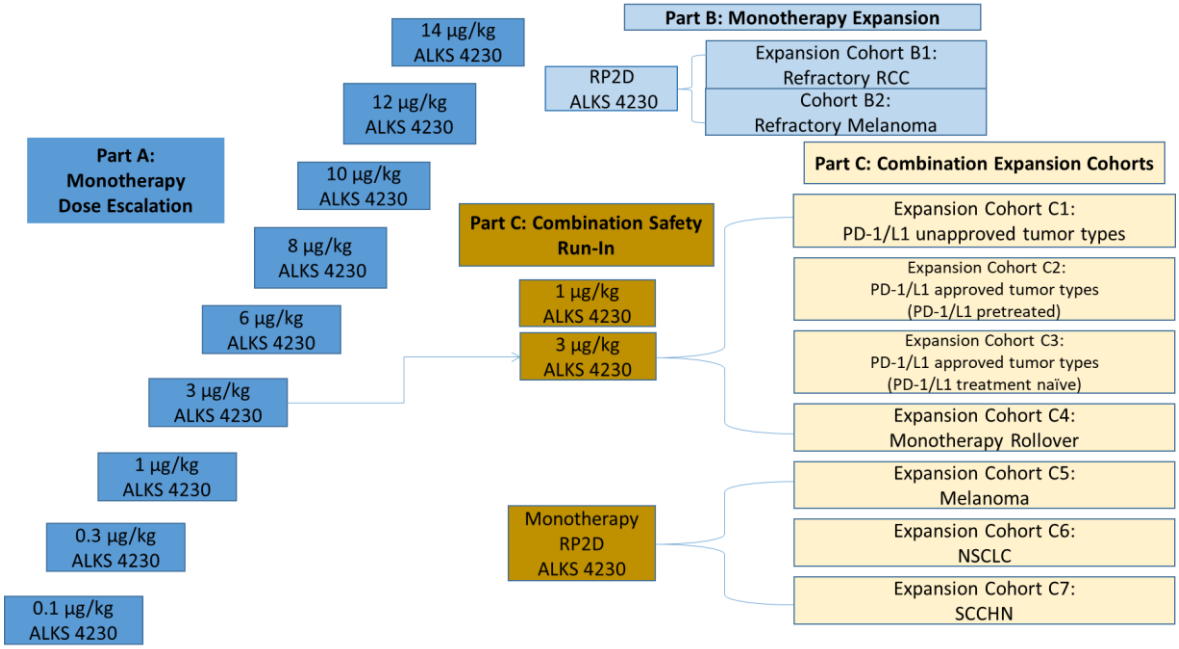
[redacted]

3.4. BRIEF DESCRIPTION

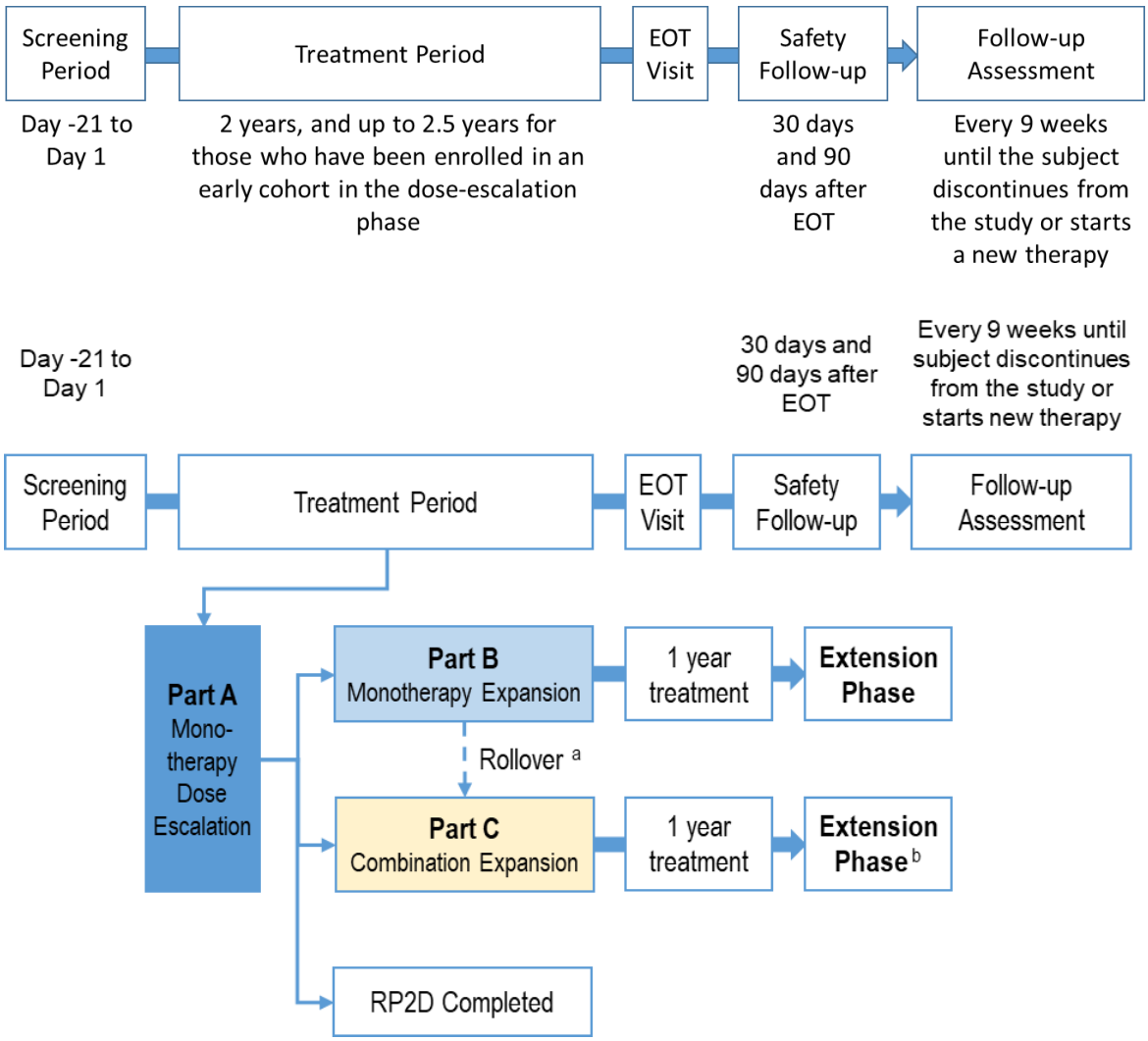
This is a global, multicenter, open-label, Phase 1/2 study. The study will be conducted in 3 parts: Part A, a dose-escalation monotherapy part; Part B, a dose-expansion monotherapy part; and Part C, a combination therapy part with pembrolizumab, as seen in the figure and table below. An Extension Phase is planned for subjects completing or who have completed 1 year of treatment in Part B or in Part C.

Figure 1: Overall Study Design Schematic

A)



B)



Abbreviations: L1=ligand-1;, EOT=End of Treatment;, NSCLC=non-small-cell lung cancer;, PD 1=programmed death receptor-1;, RCC=renal cell carcinoma;, SCCHN=squamous cell carcinoma of the head and neck;, TBD=to be determined.

[a] Rollover subjects from Part A or Part B to Part C need to complete 1 year of treatment in Part C before entering the Extension Phase.

[b] Subjects in Part C are eligible to receive combination treatment for a maximum of 2 years of treatment in total (the initial phase plus the Extension Phase of Part C). Subjects may continue ALKS 4230 as a monotherapy beyond the maximum of 2 years of treatment — both in Part B by continuing treatment or in Part C by switching to monotherapy.

Note: (Figure 1A): If a dose higher than 6 µg/kg of ALKS 4230 is found to be tolerable for Part A, that dose may be used in Part B or Part C.

Study Design Overview

Portion of the Study	Cohort	ALKS 4230 Dose (µg/kg/day)
Dose Escalation (Part A)[a]	1	0.1
	2	0.3
	3	1
	4	3
	5	6
	6	8
	7	10
	8	12
	9	14
Dose Expansion (Part B) (+ Extension Phase[b]**)**	Melanoma[a]	RP2D
	RCC	RP2D
Combination Therapy (Part C) (+ Extension Phase[b]**)**	ALKS 4230 1 µg/kg/day safety run-in	1
	ALKS 4230 3 µg/kg/day safety run-in	3
	C1: PD-1/L1 unapproved tumor types	3[c]
	C2: PD-1/L1 approved tumor types (PD-1/L1 pretreated)	3[c]
	C3: PD-1/L1 approved tumor types (PD-1/L1 treatment naive)	3[c]
	C4: Rollover	3[c]
	C5: Melanoma	6[c]
	C6: NSCLC	6[c]
	C7: SCCHN	6[c]

Abbreviations: DLT=dose-limiting toxicity, NSCLC=non-small-cell lung cancer, PD-1=programmed death receptor-1, PD-L1=programmed death ligand-1, RCC=renal cell carcinoma, RP2D=recommended Phase 2 dose, SCCHN=squamous cell carcinoma of the head and neck, TBD=to be determined.

[a] No more than 5 ocular melanoma subjects may be enrolled into this cohort.

[b] For subjects receiving clinical benefit from the treatment who are completing or have completed 1 year of treatment in Part B or Part C. Rollover subjects from Part A or Part B to Part C need to complete 1 year of treatment in Part C before entering the Extension Phase.

[c] A subject's ALKS 4230 doses may be reduced by one dose level as needed at the discretion of the Investigator.

Dose Escalation – Part A

In the dose-escalation part of the study, subjects with advanced solid tumors will receive ALKS 4230 by IV administration daily for 5 days, followed by a period off treatment in repeating cycles. During Cycle 1, the period off treatment will be 9 days, resulting in a cycle length of 14 days (2 weeks). Cycle 2 and subsequent cycles will have a period off treatment of 16 days, resulting in a cycle length of 21 days (3 weeks) for each cycle. For the first 2 treatment cycles, subjects will receive ALKS 4230 as inpatients at a medical facility with access to medical support measures and to the intensive care unit, if needed. In the absence of DLTs, subjects who remain in the study may receive subsequent doses of ALKS 4230 on an outpatient basis.

In dose escalation, cohorts in the study will use a standard 3+3 study design with 3 to 6 subjects per cohort to receive ALKS 4230 at specific dose levels described in Figure 1. The starting dose of 0.1 µg/kg/day was selected based on the minimal anticipated biologic effect level. Doses in subsequent cohorts will be increased until the optimal biologic dose is identified, or the maximum tolerated dose is reached. Additional dose levels will be considered if the RP2D or maximum tolerated dose (MTD) has not been reached within the proposed dose range.

During dose escalation, each cohort will be evaluated for safety and tolerability using a 3+3 study design with allowance for over-enrollment with 4 to 7 subjects and a minimum of 3 evaluable subjects per cohort to receive IV ALKS 4230 at the specified dose and schedule. If none of the 3 subjects experiences a DLT, then the next dose level will open for enrollment. If 1 of the 3 subjects experiences a DLT, then 3 additional subjects will be enrolled at the same dose level. If no additional DLTs are observed, then the next dose level will open for enrollment.

If 2 or more subjects experience DLTs at a dose level, no further dose escalations will occur. One or more lower dose level(s) may be tested in search of the maximum tolerated dose, defined as the dose level immediately below that in which ≥2 of 6 subjects experience DLTs. Prior to any dose escalation, a teleconference of the Safety Review Committee (SRC), to include at a minimum the study investigators who have enrolled subjects and the Sponsor's Medical Monitor, will be convened to review the safety data from the current cohort and to decide if dose escalation is warranted. An interim review of the safety data to guide the selection of the RP2D is planned prior to the start of Part B of the study using data from subjects enrolled in Part A. RP2D was determined to be 6 ug/kg.

Dose Expansion – Part B

After the RP2D is determined, the second part of the study (i.e., Part B) will begin. In this part of the study, up to 41 subjects with melanoma (including no more than 5 ocular melanoma subjects) and up to 41 subjects with RCC may be enrolled to receive ALKS 4230 at the RP2D. Enrollment to these cohorts will follow a PR (unconfirmed) Simon's two-stage design enrollment as outlined below. Response assessments will be based on the RECIST guidelines.

Simon's Two-stage Design Enrollment for Subjects in Part B

	Undesirable Rate	Desirable Rate	N1	Enroll More if	N2	Total
Expansion Cohort B1: Refractory RCC	5%	20%	21	≥2 PR/CR	20	41
Expansion Cohort B2: Refractory Melanoma[a]	5%	20%	21	≥2 PR/CR	20	41

Abbreviations: CR=complete response; PR=partial response; RCC=renal cell carcinoma
[a] No more than 5 ocular melanoma subjects may be enrolled into this cohort.

Combination Therapy - Part C

In the third part of the study (Part C), subjects will receive ALKS 4230 in combination with pembrolizumab. Part C will run independently of and concurrently with monotherapy Part A and Part B.

A 3- to 6-subject run-in phase will be utilized to assess the safety of ALKS 4230 in combination with pembrolizumab. During the safety run-in phase, subjects may be enrolled with any tumor type as described in the nonrollover cohorts. Rollover subjects (Cohort 4) are not eligible to participate in the safety run-in phase of Part C.

During the safety run-in phase, the first 3 subjects will receive ALKS 4230 at the dose level of 1 µg/kg/day. The first subject enrolled at the 1 µg/kg/day dose level will be monitored as a sentinel subject. This sentinel subject will be observed for safety for a period of 7 days (the sentinel period) from first dose of ALKS 4230. If the sentinel subject tolerates treatment adequately during this period, then up to 2 additional subjects may be enrolled into the 1 µg/kg/day dose level. If all 3 subjects tolerate therapy adequately through their first 21-day cycle as assessed by the Safety Review Committee, then the study will progress to the 3 µg/kg/day dose level. At the discretion of the Safety Review Committee, an additional 3 subjects may be enrolled at the 1 µg/kg/day dose level to further assess safety prior to opening enrollment at the 3 µg/kg/day dose level.

Once the safety run-in phase at the 1 µg/kg/day dose level is complete and the Safety Review Committee has agreed to proceed to the 3 µg/kg/day dose level, the first subject will be enrolled at the 3 µg/kg/day dose level and will be observed for 7 days as a sentinel subject. If this subject tolerates treatment adequately for 7 days, then up to 2 additional subjects may be enrolled in the following week. If the second and third subjects tolerate the 3 µg/kg/day dose level adequately for 7 days, then 3 additional subjects can be enrolled beginning the following week.

If the first 6 subjects tolerate therapy adequately for their first 21-day cycle as assessed by the Safety Review Committee, then enrollment into expansion Cohorts C1, C2, C3, and C4 will be open without restriction in the rate of enrollment at the dose determined by the Safety Review Committee.

Up to 20 subjects will be enrolled into each of Cohorts C1, C2, and C3 based on their tumor type and prior treatment with programmed death receptor-1/programmed death ligand-1 (PD-L1) pathway inhibitors as described in the inclusion criteria. Subjects with RCC or melanoma will not be eligible for enrollment in Cohorts C1, C2, or C3. Subjects on

ALKS 4230 monotherapy in Part A or Part B who have experienced disease progression after a minimum of 2 cycles or SD after a minimum of 4 cycles and who are able to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Patients who have PR or CR on monotherapy are ineligible to rollover unless demonstrating progressive disease.

Subjects will receive 200 mg of pembrolizumab every 3 weeks in combination with ALKS 4230 by IV administration daily for 5 days, followed by a period off treatment of 16 days, resulting in a cycle length of 21 days (3 weeks) for each cycle.

Once a RP2D is determined for monotherapy, enrollment into Cohorts C5, C6, and C7 will open. Should monotherapy doses above 6 µg/kg/day ALKS 4230 be shown to be tolerated, then combination dose escalation may continue for all subjects. In Cohorts C5, C6, and C7, up to 31 subjects with melanoma, up to 50 subjects with non-small-cell lung cancer (NSCLC), and up to 47 subjects with squamous cell carcinoma of the head and neck may be enrolled to receive ALKS 4230 in combination with pembrolizumab at the ALKS 4230 RP2D. Enrollment to these cohorts will follow a partial response (unconfirmed) Simon's two-stage enrollment as outlined below. Response assessments will be based on the RECIST and iRECIST guidelines.

Simon's Two-stage Design Enrollment for Subjects in Part C

	Undesirable Rate	Desirable Rate	N1	Enroll More if	N2	Total
C5: Melanoma	40%	55%	27	≥12 PR/CR	26	53
C6: NSCLC	13%	27%	18	≥3 PR/CR	24	42
C7: SCCHN	15%	30%	17	≥3 PR/CR	19	36

Abbreviations: CR=complete response; NSCLC=non-small-cell lung cancer; PR=partial response; SCCHN=squamous cell carcinoma of the head and neck

If the RP2D for the combination subjects in Cohorts C5, C6, and C7 is determined by the Safety Review Committee to be 6 µg/kg/day or above, intrapatient dose escalation may be considered for subjects in Cohorts C1, C2, C3, and C4 who had been assigned to the 1 µg/kg/day or 3 µg/kg/day dose levels and had adequately tolerated the combination therapy.

Planned Number of Subjects for Part C

Expansion Cohort: Tumor (Setting)	Number of Subjects
C1: PD-1/L1 unapproved tumor types[a]	Up to 20
C2: PD-1/L1 approved tumor types (PD-1/L1 treatment pretreated)[a]	Up to 20
C3: PD-1/L1 approved tumor types (PD-1/L1 treatment naive)[a]	Up to 20
C4: Monotherapy Rollover	Not applicable

Expansion Cohort: Tumor (Setting)	Number of Subjects
C5: Melanoma	Up to 53
C6: NSCLC	Up to 42
C7: SCCHN	Up to 36

Abbreviations: C=Cohort; NSCLC=non-small-cell lung cancer; PD-1/L1=programmed death receptor-1/programmed death ligand-1; RCC=renal cell carcinoma; SCCHN=squamous cell carcinoma of the head and neck

[a] Subjects with RCC or melanoma are not eligible for enrollment in Cohorts C1, C2, and C3.

Extension Phase (Part B and Part C only)

An Extension Phase is planned for subjects receiving clinical benefit from the treatment who are completing or have completed 1 year of treatment in Part B or in Part C. The Extension Phase will allow for assessment of long-term effectiveness, immunogenicity, and safety information in subjects receiving ALKS 4230 monotherapy or ALKS 4230 in combination with pembrolizumab, while minimizing the burden of repeated assessments for subjects and investigators.

Subjects completing 1 year of treatment will enter the Extension Phase after Cycle 18. The subjects who are already beyond 1 year of treatment will enter the Extension Phase immediately and will start following the Schedule of Assessments of the Extension Phase. The 1-year treatment period before the Extension Phase is non-cumulative, ie, in case of rollover from Part A or Part B to Part C, subjects need to complete 1 year of treatment in Part C before entering the Extension Phase.

Subjects in Part C are eligible to receive combination treatment for a maximum of 2 years of treatment in total (the initial phase plus the Extension Phase of Part C). Subjects may continue ALKS 4230 as a monotherapy beyond the maximum of 2 years of treatment — both in Part B by continuing treatment or in Part C by switching to monotherapy. Subjects will remain on the same dose and schedule when entering the Extension Phase.

3.5. SUBJECT SELECTION

The dose-escalation portion of the study (Part A) will enroll subjects with advanced solid tumors. In the monotherapy dose-expansion portion of the study (Part B), subjects with melanoma or RCC will be enrolled. In the combination therapy part of the study (Part C), subjects will be enrolled into 1 of the 7 predefined cohorts, and some subjects may be enrolled in the rollover cohort from Part A or Part B. Each subject must meet all of the inclusion and none of the exclusion criteria to participate in this study.

3.5.1. Inclusion Criteria

Each subject must meet all of the following inclusion criteria to participate in this study.

1. The subject or the subject's legal representative is willing and able to provide written informed consent.
2. The subject is aged ≥18 years.
3. For the dose-escalation portion of the study, the subject has a diagnosis of an advanced solid tumor; for the dose-expansion portion of the study (Part B), the subject has a diagnosis of melanoma or RCC.
4. In Part A, all subjects must have an advanced solid tumor (including lymphomas) that is refractory or, in the judgment of their physician, intolerant to established therapies known to provide clinical benefit for the malignancy in question. In Parts B and C, all subjects must have an advanced solid tumor and have had the minimum prior lines of therapy as defined by the specific cohort into which the subject will enroll. Treatment with prior immunotherapy is permitted, with the exception of subjects enrolling into C3, the PD-1/L1 approved tumor types (PD-1/L1 treatment naive) cohort; C5, the Melanoma cohort; and C7, the Squamous Cell Carcinoma of the Head and Neck cohort who are not permitted to have received prior treatment with an anti-PD-1/L1 therapy.
5. Subjects enrolled in the dose-expansion monotherapy part (Part B) or combination therapy part (Part C) of the study must have at least 1 lesion that qualifies as a target lesion based on RECIST.
6. Subjects enrolled in the dose-expansion monotherapy part (Part B) or combination therapy part (Part C) of the study must agree to provide archival tumor tissue biopsy sample(s). The archival tumor tissue sample does not have to be obtained prior to enrollment into the study, however every effort should be made to submit the archived tissue within 30 days of study enrollment.
7. Subjects enrolled in the combination therapy part (Part C) of the study must have completed the last dose of any broad-spectrum antibiotic at least 30 days prior to first dose (Cycle 1, Day 1).
8. Subject is ambulatory with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of at least 3 months.
9. Subjects must have adequate hematologic reserve as evidenced by:
    - Absolute neutrophil count (ANC) of ≥1000/µL,
    - Absolute lymphocyte count of ≥500/µL,
    - Platelet count of ≥75,000/µL, and
    - Hemoglobin of ≥9 g/dL (subjects may be transfused to this level if necessary).
10. Subjects must have adequate hepatic function as evidenced by aspartate transaminase and alanine transaminase values ≤3 × the upper limit of normal (ULN)

(≤5 × the ULN if the liver is known to be involved by metastatic disease) and serum total bilirubin values of ≤1.5 × ULN (≤2 × ULN for subjects with known Gilbert's syndrome) for the reference laboratory.

11. Subjects must have adequate renal function as evidenced by a serum creatinine ≤1.5 × the ULN for the reference laboratory or a calculated creatinine clearance of ≥60 mL/min by the Cockroft-Gault equation.
12. For patients with underlying chronic lung disease, and/or lung primary or metastatic disease, and/or pleural effusions, room air oxygen saturation must be ≥92%.
13. Subjects must be recovered from the effects of any previous chemotherapy, immunotherapy, other prior systemic anticancer therapy, radiotherapy, or surgery (i.e., toxicity no worse than Grade 1 [Grade 2 alopecia and treatment-associated peripheral neuropathy are acceptable]).
14. Subjects who have received standard or investigational agents must wait at least 5 half-lives or 4 weeks (whichever is shorter) following prior therapy before enrollment into the study, or 4 weeks if the half-life of the investigational agent is not known. Shorter wait periods may be permitted after discussion with the Medical Monitor.
15. Women of childbearing potential (WOCBP) must have a negative pregnancy test (serum or urine) within 7 days of the start of treatment, and on Day 1 before the first dose is administered. A woman is considered as a WOCBP (fertile) following menarche and until becoming postmenopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
16. Meets contraceptive requirements defined in the protocol. Women of childbearing potential and men (if their sexual partners are WOCBP) must use at least 2 highly effective forms of birth control, at least 1 of which is considered highly effective, throughout the study if they are heterosexually active.

In addition to the criteria listed above, to participate in Part B or Part C of the study, subjects must meet the following Part B or Part C tumor types of inclusion criteria to enroll into the cohorts identified below.

Additional Inclusion Criteria for Part B Melanoma Expansion Cohort

Subjects must have advanced melanoma. Subjects must have received an immune checkpoint inhibitor (e.g., anti-PD-(L)1 with or without anti-CTLA-4) and, if appropriate, a molecularly targeted agent (e.g., BRAF inhibitor if BRAF-mut), and no more than one prior cytotoxic chemotherapy. Patients previously treated with checkpoint inhibitor either as single-agent or in a combination regimen must have experienced objective

response or stable disease (by RECIST or iRECIST as best overall response); patients with progressive disease as best response are excluded.

Additional Inclusion Criteria for Part B Renal Cell Carcinoma Expansion Cohort

Subjects must have advanced RCC. Subjects may have received an PD-1 or PD-L1-immune checkpoint inhibitor, either given as a monotherapy or in combination with a CTLA-4 inhibitor or in combination with a VEGFR-TKI and no more than two prior systemic therapies, including the checkpoint inhibitor-based regimen. Patients previously treated with checkpoint inhibitor either as single-agent or in a combination regimen must have experienced objective response or stable disease (by RECIST or iRECIST as best overall response); patients with progressive disease as best response are excluded.

Additional Inclusion Criteria for Expansion Cohort C1: PD-1/L1 Unapproved Tumor Types

Subjects who have tumors (excluding RCC and melanoma) that have progressed following chemotherapy, and whose tumor types are not approved for treatment with pembrolizumab, may be entered in Part C, Cohort C1, if they meet the inclusion/exclusion criteria specified.

Additional Inclusion Criteria for Expansion Cohort C2: PD-1/L1 Approved Tumor Types (PD-1/L1 Pretreated): Approved Tumor Types are Based on US FDA Label

Subjects who have tumor types (other than melanoma and NSCLC, see Cohorts C5 and C6; subjects with RCC are not eligible) that are approved for treatment with pembrolizumab and have progressed on anti-PD-1/PD-L1 treatment may be entered in Part C, Cohort C2, if they meet the other inclusion/exclusion criteria specified.

Additional Inclusion Criteria for Expansion Cohort C3: PD-1/L1 Approved Tumor Types Cohort (PD-1/L1 Treatment Naive): Approved Tumor Types are Based on US FDA Label

Subjects who have tumors (excluding RCC and melanoma) that have progressed following chemotherapy and whose tumor types are approved for treatment with pembrolizumab may be entered in Part C, Cohort C3, if they have not received treatment with an anti-PD-1/PD-L1 antibody and if they meet the other inclusion/exclusion criteria specified.

Additional Inclusion Criteria for Expansion Cohort C4: Monotherapy Rollover (Rollover Subjects from Part A or Part B)

Subjects on ALKS 4230 monotherapy in Part A or Part B who have experienced disease progression after a minimum of 2 cycles or SD after a minimum of 4 cycles and who are able to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Patients who have PR or CR on monotherapy are ineligible to rollover unless demonstrating progressive disease.

Additional Inclusion Criteria for Expansion Cohort C5: Melanoma

Subjects with unresectable locally advanced (Stages IIIB, IIIC, and IIID) or distantly metastatic (recurrent or de novo Stage IV) invasive cutaneous or mucosal melanoma that is measurable and who have not received prior treatment for advanced disease and who meet the other inclusion/exclusion criteria may be considered for Part C, Cohort C5. BRAF mutation-positive patients are eligible without prior treatment or after failure of BRAF-directed inhibitor therapy. Patients treated with prior adjuvant therapy with approved agents are also eligible, provided they did not have a recurrence within the 6 months of completing adjuvant treatment.

Additional Inclusion Criteria for Expansion Cohort C6: Non-Small-Cell Lung Cancer

Subjects with Stage IIIB or IV NSCLC who have been treated with anti-PD-1/PD-L1 therapy either as single-agent or in combination with a chemotherapy regimen who responded to therapy or who had stable disease (SD) before progression after a minimum of 120 days of treatment and who meet the other inclusion/exclusion criteria may be considered for Part C, Cohort C6.

Additional Inclusion Criteria for Expansion Cohort C7: Squamous Cell Carcinoma of the Head and Neck

Subjects with recurrent and/or distantly metastatic squamous cell carcinoma of the head and neck who have not received anti-PD-1/PD-L1 therapy and who meet the other inclusion/exclusion criteria specified may be considered for Part C, Cohort C7.

3.5.2. Exclusion Criteria

Each subject must not have any of the following conditions to be qualified to participate in this study.

1. Subject is currently pregnant or breastfeeding or is planning to become pregnant during the study period.
2. Subjects with an active infection or with a fever ≥38.5°C (≥101.3°F) within 3 days of the first scheduled day of dosing
3. Subjects with active or symptomatic central nervous system metastases unless the metastases have been treated by surgery and/or radiation therapy and/or gamma knife, the subject has been tapered to a dose of 10 mg of prednisone (or equivalent) or less of corticosteroids for at least 2 weeks before the first dose, and the subject is neurologically stable.
4. Subjects with known hypersensitivity to any components of ALKS 4230

5. Subjects who require pharmacologic doses of corticosteroids (greater than 10 mg of prednisone daily, or equivalent); however, topical, ophthalmologic, and inhalational steroids are permitted.
6. Subjects with mean QT interval corrected by the Fridericia Correction Formula values of >470 msec (in females) or >450 msec (in males) at screening; subjects who are known to have congenital prolonged QT syndromes; or subjects who are on medications known to cause prolonged QT interval on ECG.
7. Subjects who developed Grade ≥3 autoimmune disorders while on prior immunotherapy (e.g., pneumonitis, nephritis, neuropathy). Subjects who have immune-mediated endocrinopathies and are stable on hormone replacement therapy are not excluded. Subjects who developed autoimmune disorders of Grade ≤2 may enroll if the disorder has resolved and the subject is off systemic steroids for ≥28 days. Subjects who experienced autoimmune colitis as a toxicity of prior immunotherapy must undergo screening colonoscopy to rule out ongoing inflammation. Vitiligo is not exclusionary.
8. Subjects with any other concurrent uncontrolled illness, including mental illness or substance abuse, which may interfere with the ability of the subject to cooperate and participate in the study; other examples of such conditions would include unstable or poorly controlled hypertension; unstable angina; myocardial infarction, or cerebrovascular accident within 6 months of study entry; New York Heart Association Grade 3 or 4 congestive heart failure; chronic obstructive pulmonary disease or diabetes mellitus that has required 2 or more hospitalizations in the last year; severe peripheral vascular disease; or recent serious trauma.
9. Subjects known to be positive for human immunodeficiency virus, hepatitis B or hepatitis C, or active tuberculosis or has a known history of tuberculosis.
10. Subjects who are employed by Alkermes, Syneos Health, the Investigator, the study center (included permanent or temporary contract workers and designees responsible for the conduct of the study), or other affiliate of this study or is immediate family of an employee of Alkermes, Syneos Health, the Investigator, the study center, or other affiliate. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
11. Subjects with known hypersensitivity to any components of pembrolizumab (Part C subjects only)
12. Subjects who have had a second malignancy within the previous 3 years. This criterion does not apply to subjects with an adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, prostate cancer Gleason score <6 with undetectable prostate-specific antigen over the previous 12 months, or ductal breast carcinoma in situ with full surgical resection.

13. Subjects with dyspnea at rest or requiring oxygen therapy.
14. Subjects with active autoimmune disease requiring systemic treatment within the past 3 months or documented history of clinically severe autoimmune disease that requires systemic steroids or immunosuppressive agents.
15. Subjects who have received systemic immunomodulatory agents within 28 days prior to C1D1. Exceptions may be granted on a case-by-case basis by the Medical Monitor
16. Subjects who have received radiotherapy within the last 4 weeks before start of study treatment administration, with the exception of limited field palliative radiotherapy.
17. Subjects who have received administration of a live, attenuated vaccine within 4 weeks before Cycle 1 Day 1.
18. Prior solid organ and/or non-autologous hematopoietic stem cell or bone marrow transplant recipients.
19. Subjects who have received prior IL-2-based or IL-15-based cytokine therapy.

3.6. DETERMINATION OF SAMPLE SIZE

The number of subjects planned to be enrolled in this study is expected to be approximately 140 to 327. This is based on an assumption of approximately 36 to 54 subjects to be enrolled in Part A, 42 to 82 subjects to be enrolled in Part B, and up to 191 subjects to be enrolled in Part C.

Number of Subjects Expected in Each Study Period

Study Period	Number of Subjects
Part A	N=36-54 (assuming 6 or 7 dose levels)
Part B	N=42-82
Part C new subjects	N=Up to 191
Part C rollover subjects	Not applicable
Part C safety run-in subjects treated at 1 µg/kg/day dose level	N=3-6
Total number of subjects exposed to ALKS 4230	N=140-327

Note: Part C rollover subjects do not contribute the total number of subjects exposed to ALKS 4230.

In Part A of the study, the number of subjects per dose level is illustrated in Overall Study Design Schematic. The number of subjects to be enrolled in Part A will depend upon the

number of dose escalations, which in turn will depend upon the safety profile of ALKS 4230. If 6 or 7 dose levels are enrolled, then the number of subjects participating in Part A is expected to be approximately 36 to 54.

Part B is designed to enroll subjects in each of 2 cohorts based on tumor type and prior therapy. The sample size of each cohort was chosen based on methodology described by Simon regarding optimal 2-stage designs for Phase 2 studies (Simon 1989). The intention in this study is to enroll cohorts that correspond to the first stage of such a design. The assumed alpha is 0.05 and power is 90%. Enrollment to these cohorts will follow a PR (unconfirmed) Simon's two-stage design enrollment as outlined in section 3.4 for Part B. Response assessments will be based on the RECIST and iRECIST guidelines.

The sample size of each cohort was chosen based on methodology described by Simon regarding optimal 2-stage designs for Phase 2 studies (Simon 1989). The intention in this study is to enroll cohorts that correspond to the first stage of such a design. The assumed alpha is 0.15 and power is 85%. Any of the following Part C cohorts may be stopped early if inadequate activity is observed:

- PD-1/L1 unapproved tumor types cohort (zero responses in the first 15 subjects)
- PD-1/L1 approved tumor types (PD-1/L1 pretreated) cohort (zero responses in the first 15 subjects)
- PD-1/L1 approved tumor types (PD-1/L1 treatment naive) cohort (≤3 objective responses in the first 20 subjects)

The Part C rollover cohort (Cohort 4) is designed to provide access to ALKS 4230 in combination with pembrolizumab for subjects initially enrolled into study Part A and Part B. It is estimated that between 0 and 54 subjects may potentially enter this cohort. Participation in the rollover cohort does not contribute to the overall number of subjects exposed to ALKS 4230. The rollover cohort will close to enrollment if the other 3 Part C cohorts have closed early due to insufficient antitumor activity. Enrollment to these cohorts will follow a partial response (unconfirmed) Simon's two-stage enrollment as outlined in section 3.4 for Part C.

3.7. TREATMENT ASSIGNMENT & BLINDING

Randomization is not planned for this open-label study.

Blinding is not applicable for this open-label study.

3.8. ADMINISTRATION OF STUDY DRUG

3.8.1. ALKS 4230 Dosing and Administration

ALKS 4230 will be administered IV as a 30-minute infusion [redacted] for 5 consecutive days, followed by a period off treatment in repeating cycles. During Cycle 1 of Parts A and B, the period off treatment will be 9 days, resulting in a cycle length of 14 days (2 weeks). Cycle 2 and subsequent cycles will have a period off treatment of 16 days, resulting in a cycle length of 21 days (3 weeks) for each cycle. Infusion for each dosing day of each cycle should begin within 2 hours (plus or minus) of the infusion start time for Day 1 of that cycle. Emergency resuscitation equipment should be available. For the first 2 treatment cycles of Part A, ALKS 4230 will be administered inpatient in a medical facility with access to medical support measures and to the intensive care unit, if needed. Subjects may be discharged on Day 6 of each of the first 2 treatment cycles if medically stable. In the absence of DLTs, subsequent treatment cycles may be administered on an outpatient basis. For Part B and Part C of the study, administration of ALKS 4230 may be done in an outpatient setting.

In Part C, on days where ALKS 4230 is administered in combination with pembrolizumab, ALKS 4230 should be administered as an infusion 60 (±30) minutes after the completion of pembrolizumab infusion. For Part C, a subject's ALKS 4230 doses may be reduced by 1 dose level as needed at the discretion of the Investigator.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes [-5 minutes/+10 minutes]).

ALKS 4230 may be infused using peripheral or central venous access per local standards of care and the treating investigator's judgement. All patients should have adequate intravenous access to allow the immediate management of toxicities. Subjects who do not have adequate peripheral venous access should have a central venous access device placed per local standards of care.

The amount of drug administered is based on subjects' body weight as measured at Day 1 (72 hours) of each cycle.

Sites must have written procedures in place detailing the healthcare personnel required to be on site during subject dosing, the availability of equipment and medications necessary to treat an emergency (should it occur) and the process for transferring a subject to a medical facility if necessary.

3.8.2. Pembrolizumab Dosing and Administration

Pembrolizumab is to be administered as an IV infusion over 30 minutes in a dose of 200 mg every 3 weeks, in accordance with the prescribing information (Keytruda

[pembrolizumab] USPI). Subjects will be monitored for at least 1 hour for potential acute reactions to pembrolizumab prior to administration of ALKS 4230.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible for either drug. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted for ALKS 4230 and pembrolizumab (i.e., infusion time is 30 minutes [-5 minutes/+10 minutes]).

Pembrolizumab is to be obtained from the study sites' pharmacies, from commercial supplies, or provided by Sponsor in countries where pembrolizumab is not yet approved.

[redacted]

3.9. STUDY PROCEDURES AND FLOWCHART

The schedules of visits and assessments for Part A, Part B, Part C, and Extension Phase of Part B and C can be found in section 8.2 of protocol.

4. ENDPOINTS

4.1. PRIMARY ENDPOINT

- The incidence of DLTs from the first dose through the end of the DLT observation period (Part A)
- The incidence and severity of treatment-emergent AEs according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher (Parts A, B, and C)
- ORR based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 (Eisenhauer et al 2009) (Part B and Part C)

4.2. SECONDARY ENDPOINTS

- Serum concentrations of ALKS 4230 and descriptive PK parameters
- Presence of anti-ALKS 4230 antibodies in serum
- Immune (i-) ORR (iORR) based on Immune RECIST (iRECIST) guidelines (Seymour et al 2017)
- Disease control rate (DCR) based on RECIST guidelines and immune DCR (iDCR) based on iRECIST guidelines
- DOR based on RECIST guidelines and immune DOR (iDOR) based on iRECIST guidelines
- DRR for Part B and Part C Cohorts C5, C6, C7 only
- Progression-free Survival (PFS) and immune PFS (iPFS) for Part B and Part C Cohorts C5, C6, C7 only
- Numbers of circulating CD8 T cells, Tregs, and NK cells in peripheral blood
- Serum concentrations of IL-6 and other cytokines

4.3. EXPLORATORY ENDPOINTS

- [redacted]

- [redacted]
- [redacted]

4.4. ANTITUMOR ACTIVITY ENDPOINTS

- Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 and Immune (i-) ORR (iORR) based on Immune RECIST (iRECIST) guidelines (Seymour et al 2017)
- Disease control rate (DCR) based on RECIST guidelines and immune DCR (iDCR) based on iRECIST guidelines
- Duration of response (DOR) based on RECIST guidelines and immune DOR (iDOR) based on iRECIST guidelines
- Progression-free Survival (PFS) based on RECIST and immune PFS (iPFS) based on iRECIST for Part B and Part C Cohorts C5, C6, C7 only
- Time to response (TTR) based on RECIST guidelines and immune TTR (iTTR) based on iRECIST guidelines

4.5. SAFETY ENDPOINTS

Safety will be assessed using the following:

- DLTs
- Treatment-emergent adverse events (TEAEs)
- Laboratory Evaluations (hematology, coagulation, chemistry, urinalysis tests)
- Vital Signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oral body temperature)
- ECG parameters (overall assessment; heart rate; RR, PR, QRS, and QTc intervals)
- ECOG Performance Status

4.6. TISSUE BIOMARKERS ENDPOINTS

Collection of fresh tumor samples via biopsy is optional during the study. Subjects with accessible tumors who are willing to undergo biopsy should provide samples at baseline and while on treatment around C2D8. A punch biopsy is preferred for tissue collection from melanoma patients.

These samples will be analyzed by immunohistochemistry and/or immunofluorescence for markers of immune activation. They can also be used for gene expression analysis using method such as NanoString. The tissue biomarker data will be presented in data listings and done separately for PART A, B and C respectively.

5. ANALYSIS SETS

5.1. SAFETY POPULATION

In Part A and Part B, the Safety Population will include all subjects who receive at least 1 dose of ALKS 4230. In Part C, the Safety Population will include all subjects who receive at least 1 dose of ALKS 4230 or pembrolizumab. The Safety Population will be used for all safety analyses.

5.2. ANTITUMOR EVALUABLE POPULATION

The Antitumor Evaluable Population consists of all subjects who complete two cycles of therapy and have at least one follow-up scan.

The Antitumor Evaluable Population will be used for the antitumor activity analyses.

5.3. PROTOCOL DEVIATIONS

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed. The list of protocol deviations will be finalized per the protocol deviation and non-compliance (PDNC) management plan and will be reviewed by the Sponsor, the principal investigator, the study statistician, and the study medical monitor and finalized before database lock. Only major protocol deviations will be summarized.

5.4. PHARMACODYNAMIC POPULATION

The Pharmacodynamic Population consists of all subjects who received at least 1 dose of ALKS 4230 and have at least 1 available post-baseline pharmacodynamics measurement.

Subjects who may have had any AEs or protocol deviations that are deemed to impact the pharmacodynamics measurements may be excluded from the pharmacodynamics analysis and summary statistics, which will be documented in the clinical study report.

The Pharmacodynamic Population will be used for the pharmacodynamic parameter calculations, graphical displays of individual data, and the listings of cytokine concentrations and pharmacodynamic parameters.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

- Data will be summarized for Part A, Part B, and Part C separately when analysis is applicable for the part. For Part A, the summary tables will be presented by dose cohorts (0.1 µg/kg, 0.3 µg/kg, 1 µg/kg, 3 µg/kg, 6 µg/kg, 8 µg/kg, and 10 µg/kg ALKS 4230) and overall, and data listings will be ordered by dose cohorts and subject ID. For Part B, the summary tables will be presented by expansion cohorts with specified tumor types (RCC and Melanoma) and overall, and data listings will be ordered by expansion cohorts and subject ID. For Part C, the summary tables will be presented by cohorts based on subject's tumor type and prior treatment with PD-1 or rollover from Part A or B (Safety Run-in 1 ug/kg, Cohort 1: PD-1/L1 unapproved tumor types plus Safety Run-in 3 ug/kg, Cohort 2: PD-1/L1 approved tumor types (PD-1/L1 pretreated), Cohort 3: PD-1/L1 approved tumor types (PD-1/L1 treatment naïve), Cohort 4: Monotherapy Rollover, Cohort 5: Melanoma, Cohort 6: NSCLC, Cohort 7: SCCHN), and overall, and data listings will be ordered by cohorts and subject ID.

- The continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum unless otherwise specified. All estimations will include a point estimate and the corresponding 95% confidence interval. All mean (arithmetic and geometric) and median values will be formatted to 1 more decimal place than the measured value. SD values will be formatted to 2 more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. The coefficient of variation (CV) % will be formatted to 1 decimal point.

- The categorical variables will be summarized using frequency counts and percentages of subjects. All percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).

- P-values will be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then it will be presented as >0.999.

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs, unless specified differently in specific analyses.

- For concomitant medications and AEs, which are not associated to a visit, the cycles are determined based on their start dates. For other collected data, the cycles are determined based on their visit dates. When there are multiple laboratory records for a scheduled visit, the one closest to the target date (relative to the Day 1 in that cycle) will be used for analysis. If there are 2 or more records (for repeated test, for example) with the same time period to the target date, the later one will be used for analysis unless specified differently in specific analyses.

- Partial AEs/concomitant medications start/end dates will be imputed on the rules specified in Section 6.3.1.
- The cumulative tumor response and AE data will be summarized for subjects who enter into the Extension Phase.
- All laboratory data will be reported using international system of units.
- All analyses will be performed using SAS® statistical software package, version 9.4 or higher.

6.2. KEY DEFINITIONS

6.2.1. Cycle 1 Day 1

Cycle 1 Day 1 (C1D1) is defined as the date of the first dose of ALKS 4230 in the first dosing cycle. For rollover patients, C1D1 is the date of first ALKS 4230 dosing for each part respectively.

6.2.2. Enrollment

A subject is considered enrolled onto the study if a patient signed a consent form. The enrollment date is set to consent date.

Screen failures will not be recorded in the database.

6.2.3. Treatment Period

The treatment period starts on C1D1 and lasts until the end of the treatment date collected in the database

6.2.4. Study Day

The study day is determined relative to C1D1 in the study, while the cycle day is the day relative to the first dose date in that cycle. The day of the first dose of study medication in Cycle 1 will be defined as Study Day 1. The day prior to the first dose of study medication is Study Day -1. There is no Study Day 0.

6.2.5. Cycle Start/End Day

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the cycle will be the date when the subject receives the first study drug of the cycle, noted as S1, S2, S3, etc. For the Lead-In Monotherapy cycle, the start date will be the first date when the subject receives ALK 4230 Monotherapy. For the combination cycles, the start date will be the first date the subject receives the ALK 4230 + Pembrolizumab combination therapy.

The end date of each cycle is calculated as the day before the start date of the following cycle: ie, $E_i = S_{i+1} - 1$. For the last cycle, the end date will be calculated based on the last study dose date. The cycle end date is the last dose date + 16 except when cycle 1 is the last cycle in Parts A and B, for which the cycle end date is the last dose date + 9.

6.2.6. Cut-Off Date of Final Analysis

This study has not specified the treatment duration. For the purpose of final analysis, the cut-off date of final analysis will be determined by the sponsor when more than 90% enrolled patients discontinued the treatment and all responders have been followed at least 6 months. This will be considered as the main analyses. A full set of SAP defined TLFs will be produced and used for preparing the clinical study report (CSR).

6.2.7. Baseline and Change from Baseline

Study Baseline

Baseline value is defined as the last value prior to the first dose of study treatment administration. This value could be the pre-infusion assessment on the first dose date or the assessment at the screening visit. If multiple values are present for the same date, the values from the last assessment will be used as the baseline unless specified. The standard 12-lead ECGs will be performed in triplicate 5 minutes apart at all time points outlined in the protocol. The median value of the last triplicate ECGs prior to the first dose of study treatment will be used for summary purposes.

Part C Baseline for Rollovers

Baseline value is defined as the last value prior to the first dose of study treatment administration in Part C. This value could be the pre-infusion assessment on the first dose date. If multiple values are present for the same date, the values from the last assessment will be used as the Part C baseline unless specified. The standard 12-lead ECGs will be performed in triplicate 5 minutes apart at all time points outlined in the protocol. The median value of the last triplicate ECGs prior to the first dose of study treatment will be used for summary purposes.

The rollover subjects have two baseline values. The study baseline values are used for Part A and Part B analysis, and Part C baseline values are used for Part C analysis.

Absolute change from baseline (CFB) = (post-baseline value – baseline value).

Fold change from baseline (FCB) = post-baseline value/ baseline value.

For the purpose of tabulations for lab, ECG and vital sign, the unscheduled post-baseline values generally will be excluded from summary tables, but will be included in the listing. Unscheduled visits will be considered for analyses of worst CTCAE laboratory grades.

6.3. MISSING DATA

All available data of the subjects who withdraw from the study for any reasons will be analyzed. There will be no imputation of missing data for the analysis, except for partial dates specified below.

If the date and/or time that an AE started is incomplete, the event will be considered a TEAE unless the partial dates/times give sufficient detail in order to prove that the AE started prior to the first dose in the study. In such cases the event will not be considered a TEAE.

For rollover subjects, if the date and/or time that an AE started is incomplete, the event will not be considered a Part C TEAE unless the partial dates/times give sufficient detail to prove that the AE started on or after the first dose of Part C in the study.

If the date that a medication started is incomplete, the medication will be considered as concomitant unless the partial date(s) give sufficient detail in order to prove that the medication was started and stopped prior to the day of first dose in the study. In such a case, the medication will be considered as prior medication.

For rollover subjects, if the date that a medication started is incomplete, the medication will be considered as Part C concomitant unless the partial date(s) give sufficient detail in order to prove that the medication was started and stopped prior to the day of first dose of Part C in the study.

6.3.1. Imputation of Missing Adverse Events/Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the same as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the same as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.

- If either the year of the partial date is before the year of the first dosing date or the year of the partial date and the first dosing date are the same but the month of partial date is before the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is after the year of the first dosing date or the year of the partial date and the first dose date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed, and the corresponding AE will be included as a TEAE of all study parts to which it is applicable.

Incomplete Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.

- If the year of the incomplete stop date is after the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.

- If either the year of the partial date is not equal to the year of the last dosing date or the year of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

6.4. VISIT WINDOWS

Data collected at unscheduled visits that occurred outside the time windows specified in the protocol (e.g., postdose laboratory tests done on days not specified in the protocol) will be included in the data listings but will not be included in analyses summarized by timepoint unless otherwise stated.

For summaries by time point, if data is collected at multiple time points within a protocol specified time window (protocol section 8.2), the result taken at the closest time to the planned nominal time point will be used, unless specified otherwise. If this time is equal to either side of the nominal time-point for 2 measures, the earlier measure will be taken.

6.5. POOLING OF CENTERS

Data from all study centers will be combined for analysis.

6.6. SUBGROUPS

Some analyses by subgroups are planned, for example subgroup analysis based on the tumor type.

6.7. HANDLING PHARMACODYNAMICS DATA BELOW THE LOWER LIMIT OF QUANTIFICATION OR MISSING

For pharmacodynamic immunophenotype results, serum cytokine concentration summary, individual serum cytokine concentration versus time curves, and mean concentration versus time graphs, the following rules will apply:

- Serum cytokine concentration values below the assay's lower limit of quantification (LLOQ) for all time points will be treated as ½ of the LLOQ.
- For baseline with missing values, the fold change from baseline for relevant pharmacodynamic parameters will not be calculated. The sampling time of pre-infusion samples relative to dosing will be treated as zero.
- If the actual time of sampling is missing, the nominal time will be used.
- No further imputation will be applied to any missing values.

- If one or both AC values are missing at a time point for NK and T_{reg} cells or for CD8 T and T_{reg} cells, then no ratios ($R_{NK/Treg}$ or $R_{CD8/Treg}$) will be calculated for the time point.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

The total number of subjects enrolled to each study part will be summarized separately for Part A, Part B, and Part C. A summary of subject disposition will be presented for the Safety Population, Antitumor Evaluable Population and subjects who discontinued from the treatment and discontinued from the study.

Reasons for treatment discontinuation and study discontinuation will be summarized for all subjects with the following categories:

- Adverse event
- Lost to follow-up
- Pregnancy
- Noncompliance resulting in a protocol deviation
- Study terminated by sponsor
- Withdrawal by subject
- Progressive disease
- Clinical progression
- Physician decision
- Rollover from monotherapy to combination therapy (Part C) (this is only applied to part A and Part B disposition tables)
- Other

Subjects' completion/discontinuation status will be listed, including subject identifier, informed consent date, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation.

Inclusion/exclusion criteria definitions and violations will be listed. If no inclusion/exclusion violations are reported, this will be noted in place of the listing.

Major protocol deviations will be summarized by categories for all subjects. All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age (years), height (cm), weight (kg), and BMI (kg/m^2) at baseline will be summarized descriptively. Sex, race, ethnicity, BMI category (underweight: < 18.5 kg/m^2, normal: 18.5 - <25 kg/m^2, overweight: 25 - <30 kg/m^2, and obesity: ≥30 kg/m^2), and ECOG performance status (0, 1, >1) will be summarized by frequency counts. Body mass index is calculated based on weight and height at baseline.

Demographic data and baseline characteristics (as detailed above) as well as informed consent data will be listed.

Descriptive statistics for prior line of therapy will be summarized.

7.3. CANCER DISEASE HISTORY

Cancer disease history will be summarized. The number and percentage of subjects in each of the following categories will be presented.

- Method of Initial Diagnosis
- Primary Origin of Tumor Type

The time from initial diagnosis to first dose (years) and time from most recent disease progression to first dose (weeks) will be summarized descriptively.

Cancer disease history will be listed for the Safety Population.

7.4. MEDICAL HISTORY

Reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher. General medical history information will be summarized by category of medical history being collected. Medical history will be listed for the Safety Population.

7.5. PRIOR SURGERIES AND THERAPIES

A frequency tabulation of the number of subjects with previous cancer-related surgery, radiation therapy, and systemic therapy will be given. In addition, tabulation will be provided by location of radiation therapy and type of previous systemic therapy.

Prior cancer-related surgery, prior radiation therapy, and prior systemic therapy will be listed.

7.6. PRIOR AND CONCOMITANT MEDICATION

Prior medications will be defined as any medications taken prior to the C1D1. Concomitant medications will be defined as medications ongoing or stopped on or after the date of the first dose of ALKS 4230.

Prior and concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary version March 2016 or higher.

The number and percentage of subjects using each concomitant medication will be displayed together with the number and percentage of subjects using at least 1 medication within each medication group and subgroup. Prior medications will be presented in a data listing only.

8. EFFICACY

Antitumor activity will be determined by the measurement of extent of known disease at baseline and approximately every 5 to 6 weeks, following each even-numbered treatment cycle. Appropriate radiological procedures (computed tomography (CT) scanning, magnetic resonance imaging (MRI), radionuclide imaging) should be conducted to evaluate areas of disease. Superficial skin tumors will be measured with calipers and photographed for evaluation. It is requested that the initial method of measurement be maintained throughout the course of the study. The determination of response will be conducted according to the standard RECIST 1.1 criteria as well as the iRECIST for part A, B, and C.

According to the guidelines for RECIST 1.1, tumors are assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Responses assigned using iRECIST have a prefix of “i” e.g., “immune” complete response (iCR) or partial response (iPR), stable disease (iSD), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1.

RECIST 1.1 and iRECIST have the same overall response until RECIST 1.1 progressive disease (PD) is reached. The iRECIST CRF will be used if patient has a RECIST disease progression and clinical stable, and continues on treatment. The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage. iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation.

As the iRECIST CRF page is only triggered after patients has iUPD and clinical stable. In the process to create iRECIST analysis dataset, the tumor response data before iUPD will be copied from RECIST 1.1

To note, determination of response is conducted according to iRECIST beginning with Amendment 10. Prior to Amendment 10 it was conducted by IrRC.

In studies with immunotherapeutic agents, CR, PR, or SD have been shown to occur after an increase in tumor burden characterized as PD by RECIST criteria. The conventional response criteria such as RECIST may not adequately assess the activity of immunotherapeutic agents. PD evaluated radiologically may not mean therapeutic failure, as responses to immune therapies may occur after conventional PD. The appearance of measureable antitumor activity may take longer for immune therapies than for cytotoxic therapies. With immunotherapeutic agents, there should be allowance for clinically insignificant PD, defined as small new lesions in the presence of other responsive lesions, which may occur even though the subject is responding to the immunotherapy. Stable disease may also represent antitumor activity with iRECIST. Therefore, RECIST and

iRECIST will be used to ensure a more comprehensive evaluation of tumor response for ALKS 4230.

Efficacy endpoints based on irRC and iRECIST will not be derived and associated analyses will not be performed as the iRECIST was implemented during the middle of the study conduct to replace irRC. The sites have not consistently record the iRECIST data which could provide misleading information.

8.1. OVERALL RESPONSE RATE (ORR)

ORR is defined as the proportion of subjects with objective evidence of complete response (CR) or partial response (PR) among the number of subjects evaluable for antitumor activity based on RECIST.

At the analysis stage, the best overall response (BOR) will be assigned for each subject as the best response recorded after initiation of study treatment, where the confirmation of CR or PR is required. The BOR assignment will follow the table below.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

If applicable, responses recorded after initiation of new anticancer treatment will be excluded.

The BOR will be calculated separately for those subjects in the dose-escalation portion of the study (Part A), in the dose-expansion portion of the study (Part B), and in the combination therapy part of the study (Part C). The BOR will be summarized by cohorts for Part A, Part B, and Part C. In addition, the subjects who have SD more than 6 months will be summarized.

Summarization of ORR will be presented by frequency counts, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

The sum of the diameters of all target lesions reported at each visit will be graphed by spider plot (% change in target lesion over time) and waterfall plot (best % change in target lesion). A swimmer plot will be used to display the characteristics of the overall responses over time.

In addition, listings of RECIST overall evaluation, target lesions, non-target lesions, and new lesion will be provided.

8.2. DISEASE CONTROL RATE (DCR)

DCR is defined as the proportion of subjects with objective evidence of CR, PR (where CR or PR requires confirmation), or SD (where the SD requires to occur at Cycle 4 or later).

The DCR will be calculated separately for those subjects in the dose-escalation portion of the study (Part A), in the dose-expansion portion of the study (Part B), and in the combination therapy part of the study (Part C).

Summarization of DCR will be presented by frequency counts, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

8.3. DURATION OF RESPONSE (DOR) (PART B AND PART C)

DOR is defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause based on RECIST.

The DOR will be calculated for RECIST responders.

Censored subjects:

- Subjects who are alive and progression free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment before initiation of any new anticancer treatment.
- Subjects with two or more consecutive missing response assessments prior to death or a visit with documented progression will be censored at the last date of tumor assessment when the subject was documented to be progression free.

Subjects who never achieve CR or PR prior to starting any new anti-cancer treatment at a lesion site will be excluded from the analysis.

If no CR/PR prior to starting any new anti-cancer treatment	excluded from the analysis
If responder (CR/PR) and then PD/death Without start of new anticancer	no censor

If responder (CR/PR) and then start of new anticancer (with PD/death or not, after this start of new anticancer)	date of last evaluable tumor response assessment before new anticancer is censor date
If responder (CR/PR) and then PD/death Without start of new anticancer But with two or more consecutive missing response assessments prior to PD/death	date of tumor assessment when the subject was documented to be progression free is censor date

For Part B, the DOR will be calculated as follows (in weeks):

(date of PD /death in Part B – date of first response (CR or PR) in Part B + 1)/7

For Part C, the DOR will be calculated as follows (in weeks):

(date of PD/death in Part C – date of first response (CR or PR) in Part C + 1)/7

The distribution of DOR will be estimated for Part B and Part C using Kaplan-Meier methodology. The median point estimate DOR will be provided along with the two-sided 95% CIs for the antitumor evaluable population. Kaplan-Meier curves will be provided.

Part A DOR information will be listed only.

To help in interpretation of the response data, a table with change on the frequency of scans may be provided.

8.4. DURABLE RESPONSE RATE (PART B AND PART C)

Durable response rate is defined as the percentage of patients with an objective response (complete or partial response per RECIST1.1) lasting continuously for 6 months and starting any time within 12 months of initiating the study drug. The DRR will be summarized by each tumor type.

Summarization of DRR will be presented by frequency counts, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

Analysis of Durable Response Rate will only be conducted as needed as the data allows.

8.5. PROGRESSION-FREE SURVIVAL (PFS) (PART B AND PART C COHORTS C5, C6, C7 ONLY)

PFS is defined as the time from the first dose of ALKS 4230 to the first documentation of objective tumor progression based on RECIST or death due to any cause.

The protocol stated that the PFS analysis will be only performed for Part B and Part C (Cohorts 5-7). The additional PFS analysis in ovarian patients from the PD-L1 unapproved

cohort will be conducted as ovarian is identified as one of tumor types to advance further clinical development in ALKS 4230 in combination with Pembrolizumab.

Subjects who do not have disease progression or have not died will be censored at the last known time that the subject was progression-free.

Censored subjects:

- If a subject begins a new anticancer treatment (either systemic or local) prior to documented progression or death, or a subject is removed from the study due to undocumented clinical disease progression, then the subject will be censored at the last assessment where the subject was documented as progression-free prior to the intervention.
- Subjects with two or more consecutive missing response assessments prior to a visit with documented progression (or death) will be censored at the last date of tumor assessment when the subject was documented to be progression free.

If no PD/death Without start of new anticancer	the last known time that the subject was progression-free is censor date
If start of new anticancer prior to PD/death or a subject is removed from the study due to undocumented clinical disease progression	date of last assessment where the subject was documented as progression-free prior to the intervention is censor date
If two or more consecutive missing response assessments prior to PD/death	date of the last date of tumor assessment when the subject was documented to be progression free is censor date

For Part B, the PFS will be calculated as follows (in weeks):

(date of PD /death in Part B – first dose date in Part B + 1)/7

For Part C, the PFS will be calculated as follows (in weeks):

(date of PD /death in Part C– first dose date in Part C + 1)/7

The survival distribution of PFS will be estimated using Kaplan-Meier methodology. The median RECIST PFS will be provided along with the two-sided 95% CIs based on the antitumor evaluable population. In addition, Kaplan-Meier curves will be provided. The 6-month and one-year PFS rate will be estimated using the Kaplan-Meier estimate.

8.6. TIME TO RESPONSE (TTR) (PART B AND PART C)

TTR is defined as the time from the date of first dose of study drug to the first documentation of response (CR or PR) based on the RECIST.

The TTR will be calculated for RECIST responders.

For Part B, the TTR will be calculated as follows (in weeks):

(date of first response (CR or PR) in Part B – date of first study drug in Part B + 1)/7

For Part C, the TTR will be calculated as follows (in weeks):

(date of first response (CR or PR) in Part C – date of first study drug) in Part C + 1)/7

The TTR will be summarized with descriptive statistics by cohorts for Part B and Part C.

9. SAFETY ANALYSES

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of AEs, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

9.1. EXTENT OF EXPOSURE

The ALKS 4230 administration profile will be summarized by each part and cohort for the safety population with respect to duration of exposure, number of doses by cycle, cumulative doses received, number of cycles, average number of ALKS 4230 per cycle, relative dose intensity, duration of treatment and duration of study follow-up time. Number of patients who missed the dose will also be summarized by planned dosing day and by cycle. Data will also be summarized for subjects with any infusion interruptions and reason for interruption, and subjects with dose adjustments.

For rollover subjects from Part A or Part B, subjects will start with 3ug/kg as per protocol. However, some subjects might start with 6ug/kg as Part C C1D1 dosing. Therefore, the 6ug/kg should be used in relative dose intensity calculation in the denominator as planned dose.

In addition, the dose might be adjusted (either increase or decrease the dose) due to tolerability or other reasons after C1D1. In the relative dose intensity calculation, C1D1 dose is carried forward to the end of treatment as planned dose regardless dose changes during the treatment period.

Duration of exposure (days) = last dose date – first dose date + 1.

Treatment duration (days) = end of treatment (EOT) date – first dose date + 1, in which the last cycle end date will replace EOT date if the latter is missing.

In case of missing last cycle end date for rollover subjects in Part A or Part B, treatment duration (days) will be calculated as Part C cycle 1 day 1 date – Part B cycle 1 day 1 date + 1. If rollover subjects missing last cycle end date in Part C, take the last dose date in Part C + 16 days as the last cycle end date.

Relative dose intensity (%) = 100 × [total dose received (ug/kg) / total protocol planned dose (ug/kg)].

Duration of study (days) = end of study (EOS) date – first dose date + 1.

For those subjects with infusion interruptions, the reason for interruption will be summarized. If the subject has multiple interruptions caused by the same reason, the subject is only counted once per reason category.

Dose reductions and treatment discontinuations will be recorded on the eCRF, along with the AE/SAE or DLT that was associated with the change in dosing.

ALKS 4230 and pembrolizumab will be administered at a medical facility or study center by study staff; therefore, compliance is ensured. The treatment compliance will not be analyzed.

9.2. DOSE-LIMITING TOXICITIES

A DLT is defined by any of the following events possibly, probably, or definitely related to ALKS 4230 that are observed during the interval from C1D1 through C2D15:

- Grade 4 neutrophil count decreased (neutropenia) that has not recovered to Grade 2 (≥1,000 cells/mm3) within 15 days of the start of the cycle or requires an urgent intervention (e.g., use of hematopoietic colony-stimulating factors) or is associated with clinically significant infection. Dosing with ALKS 4230 in the current cycle will not be stopped due to neutropenia in the absence of urgent intervention or clinically significant infection

- Febrile neutropenia (ANC <1,000 cells/mm3 with temperature >38.3° C [101° F]) that persists for more than 48 hours or requires an urgent intervention (eg, use of hematopoietic colony-stimulating factors) or is associated with clinically significant infection

- Grade 4 thrombocytopenia that does not recover to Grade ≤2 within 15 days of the start of the treatment cycle

- Thrombocytopenia with a platelet count <30,000 with clinically significant bleeding

- Any Grade 3 cardiac or central nervous system toxicity

- Liver transaminase elevation higher than 8 × ULN or total bilirubin higher than 6 × ULN that does not recover to Grade ≤2 or baseline within 1 week

- Grade 4 hypoalbuminemia

- Fever >40°C sustained for >24 hours

- Hypotension requiring the use of pressors (eg, phenylephrine or dopamine, administered for the purpose of increasing blood pressure) or prolonged hospitalization (>48 hours) for hypotension requiring medical intervention

- Grade 3 or higher electrolyte abnormalities that do not recover to Grade ≤1 within 48 hours following medical management

- Increase in amylase or lipase that meets 1 of the following criteria:
    - Asymptomatic Grade 4 elevation
    - Asymptomatic Grade 3 elevation that does not resolve within 14 days
    - >3 × ULN with acute severe abdominal pain (other mild symptoms at Grade 3 will not be considered as DLTs)
- Grade 3 or higher nausea, vomiting, or diarrhea lasting longer than 48 hours despite maximum supportive care is a DLT.
- Any other Grade 4 non-hematologic toxicity or any other Grade 3 non-hematologic toxicity that does not resolve to Grade ≤2 within 96 hours, other than fatigue or anorexia. Fatigue and anorexia will not be considered DLTs.
- Any other toxicity or AE not defined above that results in subject removal from the study or discontinuation of dosing by the Investigator (dose delays during Cycle 2 or later are not considered DLTs)

Any laboratory value that meets the DLT criteria as described above must be confirmed with a second laboratory test for DLT criteria to be met.

Subjects without a DLT who receive fewer than 10 doses through C2D15 will be replaced at the same dose level if the minimum number of evaluable subjects has not been reached for the cohort. However, the subject may remain in the study if the Investigator feels the risk/benefit ratio is acceptable.

All DLTs will be summarized by system organ class and preferred term, and by cohort for Part A, and a corresponding listing of DLTs-like will be provided for Part A.

9.3. ADVERSE EVENTS

Adverse events will be analyzed in terms of TEAEs, which are defined as AEs that are newly occurring or worsening from the time of the first dose of study drug. Reported AE terms will be coded using MedDRA version 25.0 or higher. The severity of the toxicities of AEs will be graded according to the NCI CTCAE version 4.03 or higher.

The severity of toxicities of AE is graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or fatal (grade 5).

The relationship to study treatment is evaluated as definitely related, probably related, possibly related, probably not related, and definitely not related. Events will be classified as related vs non-related. A related AE is an event with a relationship to treatment as definitely related, probably related, or possibly related to study drug; a non-related AE is an event with relationship to treatment as probably not related, or definitely not

related. If the relationship to the study treatment is missing, the TEAE will be considered to be treatment-related for table summary purposes.

TEAEs will be summarized by SOC and PT and by cohort. Some outputs with TEAEs based on tumor type may be produced for submission purpose. TEAEs with onset after the last dose of the study treatment period are attributed to the treatment received during the treatment period. Both event and subject counts will be summarized. Subject counts will be complemented by percentages calculated using the number of subjects exposed to study drug as the denominator.

The following summaries will be provided:

- An overall summary of the number and percentage of subjects reporting TEAEs, serious TEAEs, grade 3 or higher AEs, death, treatment-related TEAEs, and TEAEs leading to study discontinuation, leading to treatment discontinuation, leading to dose reduction, leading to dose interruption
- TEAEs by SOC and PT (including all severity grades)
- Most common (>= 10%) TEAEs by SOC and PT
- TEAEs by SOC, PT, and worst severity grade
- TEAEs by SOC, PT, and highest relationship (Related, Not Related), for Part C the highest relationship to ALKS and Pembrolizumab will be summarized in separate tables
- ALKS 4230-related TEAEs by SOC and PT
- Pembrolizumab-related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Treatment-related Serious TEAEs by SOC and PT
- Grade 3 or higher related TEAEs by SOC and PT
- TEAE leading to treatment discontinuation by SOC and PT
- TEAE leading to dose reduction by SOC and PT
- TEAE leading to dose interruption by SOC and PT
- Treatment-related TEAE leading to dose interruption
- TEAEs leading to study discontinuation by SOC and PT

- Related TEAEs leading to study discontinuation by SOC and PT
- TEAEs meeting DLT leading to study discontinuation by SOC and PT

The tables will be sorted by overall SOC alphabetically and then, within a SOC, by overall descending frequency of PT based on the subject count for the overall column.

5 PTs including Neutrophil count decreased, Haemoglobin decreased, Platelet count decreased, Supraventricular tachycardia, and Lymphocyte count decreased will be grouped into new PTs as Neutropenia, Anaemia, Thrombocytopenia, Supraventricular extrasystoles, and Lymphopenia respectively. The new grouped SOCs will be Cardiac disorders for the original PT of Supraventricular tachycardia, and Blood and lymphatic system disorders for the rest of 4 original PTs.

For summaries by SOC, PT, and intensity, subject is counted only once at the highest grade for which the event occurred in the SOC and the highest grade for each unique PT within that SOC.

In addition, AEs reported post 30 days of safety follow-up period may be summarized by SOC and PT and/or listed separately.

The original date and time will be shown on all listings of AEs. Listings will be provided for all TEAEs, AEs resulting in death, serious TEAEs, AESIs, DLTs and AEs leading to dose reduction, dose interruption and discontinuation.

9.4. LABORATORY EVALUATIONS

Clinical laboratory data are collected at the time points specified in study procedures and flow chart. The assessments are presented in the table on next page.

<table>
<tr>
<td>Hematology
Hematocrit
Hemoglobin
Red blood cell count
Total and differential (absolute) white blood cell count
Platelets
Coagulation
International normalized ratio
Partial thromboplastin time / Activated partial thromboplastin time</td>
<td>Biochemistry
<u>General Chemistry</u>
Albumin
Bicarbonate
Calcium
Chloride
Creatine phosphokinase
Glucose
Magnesium
Phosphorus
Potassium
Sodium
Total protein
Uric acid
<u>Liver Function Tests</u>
Alanine transferase
Alkaline phosphatase
Aspartate transferase
Lactic dehydrogenase
Total bilirubin
<u>Renal Function Tests</u>
Blood urea nitrogen
Creatinine
Thyroid Test
Thyroid-stimulating hormone
Serum Tumor Marker
CA125 (ovarian cancer subjects only)
CA19-9 (gastric and pancreatic cancer subjects only)
PSA (prostate cancer subjects only)
CEA (colorectal cancer subjects only)</td>
<td>Urinalysis
Bilirubin
Color and appearance
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
pH
Protein
Specific gravity
Urobilinogen
Microscopic examination of sediment, only if urinalysis dipstick results are abnormal. Microscopic examination is not needed if urinalysis is abnormal for bilirubin, glucose, or ketones.
Microbiology (as Applicable)
Blood
Urine
Other</td>
</tr>
</table>

A serum or urine pregnancy test will be administered to all women of childbearing potential. At the screening visit, results must be negative for the subject to be eligible for the study.

Separate analysis table for CA125 for ovarian pts will be displayed.

In addition, the hematology, coagulation, and chemistry laboratory parameters will be graded according to NCI CTCAE (version 5.0 or higher) where applicable.

Subjects who meet the potentially clinically significant (PCS) criteria in selected lab parameters will be summarized by treatment cohort, the PCS is defined as Grade 3 or above per CTCAE.

Lab shift table of CTCAE grade (1 to 5) will be summarized from baseline grade to minimum, maximum, and final grade.

Number of subjects who meet the following liver function test criteria will be summarized and corresponding listing will be presented:

- An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is ≥3× the upper limit of normal (ULN) and an elevated total bilirubin laboratory value that is ≥2× ULN and an alkaline phosphatase laboratory value that is <2× ULN within 3 days.

The corresponding listing will present all AST, ALT, total bilirubin, and alkaline phosphatase laboratory data for any subject meeting the aforementioned criteria at least one time.

Listings will be provided for the hematology, coagulation, chemistry, urinalysis, and pregnancy tests results.

9.5. VITAL SIGNS

Vital signs assessments include respiratory rate, temperature, blood pressure, body weight, and heart rate.

The vital signs assessments will be graded according to NCI CTCAE (version 5.0 or higher) where applicable.

Subjects who meet the potentially clinically significant (PCS) criteria in vital sign will be summarized by treatment cohort, the PCS is defined as Grade 3 or above per CTCAE.

Vital signs shift table of CTCAE grade (1 to 5) will be summarized from baseline grade to minimum, maximum, and final grade.

9.6. ECG

The standard 12-lead ECGs will be performed in triplicate 5 minutes apart at all time points outlined in the protocol. The mean value will be used for summary purposes.

The QTcF Intervals fulfilling grade 3 or above per CTCAE will be tabulated separately.

Subjects who meet the potentially clinically significant (PCS) criteria in the QTcF will be summarized by treatment cohort, the PCS is defined as QTcF >=501 msec or >60 msec change from baseline.

The QTcF shift table of CTCAE grade (1 to 5) will be summarized from baseline grade to minimum, maximum, and final grade.

9.7. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

The ECOG performance status assesses the subjects' activity status and will be assessed at the time points specified in Table 3, Table 4, Table 5, Table 6, and Table 7. Possible scores are 0 to 5. Descriptions of activity status are presented in Table 12. The data will be listed.

Table 12: Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al, 1982.

9.8. PHYSICAL EXAMINATION

A full physical examination will be performed at screening and end-of-treatment visits. If possible, a brief physical examination focused on areas of disease or AE will be assessed at Day 1 of each cycle. These data will be available for reference.

10. INTERIM ANALYSES

No formal interim analysis is planned with respect to stopping the study early or for lack of antitumor activity purposes. Interim data cuts will be conducted to support abstract submissions, conference presentations, and/or manuscript(s).

Responses in each N1 stage will be assessed to determine whether progression to the N2 stage is warranted, based on criteria defined in Section 3.6.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Durable response rate is listed as secondary endpoint but no summaries are planned.

Analysis based on irRC and iRECIST will not be performed as the iRECIST was implemented during the middle of the study conduct to replace irRC. The sites have not consistently record the iRECIST data which could provide misleading information.

The protocol stated that the PFS analysis would be only performed for Part B and Part C (Cohorts 5-7). The additional PFS analysis in ovarian patients from the PD-L1 unapproved cohort will be conducted as ovarian is identified as one of tumor types to advance further clinical development in Nemvaleukin in combination with Pembrolizumab.

12. REFERENCE LIST

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

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13. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), statistical analyses, and non-PK parameter related derivations will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing, and figure outputs will adhere to the following specifications below.

PK parameters will be derived using Phoenix WinNonlin ver 6.4 (Certara, Princeton, NJ, USA) by Alkermes who will also be responsible for quality control of the derived parameters.

13.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 guidance.

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are

appropriate to help display math symbols (eg, μ). Certain subscripts and superscripts (eg, cm^2, C_{max}) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

  Alkermes, Inc.

  Protocol ALK4230-A101

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (ie, the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- The title will be centered. The analysis set will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line as per the example below.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set
_____

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by columns for cohorts and total column (if applicable).

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each cohort in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of non-missing subjects in the analysis set.

- The order of cohorts in the Part A tables and listings will be by the order of dose escalation, as dose level: 0.1 µg/kg, 0.3 µg/kg, 1 µg/kg, 3 µg/kg, 6 µg/kg, 10 µg/kg, 15 µg/kg, overall (if applicable). The order of cohorts in the Part B tables and listings will be: Melanoma, RCC, overall (if applicable). The order of cohorts in the Part C tables and listings will be: PD-1 unapproved tumor types, PD-1 approved tumor types (PD-1/L1 pretreated), PD-1 approved tumor types (PD-1/L1 treatment naïve), Rollover, overall (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;

- whole numbers (eg, counts) are right-justified; and

- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all cohorts in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

- Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999.

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the cohort who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.

- All tabular displays of AE data should be presented by SOC with the highest occurrence in the Overall group in decreasing order, assuming all terms are coded. Within SOC, AEs should be displayed in decreasing order of preferred term. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

- Tabular display of data for concomitant medications should be presented by ATC4 Code with the highest occurrence in the Overall group in decreasing order, assuming all terms are coded. Within the ATC4 drug class, concomitant medications should be displayed in decreasing order of Preferred Term. If medications for more than 1 term are identical, they should then be sorted alphabetically.

- Tabular display of data for medical history should be presented by the medical history category with the highest occurrence in the Overall group in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

- Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant cohort (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of cohorts as above, subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., the mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.

- Subject specific footnotes should be avoided, where possible.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program: myprogram.sas Listing source: 16.x.y.z’).

14. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Quality Deliveries (SDTM, ADaM, TLF) (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

Syneos Health SOP Pharmacokinetic and Related Data Analyses and Reporting (03.016) describes the procedure for the generation and reporting of PK and pharmacodynamics data.

15. MOCK SHELLS OF TABLES, FIGURES, AND LISTINGS

Templates of the TLFs are provided in a separate document.