CLINICAL STUDY PROTOCOL

ALK4230-A101

Study Title	A Phase 1/2 Study of ALKS 4230 Administered Intravenously as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors - ARTISTRY-1
EudraCT Number	2019-001998-90
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Sponsor	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 4230	
Name of Active Ingredient: Not applicable.	
Title of Study: A Phase 1/2 Study of ALKS 4230 Administered Intravenously as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors - ARTISTRY-1	
Investigators/Study Sites: The study will be conducted in globally with up to 36 sites.	
Study Period: Date of first subject's consent: September 2016 Estimated duration of study (excluding the Extension Phase): 5 years	**Phase of Development:** 1/2

Primary Objectives:

- To investigate the safety and tolerability of ALKS 4230 and to determine the maximum tolerated dose and the recommended Phase 2 dose (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 intravenously (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)

Secondary Objectives:

- To characterize the clinical pharmacokinetic (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 the 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)

Exploratory Objectives:

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

- [redacted]

Primary Endpoints:

- 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 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)

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 based on RECIST and immune DRR (iDRR) based on iRECIST guidelines 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, regulatory T cells (T_{regs}), and natural killer (NK) cells in peripheral blood
- Serum concentrations of IL-6 and other cytokines

Exploratory Endpoints:

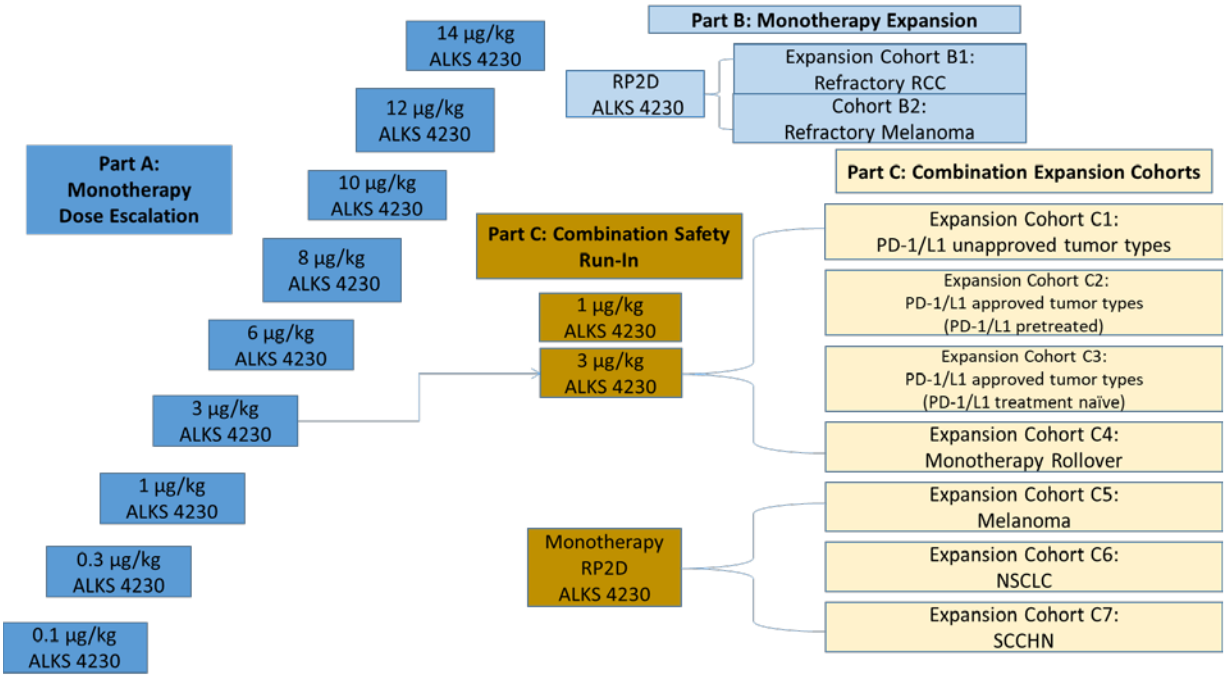
- [redacted]

Methodology: 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 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)



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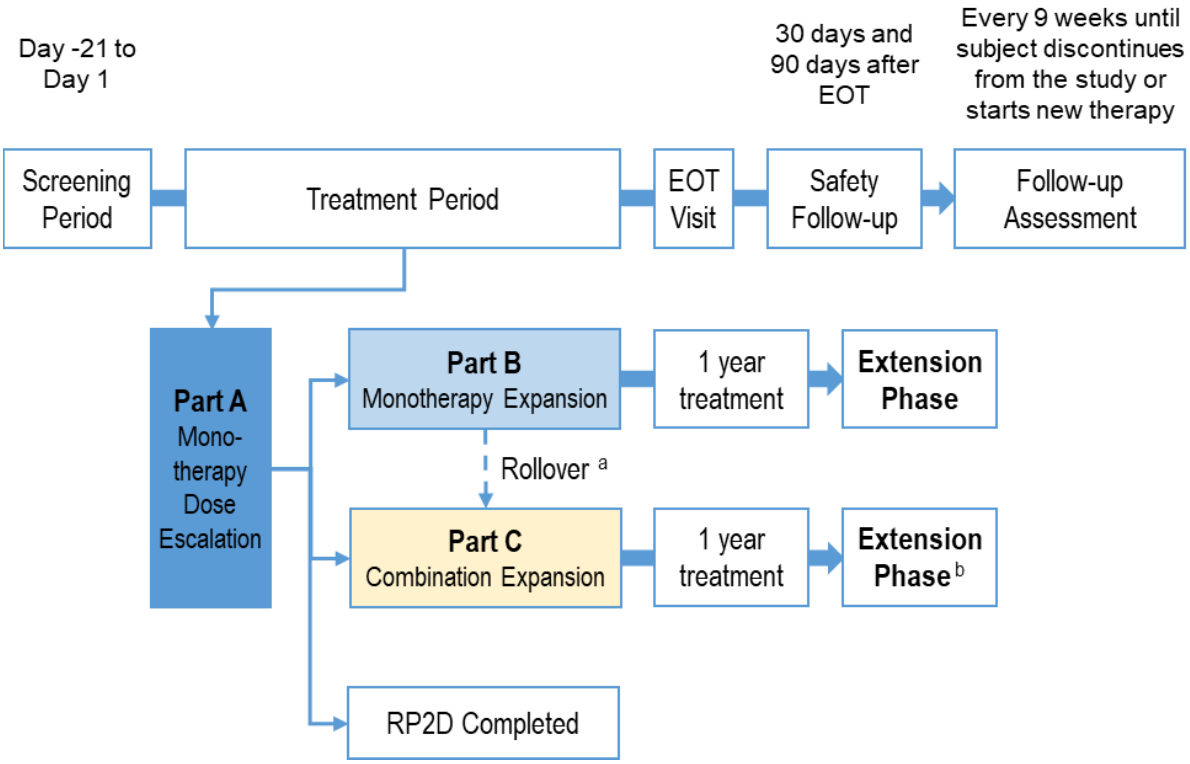

Abbreviations: L1=ligand-1, EOT=End of Treatment, NSCLC=non–small-cell lung cancer, PD-1=programmed death receptor-1, RCC=renal cell carcinoma, SCCHN=squamous cell carcinoma of the head and neck, TBD=to be determined.

[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 1 A): 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.

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 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 MTD, 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.

Part B

After the RP2D is determined, the second part of the study (ie, Part B) will begin. In this part of the study, up to 41 subjects with melanoma and up to 41 subjects with RCC may be enrolled to receive ALKS 4230 at the RP2D. Enrollment to these cohorts will follow a partial response (unconfirmed) Simon's two-stage design enrollment as outlined below. Response assessments will be based on the RECIST guidelines.

	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.

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 SRC, then the study will progress to the 3 µg/kg/day dose level. At the discretion of the SRC, 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 SRC 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 SRC, 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 SRC.

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 stable disease (SD) after a minimum of 4 cycles and who are expected to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Subjects who have partial response (PR) or complete response (CR) on monotherapy are ineligible to rollover unless subsequently 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 the dose of ALKS 4230 in the combination arms may be increased. In Cohorts C5, C6, and C7, up to 53 subjects with melanoma, up to 42 subjects with non–small-cell lung cancer (NSCLC), and up to 36 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 PR (unconfirmed) Simon's two-stage enrollment as outlined below. Response assessments will be based on the RECIST and iRECIST guidelines.

	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 monotherapy RP2D is determined by the SRC 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
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 (Table 8). 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.

Number of Subjects Planned:

Part A: Approximately 36 to 54 subjects

Part B: Approximately 42 to 82 subjects with melanoma or RCC

Part C: Up to 191 subjects

Main Criteria for Inclusion: Eligible subjects must be aged ≥18 years, and the subjects (or the subject's legal representative) must be willing and able to provide informed consent. In Part A, all subjects must have an advanced solid tumor (including lymphomas) that is refractory or intolerant to established therapies known to provide clinical benefit for the malignancy in question, or be in the judgment of their physician intolerant of established therapies. 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. For Part A of the study, the subject must have a diagnosis of an advanced solid tumor. For Part B of the study, the subject must have a diagnosis of melanoma or RCC and meet other inclusion/exclusion criteria specified for Part B cohorts. The subject must be ambulatory with an Eastern Cooperative Oncology Group performance status of 0 or 1 and an estimated life expectancy of at least 3 months. Subjects must otherwise meet all inclusion/exclusion criteria specified in Section 7. All subjects must be recovered from the effects of any previous chemotherapy, immunotherapy, other previous systemic anticancer therapy, radiotherapy, or surgery (ie, toxicity no worse than Grade 1 [Grade 2 alopecia and treatment-associated peripheral neuropathy are acceptable]). Subjects in the dose-expansion part of the study (Part B) and in the combination therapy part of the study (Part C) must have at least one lesion that qualifies as a target lesion based on RECIST guidelines.

Subjects must wait at least 5 half-lives or 4 weeks (whichever is shorter) following prior therapy before enrollment into the study. Shorter wait periods may be permitted after discussion with the Medical Monitor. 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).

For enrollment into Parts B and C, subjects must agree to provide archival tumor tissue biopsy sample(s), if available. 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.

Subjects should be willing and able to meet contraceptive requirements listed in Section 8.4.2 during the study and for 90 days after the last dose (for subjects in Part A and Part B) and 4 months after the last dose (for subjects in Part C). Females of childbearing potential must have a negative urine or serum pregnancy test within 7 days of the start of treatment, and on Day 1 before the first dose is administered.

For monotherapy expansion cohorts (Part B) and the combination therapy part of the study (Part C), subjects must meet the following criteria to enroll into the cohorts identified below.

Additional Inclusion Criteria for Part B Melanoma Expansion Cohort

Subjects must have advanced melanoma. Subjects should have received an immune checkpoint inhibitor (eg, anti-PD-[L]1 with or without anti-CTLA-4) and, if appropriate, a molecularly targeted agent (eg, BRAF inhibitor if BRAF-mut), and no more than one prior regimen of cytotoxic chemotherapy. Subjects previously treated with checkpoint inhibitor either as single-agent or in a combination regimen should have experienced objective response or SD (by RECIST or iRECIST) as best overall response. Subjects with progressive disease as best overall response may be included on a case-by-case basis by the Medical Monitor.

Additional Inclusion Criteria for Part B Renal Cell Carcinoma Expansion Cohort

Subjects must have advanced RCC. Subjects must have received a 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 lines of systemic therapies, including the checkpoint inhibitor-based regimen. Subjects previously treated with checkpoint inhibitor either as single-agent or in a combination regimen should have experienced objective response or SD (by RECIST or iRECIST) as best overall response. Subjects with progressive disease as best response may be included on a case-by-case basis by the Medical Monitor.

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 (excluding RCC and melanoma; subjects with NSCLC should enroll in C6 if 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 (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 expected to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Subjects who have PR or CR on monotherapy are ineligible to rollover unless subsequently 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. Subjects that are known to be BRAF mutation-positive are eligible without prior treatment or after failure of BRAF-directed inhibitor therapy. Subjects 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 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.

Main Criteria for Exclusion

The following subjects will be excluded:

- Subjects currently pregnant or breastfeeding or is planning to become pregnant during the study period
- Subjects who have an active infection and/or a fever ≥38.5°C (≥101.3°F) within 3 days of the first scheduled day of dosing
- 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.
- Subjects with known hypersensitivity to any components of ALKS 4230.
- Subjects who require pharmacologic doses of corticosteroids (greater than 10 mg of prednisone daily, or equivalent); however, topical, ophthalmologic, and inhalational steroids are permitted.
- 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; subjects who are on medications known to cause prolonged QT interval on standard 12-lead electrocardiogram.
- Subjects who developed Grade ≥3 autoimmune disorders while on prior immunotherapy (eg, 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.
- 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.

- Subjects known to be positive for human immunodeficiency virus are excluded. Subjects with active tuberculosis or a known history of tuberculosis are excluded. Subjects with active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) are excluded, however, subjects with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) may be enrolled provided that prior testing/known status for HBV DNA is negative. Subjects with active hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] are detected) are excluded, however, subjects with cured hepatitis C (negative HCV RNA prior test/known status) may be enrolled.
- Subjects who are investigational site staff members directly involved in the conduct of the trial and their immediate family members, site staff members otherwise supervised by the Investigator, or subjects who are Alkermes or Syneos Health employees directly involved in the conduct of the study. (Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.)
- Subjects with a known hypersensitivity to any components of pembrolizumab (Part C subjects only)
- 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, ductal breast carcinoma in situ with full surgical resection.
- Subjects with dyspnea at rest or requiring oxygen therapy
- Subjects with active autoimmune disease requiring systemic treatment within the past 3 months or documented history of clinically severe autoimmune disease that has required systemic steroids and/or immunosuppressive agents.
- 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
- Subjects who have received radiotherapy within the last 4 weeks before start of study treatment administration, with the exception of limited field palliative radiotherapy at the discretion of the Medical Monitor.
- Subjects who have received administration of a live, attenuated vaccine within 4 weeks before Cycle 1 Day 1.
- Prior solid organ and/or non-autologous hematopoietic stem cell or bone marrow transplant recipients.
- Subjects who have received prior IL-2-based or IL-15-based cytokine therapy.

Investigational Product, Dosage, Duration, and Mode of Administration: [redacted]

[redacted]

Reconstituted ALKS 4230 is administered via a 30-minute IV infusion once daily for 5 consecutive days, followed by 9 days off for Cycle 1 (Parts A and B) and 16 days off for all subsequent cycles.

In Part C, on days where ALKS 4230 is administered in combination with pembrolizumab, ALKS 4230 should be administered by infusion 60 (±30) minutes after the completion of pembrolizumab infusion.

Pembrolizumab is to be administered as an IV infusion over 30 minutes in a dose of 200 mg every 3 weeks.

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 (ie, 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. [redacted]

Duration of Treatment: In Parts A and B, Cycle 1 consists of 5 consecutive days of treatment with ALKS 4230 followed by 9 days off treatment, for a total of 14 days. Cycle 2 and all subsequent cycles of treatment consist of 5 consecutive days of treatment with ALKS 4230 followed by 16 days off treatment, for a total of 21 days for each cycle. Subjects may continue additional cycles of treatment until evidence of progressive disease, intolerance to ALKS 4230, removal by the Investigator, withdrawal of consent, or any other criteria for study removal.

In Part C, all cycles of treatment consist of pembrolizumab administration every 3 weeks in combination with 5 consecutive days of treatment with ALKS 4230 followed by 16 days off treatment, for a total of 21 days for each cycle. Subjects may continue additional cycles of treatment until evidence of progressive disease, intolerance to ALKS 4230, removal by the Investigator, withdrawal of consent, or any other criteria for study removal. For Part C, subjects who discontinue one drug (eg, due to unacceptable toxicity that cannot be managed by dose modification) must discontinue the entire study treatment.

In the Extension Phase, the treatment duration of monotherapy with ALKS 4230 may be extended until disease progression or until the subject meets any other criteria for treatment discontinuation (Section 7.3). 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) for as long as the subject appears to be deriving clinical benefit (ie, objective response or SD) and has tolerated therapy well. 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, at the joint discretion of the Investigator and Sponsor and if they do not meet any other criteria for discontinuation.

Antitumor Activity: Tumor assessments will be performed throughout study treatment and analyzed using RECIST and iRECIST guidelines.

Pharmacokinetics/Pharmacodynamics, Immunogenicity, and Other Biomarkers: [redacted]

[redacted]

Statistical Methods:

[redacted]

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4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or Term	Explanation or Definition
AE	adverse event
ANC	absolute neutrophil count
C2D15	Cycle 2, Day 15
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum drug concentration in serum
CR	complete response
CSA	Clinical Study Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	standard 12-lead electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
i-	immune-
iAE	immune adverse event
ICF	informed consent form
ICH	International Council for Harmonisation
iCR	immune complete response
iDCR	immune disease control rate
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
iPR	immune partial response
IRB	Institutional Review Board

Abbreviation or Term	Explanation or Definition
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
iSD	immune stable disease
IV	intravenous(ly)
MP	memory-phenotype
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer [cells]
NSCLC	non–small-cell lung cancer
ORR	overall response rate
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QD	once daily
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
rhIL-2	recombinant human interleukin-2
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SPD	sum of the products of the two longest perpendicular diameters
TID	3 times daily
T_{regs}	regulatory T cells
ULN	upper limit of normal
USP-NF	United States Pharmacopeia-National Formulary
WOCBP	women of childbearing potential

5. INTRODUCTION

Alkermes Inc. (Alkermes) is developing ALKS 4230 for the treatment of subjects with advanced malignancies.

Cancer is widely recognized as a prominent cause of illness and death. Approximately 14.1 million cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide (Torre et al, 2015). It is projected that in the United States in 2015, over 1.6 million new cancer cases will arise and over half a million patients will die of the disease (Siegel et al, 2015).

The potential of immunotherapy to bring clinical benefit to patients with advanced cancer has been recognized for over a century, beginning with the demonstration of activity of Coley's toxins, published in 1893 (Parish 2003). The field advanced further during the 1980s and 1990s, with the FDA granting approval for interferon-α for the treatment of various malignancies intron (Intron A USPI) and interleukin-2 (IL-2, also known as aldesleukin) for the treatment of metastatic renal cell carcinoma (RCC) and metastatic melanoma (Proleukin USPI). More recently there has been substantial progress in the field through the blockade of immune checkpoints using monoclonal antibodies. The first of these to be approved by the FDA was the anticytotoxic T-lymphocyte associated protein-4 antibody ipilimumab, approved for patients with unresectable or metastatic melanoma in 2011 and more recently in combination with nivolumab for patients with unresectable or metastatic melanoma (Yervoy USPI). The antiprogrammed death receptor-1 (PD-1) antibodies pembrolizumab and nivolumab were both approved in the United States initially for patients with unresectable or metastatic melanoma who had already received other FDA-approved therapies and then subsequently for patients with unresectable or metastatic melanoma and in certain patients with non–small-cell lung cancer (NSCLC; Keytruda [pembrolizumab] USPI; Opdivo [nivolumab] USPI). Opdivo® [nivolumab] was recently approved for patients with advanced RCC who have received prior antiangiogenic therapy. Despite this progress, many tumors do not respond to PD-1 pathway inhibitor therapy, and many subjects who have responded go on to have progression in their tumors. Opportunities remain within the field of immunotherapy for novel anticancer agents or novel combinations of these agents. Combination of PD-1 pathway inhibition with cytokine therapy such as ALKS 4230 might enhance the antitumor effect of anti-PD-1 monotherapy. The first published clinical evidence of combination PD-1 pathway inhibition and cytokine therapy came from a study of IL-15 superagonist ALT-803 and nivolumab treatment, which yielded encouraging antitumor activity in patients with PD-1 pathway inhibitor relapsed and refractory NSCLC (Wrangle et al 2018). Several clinical studies (eg, NCT02983045, NCT02523469, NCT03388632, and NCT02964078) are currently underway to further assess the safety and antitumor activity of combination therapy with these two classes of agents, including a combination study of NKTR-214 (a pegylated IL-2) with nivolumab, which has reported antitumor responses in immunotherapy treatment naive patients (Diab 2017).

ALKS 4230 is an engineered fusion protein composed of a circularly permuted IL-2 and IL-2 receptor (IL-2R) α designed to selectively activate the intermediate-affinity IL-2R, but not the high-affinity IL-2R. The intermediate-affinity IL-2R is expressed predominantly on effector lymphocytes, which play an important role in driving antitumor immune responses. In contrast, IL-2 preferentially activates the high-affinity IL-2R, driving the expansion of high-affinity IL-2R-expressing cell types including immunosuppressive CD4+ regulatory T cells (T_{regs}), which limit anticancer activity by recombinant human IL-2 (rhIL-2, aldesleukin). The high-affinity

IL-2R is also expressed on vascular and pulmonary endothelial cells and may contribute to rhIL-2-mediated toxicity via capillary leak syndrome. Thus, selective activation of the intermediate-affinity IL-2R by ALKS 4230 has the potential to provide enhanced tumor killing as well as improved safety and tolerability. Pharmacology data supports the thesis that ALKS 4230 signals through the intermediate-affinity IL-2R leading to the expansion and activation of effector cells while minimizing the expansion and activation of immunosuppressive CD4+ T_{regs}.

ALK4230-A101 is a Phase 1/2 study of ALKS 4230 administered intravenously as monotherapy and in combination with pembrolizumab in subjects with advanced solid tumors.

Based on a minimal anticipated biological effect level dose of 0.1 µg/kg/day and projected minimal efficacious dose of 0.7 to 1.6 µg/kg/day, the proposed doses to be evaluated in the Phase 1/2 FIH study by cohort escalation design are 0.1, 0.3, 1, 3, 6, 8, 10, 12, and 14 µg/kg/day. If the recommended Phase 2 dose (RP2D) has not been reached within the proposed dose range, additional dose escalation will be considered. Following the identification of the RP2D, ALKS 4230 will be evaluated in a dose-expansion phase as monotherapy (Part B).

In Part C (the combination therapy part of the study), ALKS 4230 will be evaluated at the 1, 3, and 6 µg/kg/day dose levels in combination with pembrolizumab (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 C). If the data from this initial study are promising, it is expected that ALKS 4230 and/or ALKS 4230 in combination with pembrolizumab will progress into further Phase 2 and/or Phase 3 studies. Depending on the data from Phase 1 or later studies, ALKS 4230 may be further tested in studies that combine it with other anticancer agents.

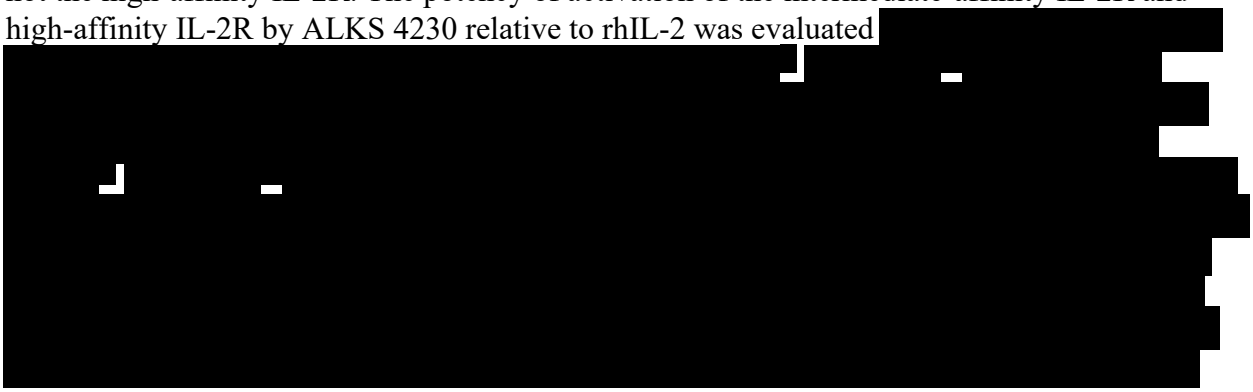
ALKS 4230 will be studied under IND 128,159. This study will be conducted according to the protocol, Good Clinical Practice (GCP) requirements, and other applicable regulatory requirements.

5.1. Nonclinical Pharmacology Evaluation

ALKS 4230 has been studied using *in vitro* and *in vivo* nonclinical methods to characterize its pharmacology. Results from selected studies are briefly described below.

5.1.1. In Vitro Primary Pharmacology

ALKS 4230 was designed to selectively bind to and activate the intermediate-affinity IL-2R, and not the high-affinity IL-2R. The potency of activation of the intermediate-affinity IL-2R and high-affinity IL-2R by ALKS 4230 relative to rhIL-2 was evaluated [redacted]



[redacted]

5.1.2. In Vivo Primary Pharmacology

[redacted]

[redacted]

5.2. Nonclinical Pharmacokinetic Evaluation

The pharmacokinetics (PK) of ALKS 4230 were determined in male cynomolgus monkeys after single intravenous (IV) administration (Study Number AK-4230-01) at 0.03, 0.1, or 0.3 mg/kg. After a single IV bolus administration, the PK of ALKS 4230 was characterized by a mean serum clearance of 11.9 to 16.6 mL/h/kg and mean steady-state volume of distribution of 80 to 138 mL/kg. The mean elimination half-life ranged from 20 to 34 hours and the mean residence time ranged from 6.7 to 8.2 hours. Systemic exposure to ALKS 4230 (maximum drug concentration in serum [C_{max}] and area under the curve from time zero to infinity) increased with increase in dose; the increase in area under the curve from time zero to infinity appeared to be slightly less than dose proportional over the dose range of 0.03 to 0.3 mg/kg.

The toxicokinetics of ALKS 4230 and anti-ALKS 4230 antibody data were determined in cluster of differentiation (CD)-1 mice and cynomolgus monkeys as part of the pivotal repeat-dose toxicity studies.

After QD IV (30-second infusion) administration of ALKS 4230 to CD-1 mice for up to 28 consecutive days in the repeat-dose pivotal toxicity study, ALKS 4230 exposures (C_{max} and area under the curve from time zero to 24 hours postdose) increased with increase in dose; the increase in exposures was generally dose proportional over the dose range of 0.03 to 0.3 mg/kg/day. No sex difference in ALKS 4230 exposures and no accumulation of ALKS 4230 was observed in CD-1 mice after repeat-dose administration of ALKS 4230. Overall, 31 out of the 90 toxicity animals (34.4%) dosed with ALKS 4230 tested positive for anti-ALKS 4230 antibodies. The direct impact of anti-ALKS 4230 antibody development on ALKS 4230 toxicokinetics could not be determined as the presence of anti-ALKS 4230 antibodies were evaluated in samples collected from the toxicity animals and not from the toxicokinetic animals.

After IV (30-minute infusion) administration of ALKS 4230 to cynomolgus monkeys QD for 35 consecutive days or for a total of 15 doses (3 cycles of daily dosing for 5 days followed by 9 days of no dosing) in the pivotal repeat-dose toxicity study, ALKS 4230 exposures (C_{max} and area under the curve from time zero to 24.5 hours postdose) increased with the increase in dose. The increase in ALKS 4230 exposures was generally dose proportional over the dose range of 1 to 30 µg/kg/day evaluated in the daily dosing regimen and over the dose range of 10 to 300 µg/kg/day evaluated in the cycle dosing regimen with the exception of a greater than dose proportional increase in ALKS 4230 exposure from 100 to 300 µg/kg/day in male monkeys. No sex difference in ALKS 4230 exposures and no accumulation of ALKS 4230 were observed in monkeys after repeat-dose administration of ALKS 4230. Overall, 11 out of the 40 animals (27.5%) dosed with ALKS 4230 tested positive for anti-ALKS 4230 antibodies. However, the presence of anti-ALKS 4230 antibodies in animals that were positive for anti-ALKS 4230 antibodies did not appear to impact the ALKS 4230 concentration profile or exposure. Also, the prevalence of anti-ALKS 4230 antibodies did not appear to be dose related.

The starting dose for the ALKS 4230 FIH Phase 1/2 clinical study is proposed to be 0.1 µg/kg based upon the minimal anticipated biological effect level approach recommended by the

regulatory agency ICH Guidance: S9 Nonclinical Evaluation (International Council for Harmonisation 2010). This starting dose is projected to result in an immediate postinfusion concentration (C_{max}) of 0.0031 µg/mL. The projected minimal efficacious dose in humans for activation of IL-2R complex ranges from 0.7 to 1.6 µg/kg and is projected to result in a C_{max} range of 0.016 to 0.038 µg/mL. Therefore, the proposed doses to be evaluated in the FIH Phase 1/2 study are 0.1, 0.3, 1, 3, 6, 8, 10, 12, and 14 µg/kg. In comparison, the no-observed-adverse-effect–level for the cycle dosing regimen in the pivotal repeat-dose toxicology study in monkeys is 100 µg/kg; the observed C_{max} on the last day of dosing was 2.43 µg/mL in males and 2.61 µg/mL in females. In addition, the C_{max} at the proposed starting dose of 0.1 µg/kg (0.0031 µg/mL) is about 3-fold lower than the lowest concentration of ALKS 4230 (0.01 µg/mL) tested in the ProStorm® Cytokine Release Assays at which only slight elevations were observed for IL-6, IL-8, and interferon-γ in a small number of donor samples, similar to those in the low-response control across the concentration range evaluated. Therefore, 0.1 µg/kg is considered a safe starting dose for the FIH study. If the maximum tolerated dose (MTD) or the RP2D has not been reached within the proposed dose range, additional dose escalation will be considered.

5.3. Nonclinical Toxicology Studies

5.3.1. General Toxicology Studies

The nonclinical toxicology studies were carried out to evaluate ALKS 4230 safety and to inform the selection of a safe FIH starting dose. Relevant species selection was contingent on exploratory pharmacology work. Species used in the general toxicology program were CD-1 mice and cynomolgus monkeys for rodent and nonrodent species, respectively.

Targets/target organs identified in general toxicology studies included lung, liver, and spleen as noted with microscopic pathology. Mortality was seen in nonpivotal dose range-finding in CD-1 mice at 0.6 mg/kg/day, the pivotal CD-1 mouse study at 0.3 mg/kg/day, and in the pivotal monkey study at 0.3 mg/kg/day. Clinical observations of hypoactivity, inappetence, and gastrointestinal effects (vomiting, soft feces) were noted in monkeys at doses ≥0.3 mg/kg/day.

Mortality in mice and monkeys was attributed to lung findings of mononuclear cell infiltrate in mouse at ≥0.3 mg/kg/day and moderate hemorrhage peribronchial/perivascular in the 1 monkey death at 0.3 mg/kg/day.

5.3.2. In Vivo General Toxicology

In toxicology studies in both mouse and monkey, ALKS 4230 target organs were lung, liver, and spleen. Increased lymphocytic and/or mononuclear cell infiltrations were observed in the Good Laboratory Practice (GLP) and non-GLP studies in both species. Mononuclear cell infiltrates were noted in other tissues as well but without clinical pathology or clinical observations. These findings were not considered adverse in animals receiving low doses of ALKS 4230 because these animals survived to termination and the extent of cellular infiltration was reduced during recovery. In mice treated at higher doses, fatalities were attributed to cellular infiltration in the lungs. One female monkey died early in the GLP study. Her death was attributed to moderate peribronchial/perivascular hemorrhage in the lung. The no-observed-adverse-effect–level in mouse was determined to be 0.1 mg/kg/day. The no-observed-adverse-effect–level in monkey

was determined to be 0.001/0.03 mg/kg/day for daily dosing and 0.1 mg/kg/day for cyclical dosing.

Systemic exposure is dose-dependent in both animal species. In the GLP monkey study, formation of anti-ALKS 4230 antibodies did not alter serum PK or toxicokinetic profiles.

ALKS 4230 exposure in the GLP studies of mouse and monkey are more than 700-fold higher than the exposure that is expected in the FIH Phase 1/2 study at the starting dose of 0.1 μg/kg/day. This dose is projected to deliver a postinfusion concentration (C_{max}) of 0.0031 μg/mL.

6. STUDY OBJECTIVES

6.1. Primary Objectives

- 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 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)

6.2. 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)

6.3. Exploratory Objectives

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

6.4. Primary Endpoints

- 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)

6.5. 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 based on RECIST and immune durable response rate (iDRR) based on iRECIST guidelines 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, T_{regs}, and NK cells in peripheral blood
- Serum concentrations of IL-6 and other cytokines

6.6. Exploratory Endpoints

- [redacted]

7. SELECTION AND WITHDRAWAL OF SUBJECTS

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 in to 1 of the 6 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.

7.1. Subject 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 one 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), if available. 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 subjects 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 (ie, 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. See Section 8.4.2 for further details regarding pregnancy requirements.
16. Meets contraceptive requirements defined in the protocol in Section 8.4.2. Women of childbearing potential and men (if their sexual partners are WOCBP) must use at least two forms of birth control, at least one of which is considered highly effective, throughout the study if they are heterosexually active. See Section 8.4.2 for a definition of WOCBP and a complete description of contraceptive requirements.

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 inclusion criteria to enroll into the cohorts identified below.

Additional Inclusion Criteria for Part B Melanoma Expansion Cohort

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

disease (SD; by RECIST or iRECIST) as best overall response. Subjects with progressive disease as best response may be included on a case-by-case basis by the Medical Monitor.

Additional Inclusion Criteria for Part B Renal Cell Carcinoma Expansion Cohort

Subjects must have advanced RCC. Subjects must have received a 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 lines of systemic therapies, including the checkpoint inhibitor-based regimen. Subjects previously treated with checkpoint inhibitor either as single-agent or in a combination regimen should have experienced objective response or SD (by RECIST or iRECIST) as best overall response. Subjects with progressive disease as best response may be included on a case-by-case basis by the Medical Monitor.

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 (excluding RCC and melanoma; subjects with NSCLC should enroll in C6 if 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 expected to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Subjects who have partial response (PR) or complete response (CR) on monotherapy are ineligible to rollover unless subsequently 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. Subjects that are known to be BRAF mutation-positive are eligible without prior treatment or after failure of BRAF-directed inhibitor therapy. Subjects 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 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.

7.2. Subject 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 (eg, 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 are excluded. Subjects with active tuberculosis or a known history of tuberculosis are excluded. Subjects with active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) are excluded, however, subjects with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) may be enrolled provided that prior testing/known status for HBV DNA is negative. Subjects with active hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] are detected) are excluded, however, subjects with cured hepatitis C (negative HCV RNA prior test/known status) may be enrolled.
10. Subjects who are investigational site staff members directly involved in the conduct of the trial and their immediate family members, site staff members otherwise supervised by the Investigator, or subjects who are Alkermes or Syneos Health employees directly involved in the conduct of the study. (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 has required systemic steroids and/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 at the discretion of the Medical Monitor.
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.

7.3. Subject Discontinuation From Treatment

A subject may choose to withdraw or may be discontinued from treatment at any time if the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for withdrawal or discontinuation include:

- Unacceptable toxicity that cannot be managed by dose modification
- Pregnancy
- Immune confirmed progressive disease (iCPD) by iRECIST or clinical progression (worsening of symptoms or declining performance status)
- Severe noncompliance as judged by the Investigator and/or Sponsor
- Study terminated by Sponsor
- Subject request (Note: All reasonable efforts should be made to encourage subjects to remain on study for follow-up evaluations even if they withdraw from treatment)
- Physician's decision
- Death

For Part C, subjects who discontinue 1 drug (eg, due to unacceptable toxicity that cannot be managed by dose modification) must discontinue the entire study treatment.

Subjects who request to discontinue treatment will be asked to continue the study visits and assessments as outlined in the Schedule of Assessments (Table 5, Table 6, Table 7, and Table 8). The ET/EOT visits must be completed for all subjects regardless of whether they actually return to the clinic for those visits. However, if a subject completes Cycle 9 and is then lost to follow-up or withdraws consent, the site must complete the ET/EOT as well as end of study (EOS) CRFs accordingly.

7.4. Subject Discontinuation From Study

Subjects may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the subject, who is at any time free to discontinue his or her participation in the study
- Death
- Lost to follow-up
- Sponsor decision to terminate study

If a subject withdraws or is discontinued from the study for any reason, any ongoing treatment-related AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's

rights. Enrolled subjects are to be asked to return to the clinic for an early termination visit. The early termination visit should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at the end of treatment (EOT) visit. Subjects who withdraw from or are discontinued from the study will also be asked to complete the safety follow-up visits. The EOS visits must be completed for all subjects regardless of whether they actually return to the clinic for those visits. For example, if a subject completes Cycle 9 and is then lost to follow-up or withdraws consent, the site must still complete the EOS CRF accordingly.

If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone to assess as many safety and antitumor activity parameters as possible. If a subject is lost to follow-up, attempts should be made to contact the subject to determine the reason for discontinuation. For subjects who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the subject before considering the subject lost to follow-up.

The Investigator must maintain a record of all subjects who fail to complete the study. A full explanation of the reason for study withdrawal or discontinuation will be made on the appropriate electronic case report form (eCRF). The reason for discontinuation will be documented.

7.5. Replacement of Subjects

In the dose-escalation part of the study, subjects without a DLT who receive fewer than 10 doses through Cycle 2, Day 15 (C2D15) will be considered unevaluable for DLT assessment and 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. There will be no replacements of subjects other than subjects who are considered unevaluable for DLT assessment.

Subjects who discontinue for any reason, including disease progression, prior to the completion of the C2D15 visit in the dose-expansion part of the study (Part B) or in the combination therapy part of the study (Part C) will be replaced.

Data from subjects who are replaced will be included in the data analysis.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a global, multicenter, open-label, sequential groups Phase 1/2 study. The study will have three parts: Part A, a dose-escalation monotherapy part; Part B, a dose-expansion monotherapy part; and Part C, a combination therapy part with pembrolizumab.

In Part A 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 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 dose levels described in Figure 1. The starting dose of 0.1 µg/kg/day was selected based on minimal anticipated biological effect level. Doses in subsequent cohorts will be increased according to Table 1 until stopped for DLTs or an MTD is reached. Additional dose levels will be considered if the RP2D or 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 MTD, defined as the dose level immediately below that in which ≥2 of 6 evaluable 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.

Table 1: 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 dose may be reduced by one dose level as needed at the discretion of the Investigator.

If a subject without a DLT receives fewer than 10 doses before completing the C2D15 visit, the subject will be replaced, unless the minimum number of evaluable subjects for the cohort has been reached.

If dose escalation is not felt to be warranted, an intermediate dose between the current dose and the prior dose may be explored. Alternative dosing frequency (dosing less than 5 consecutive days in each treatment cycle) may also be explored depending on safety, PK, and pharmacodynamic observations during the dose-escalation portion of the study.

Dose-limiting toxicity will be defined by any of the following events possibly, probably, or definitely related to ALKS 4230 that are observed during the interval from Cycle 1, Day 1 through C2D15:

- Grade 4 Neutrophil Count Decreased (neutropenia) that has not recovered to Grade 2 (≥1000 cells/μL) within 15 days of the start of the cycle or requires an urgent intervention (eg, 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 <1000 cells/μL with temperature >38.3°C [100.9°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
- CTCAE Grade 4 thrombocytopenia that does not recover to Grade ≤2 within 15 days of the start of the treatment cycle
- Thrombocytopenia equivalent to 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 that does not recover to Grade ≤2 or baseline within 1 week 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 (>104°F) 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 one 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.
- Any other Grade 4 nonhematologic toxicity or any other Grade 3 non-hematologic toxicity that does not resolve to Grade ≤ 2 within 96 hours, except fatigue or anorexia. Fatigue and anorexia are not 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 result 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.

Under certain circumstances an individual subject may be permitted to have his/her dose escalated (ie, intrapatient dose escalation). Refer to Section 9.6 for further details.

Subjects may remain on treatment until criteria for treatment discontinuation are met as described in Section 7.3. Subjects may remain on study until criteria for study discontinuation are met as described in Section 7.4. Note: all reasonable efforts should be made to encourage subjects to remain on study for follow-up evaluations even if they withdraw from treatment. For Part C, subjects who discontinue 1 drug (eg, due to unacceptable toxicity that cannot be managed by dose modification) must discontinue the entire study treatment.

In the Extension Phase, the treatment duration of monotherapy with ALKS 4230 may be extended until disease progression or until the subject meets any other criteria for treatment discontinuation (Section 7.3). 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) for as long as the subject appears to be deriving clinical benefit (ie, objective response or SD) and has tolerated therapy well. 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, at the joint discretion of the Investigator and Sponsor and if they do not meet any other criteria for discontinuation.

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.

After the RP2D is determined, the second part of the study (ie, 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 in Table 2. Response assessments will be based on the RECIST guidelines.

Table 2: 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.

The RP2D will be equal to or less than the MTD and its associated dosing schedule and will be selected based on the safety, PK, pharmacodynamics, and preliminary antitumor activity data observed during dose escalation.

An independent data monitoring committee (IDMC) will review accumulating safety and efficacy data at regular intervals and monitor overall study conduct beginning in the second stage (N2) of Part B cohorts and Part C C5, C6, and C7 cohorts (see Section 14.6 for details).

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 SRC, then the study will progress to the 3 µg/kg/day dose level. At the discretion of the SRC, 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 SRC 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 SRC, 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 SRC.

Up to 20 subjects will be enrolled into each of Cohorts C1, C2, C3 based on their tumor type and prior treatment with PD-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 expected to tolerate treatment with combination therapy are eligible for treatment in Part C, Cohort C4. Subjects who have PR or CR on monotherapy are ineligible to rollover unless subsequently 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 the dose of ALKS 4230 in the combination arms may be increased. In Cohorts C5, C6, and C7, up to 53 subjects with melanoma, up to 42 subjects with NSCLC, and up to 36 subjects with squamous cell carcinoma of the head and neck may be enrolled to receive ALKS 4230 in combination with pembrolizumab at the RP2D. Enrollment to these cohorts will follow a PR (unconfirmed) Simon's two-stage enrollment as outlined below. Response assessments will be based on RECIST and iRECIST guidelines.

Table 3: 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 monotherapy RP2D is determined by the SRC 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.

Table 4: 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
C5: Melanoma	Up to 53

Table 4: Planned Number of Subjects for Part C (Continued)

Expansion Cohort: Tumor (Setting)	Number of Subjects
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.

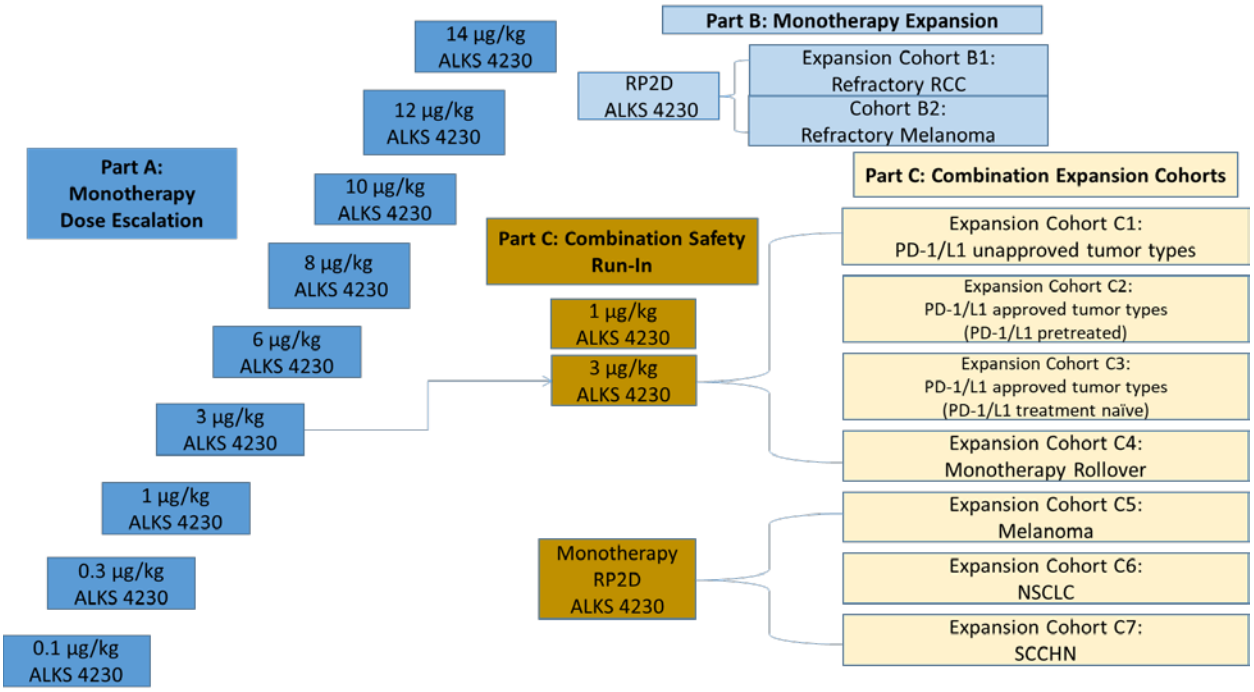
Subjects completing 1 year of treatment will enter the Extension Phase after Cycle 18. The subjects who are already beyond 1 year of treatment will enter the Extension Phase immediately and will start following the Schedule of Assessments of the Extension Phase (Table 8). The 1-year treatment period 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.

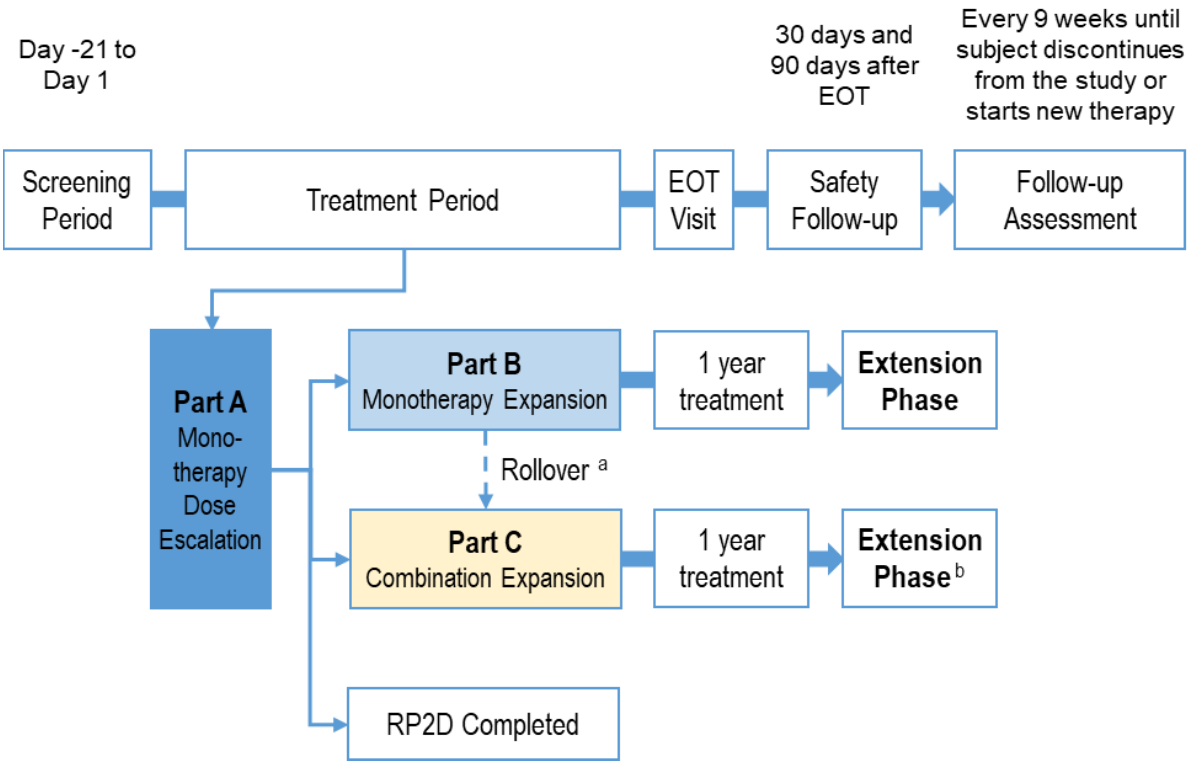
An overall schematic of the study design is provided in Figure 1. A dose-escalation flow chart is provided in Figure 2. A schematic for Part A Cycle 1 is provided in Figure 3 and for Part A Cycle 2 and subsequent cycles in Figure 4. A schematic for Part B Cycle 1 is provided in Figure 5 and for Part B Cycle 2 and subsequent cycles in Figure 6. A schematic for Part C is provided in Figure 7.

Figure 1: Overall Study Design Schematic

A)



B)



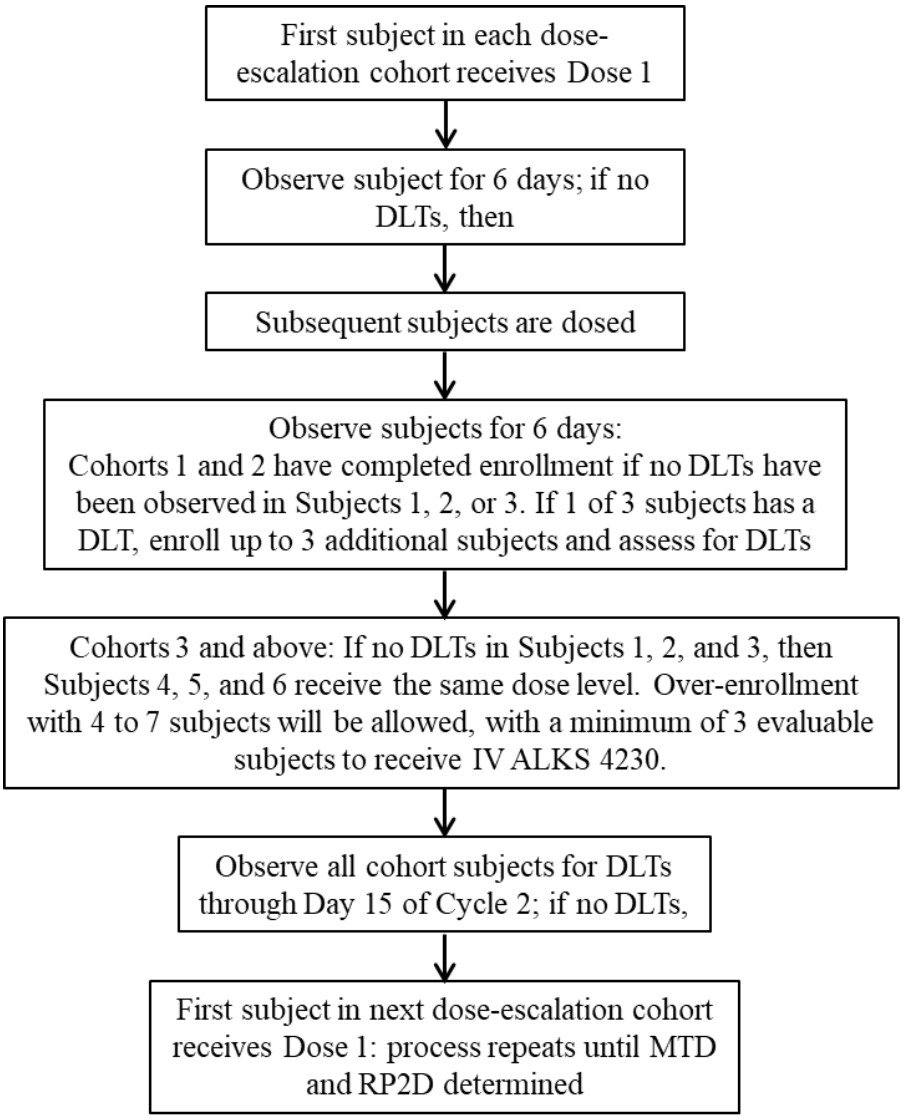
Abbreviations: L1=ligand-1, EOT=End of Treatment, NSCLC=non–small-cell lung cancer, PD-1=programmed death receptor-1, RCC=renal cell carcinoma, SCCHN=squamous cell carcinoma of the head and neck, TBD=to be determined.

[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.

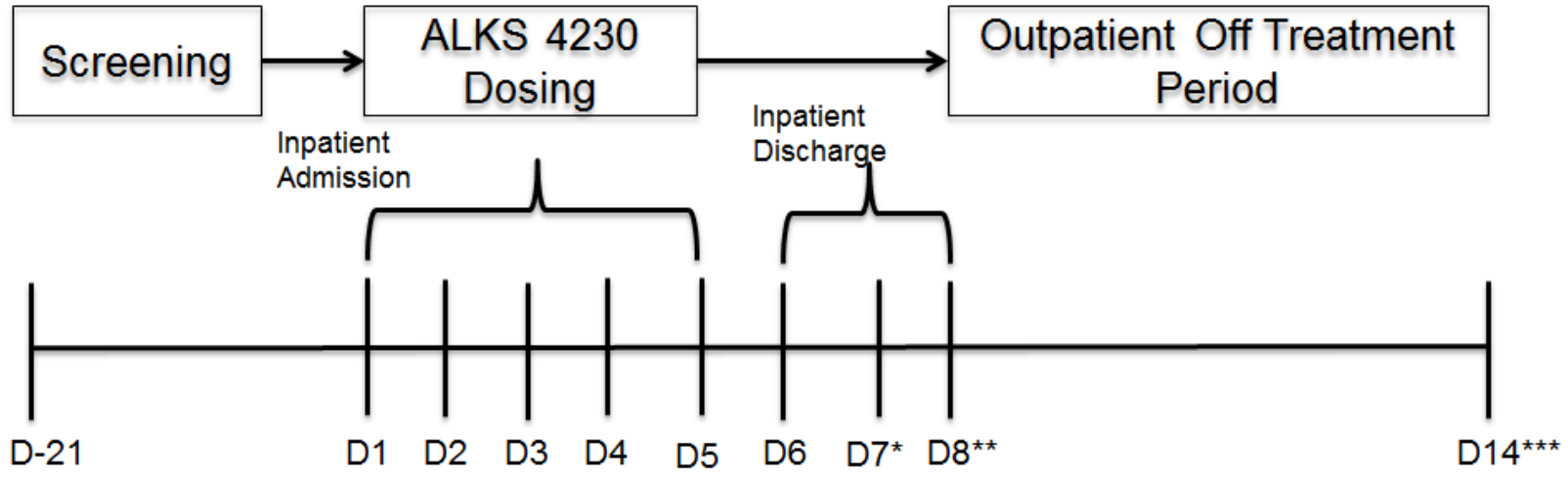
Note (Figure 1A): If a dose higher than 6 µg/kg of ALKS 4230 is found to be tolerable for Part A, that dose may be used in Part B or Part C.

Figure 2: Part A Dose Escalation Flow Chart



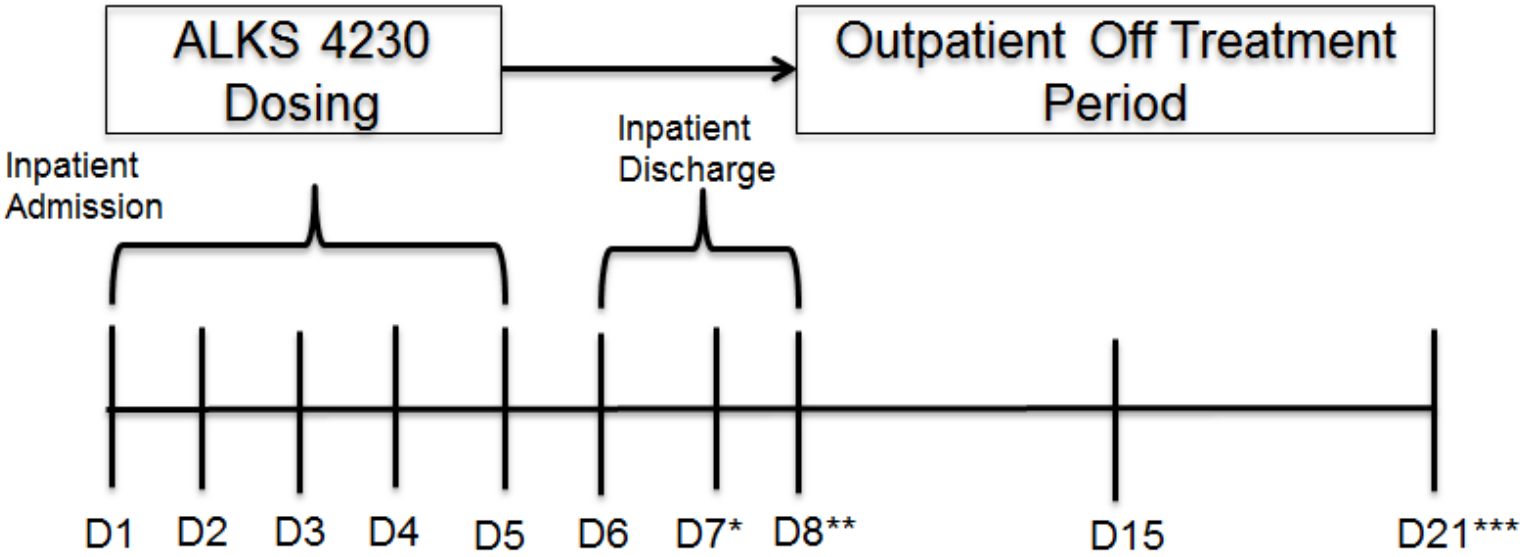
Abbreviations: DLT=dose-limiting toxicity, MTD=maximum tolerated dose, RP2D=recommended Phase 2 dose.

Figure 3: Treatment Cycle Schematic for Part A, Cycle 1



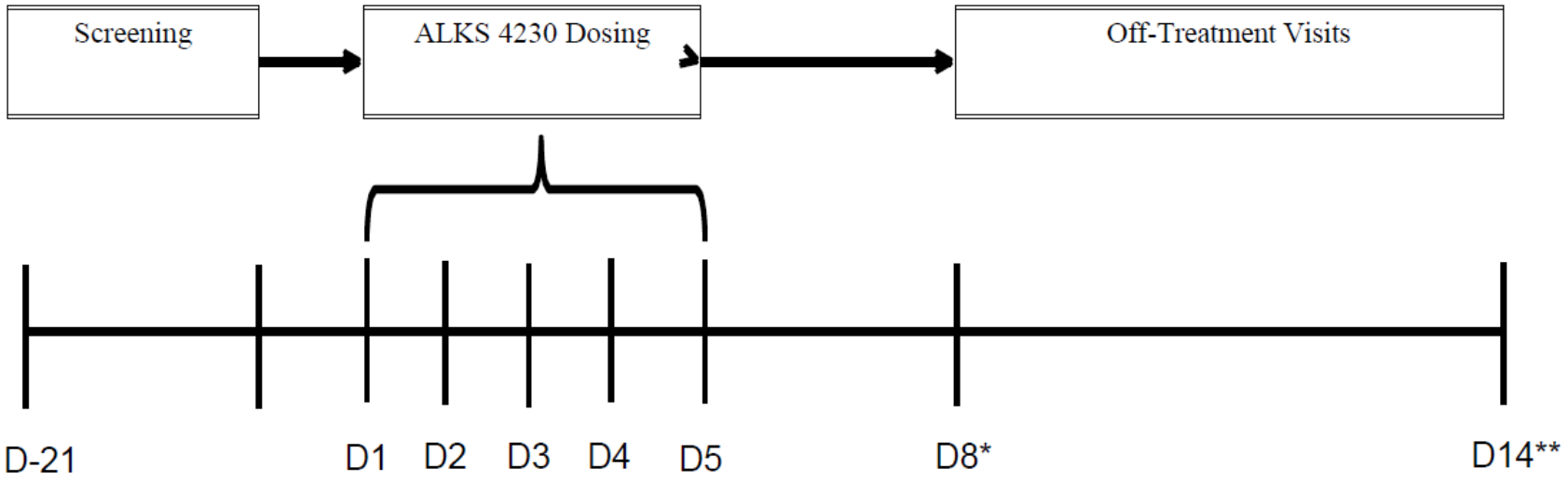
Abbreviations: D=day.
* Day 7 only required if subject experiences neutropenia requiring inpatient monitoring per criteria in Section 9.7. Timing of discharge is dependent on subject recovery per Section 9.7.
** There is a +2 day window for the Day 8 visit (Day 8 to 10).
***Signifies end of Cycle 1; there is no visit associated with Day 14.

Figure 4: Treatment Cycle Schematic for Part A, Cycle 2 and Subsequent Cycles



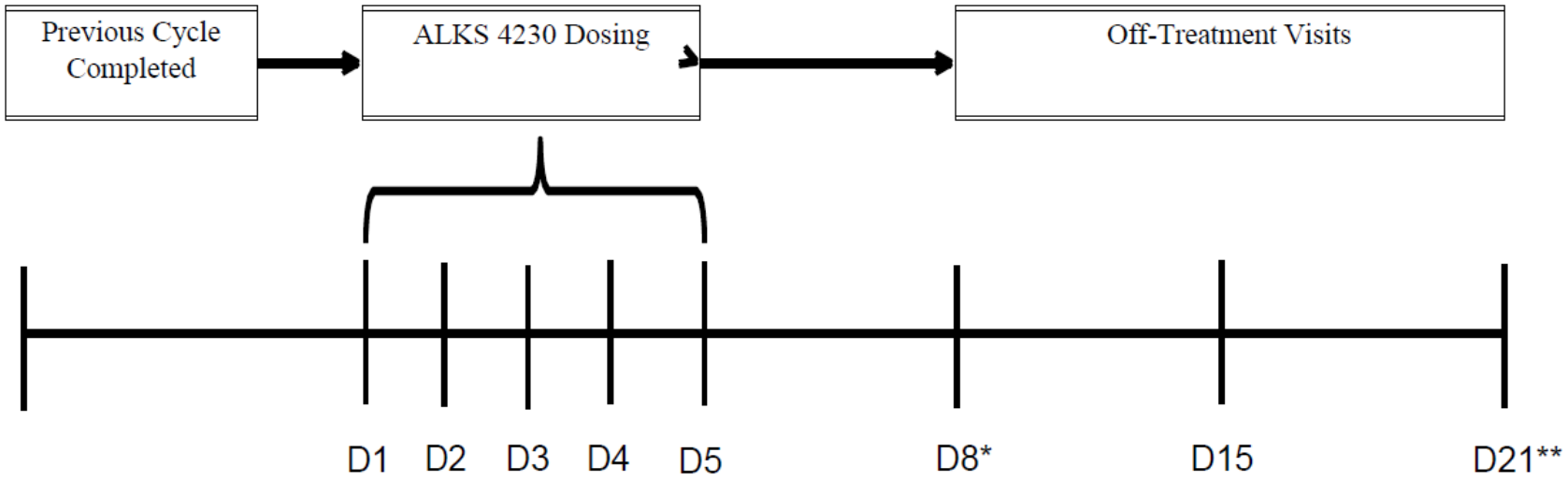
Abbreviations: D=day.
* Inpatient treatment not required for Cycles 3 and beyond. Day 7 only required if subject experiences neutropenia requiring inpatient monitoring per criteria in Section 9.7. Timing of discharge is dependent on subject recovery per Section 9.7.
** There is a +2 day window for the Day 8 visit (Day 8 to 10). For Cycle 3 and beyond, Day 8 visits will be virtual/phone visits.
***Signifies end of Cycle 2; there is no visit associated with Day 21.

Figure 5: Treatment Cycle Schematic for Part B, Cycle 1



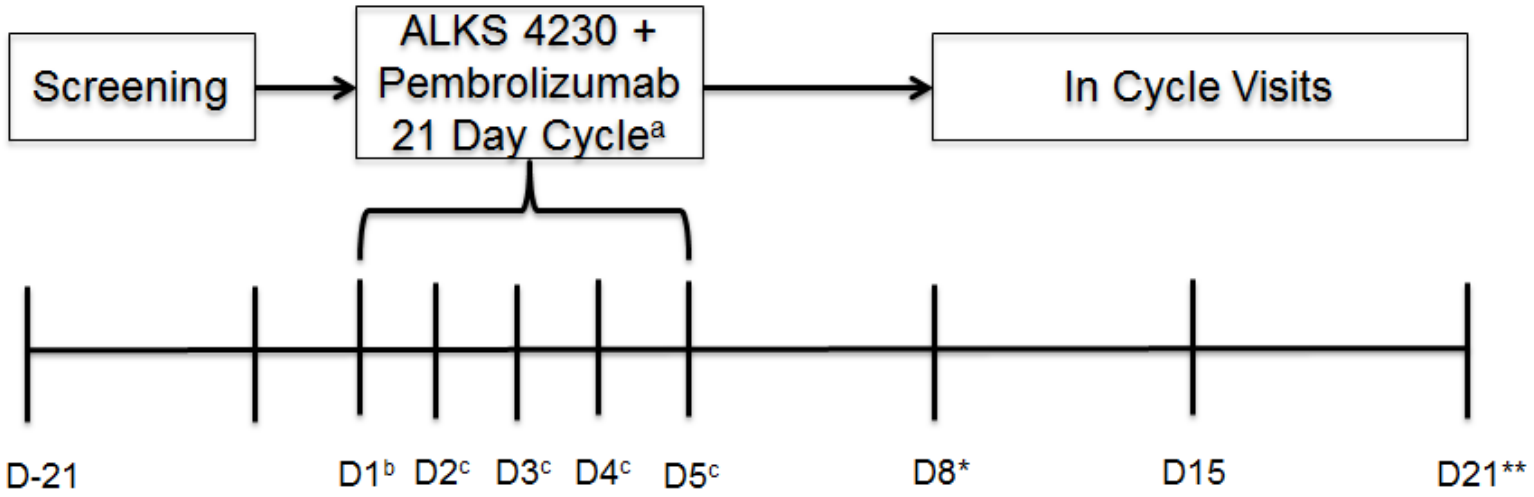
Abbreviations: D=day.
* There is a +2 day window for the Day 8 visit (Day 8 to 10).
** Signifies end of Cycle 1; there is no visit associated with Day 14.

Figure 6: Treatment Cycle Schematic for Part B, Cycle 2 and Subsequent Cycles



Abbreviations: D=day.
* There is a +2 day window for the Day 8 visit (Day 8 to 10). For Cycle 3 and beyond, Day 8 visits will be virtual/phone visits.
** Signifies end of cycle; there is no visit associated with Day 21.

Figure 7: Treatment Cycle Schematic for Part C, Cycle 1 and Subsequent Cycles



Abbreviations: D=day, SD=stable disease.
[a] Subjects will continue treatment for as long as they appear to be deriving clinical benefit (ie, objective response or SD) and have tolerated therapy well.
[b] Dosing of ALKS 4230 + pembrolizumab
[c] Dosing of ALKS 4230
* There is a +2-day window for the Day 8 visit (Days 8 to 10). For Cycle 3 and beyond, Day 8 visits will be virtual/phone visits.
** Signifies end of cycle; there is no visit associated with Day 21.

8.2. Schedules of Visits and Assessments

The schedules of visits and assessments for Part A, Part B, and Part C are shown in Table 5, Table 6, and Table 7, respectively. The schedule of visits and assessments for the Extension Phase of Parts B and C is shown in Table 8.

Table 5: Schedule of Assessments and Study Visits - Part A

Procedure	Screening (D-21 to D1)	CYCLE 1 (14 DAYS/CYCLE)								CYCLE 2 (21 DAYS/CYCLE)									CYCLE 3 AND BEYOND (21 DAYS/CYCLE)							EOT[a]	Safety Follow-Up Period	Follow-Up Assessments
Day		1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	15	1	2	3	4	5	8	15			
Window (days)									+2								+2	+1						+2	+1			
Informed consent	X																											
Eligibility criteria review	X																											
Demographics and medical history	X																											
Physical examination[b]	X	X								X									X							X		
Airway evaluation[c]	X	X								X									X							X		
Vital signs[d]	X	X	X	X	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Weight and height[f]	X	X								X									X									
ECOG performance score	X	X							X	X								X	X							X		
12-lead ECG	X[h]	X[g]				X[g]			X[g]	X[h]									X[h]							X[h]		
Hematology[i]	X	X		X		X			X	X		X		X			X	X	X				X			X		
Biochemistry[i]	X	X		X		X			X	X		X		X			X	X	X				X			X		
TSH[i]	X									X									X							X		
Serum tumor markers[j]	X									X[j]									X									
Coagulation panel[i]	X	X							X	X									X							X		
Pregnancy test[k]	X	X								X									X							X		
Urinalysis[i]	X	X							X	X									X							X		
Tumor imaging[l]	X																	X							X			X[m]

Table 5: Schedule of Assessments and Study Visits - Part A (Continued)

Procedure	Screening (D-21 to D1)	CYCLE 1 (14 DAYS/CYCLE)								CYCLE 2 (21 DAYS/CYCLE)									CYCLE 3 AND BEYOND (21 DAYS/CYCLE)							EOT[a]	Safety Follow-Up Period	Follow-Up Assessments
Day		1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	15	1	2	3	4	5	8	15			
Window (days)									+2								+2	+1						+2	+1			
Administration of ALKS 4230 (mandatory inpatient)[n]		X	X	X	X	X				X	X	X	X	X														
Administration of ALKS 4230 (optional outpatient)[n]																			X	X	X	X	X					
PK sampling[o]		X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X		X		X					
Immunophenotype sampling[p]		X	X	X	X	X			X	X	X	X	X	X			X	X	X				X					
Cytokine sampling[q]		X	X	X	X	X	X		X	X	X	X	X	X	X		X	X										
Immunogenicity sample[r]		X								X									X							X		
Archival tumor tissue sample[s]	X																											
Tumor biopsy[t]	X																X											
Prior and concomitant medications[u]	X	X	X	X	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[u v]	X	X	X	X	X	X	X	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[w]	

Abbreviations: ANC=absolute neutrophil count, ECG=standard 12-lead electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, IFN=interferon, IL=interleukin, iRECIST=Immune Response Evaluation Criteria in Solid Tumors, NK=natural killer, PK=pharmacokinetic, RECIST=Response Evaluation Criteria in Solid Tumors, TNF=tumor necrosis factor, TSH=thyroid-stimulating hormone.

[a] End-of-treatment assessments must be completed for all subjects. Once subjects have completed the EOT visit, subjects will be followed for the Safety Follow-up Period.

[b] Comprehensive physical examination to be done at screening and EOT. Brief physical examination focused on areas of disease or adverse events to be done on Day 1 of all treatment cycles.

[c] Airway evaluation to be done at times of the physical exam. Subjects with head and neck cancer only. See Section 8.3.7.1 for details of the Screening Airway Evaluation and Section 8.3.7.2 for details of the On Study Airway Evaluation.

[d] During dosing in Cycle 1 and Cycle 2, vital signs should be collected pretreatment, during the infusion, at end of infusion, and after the infusion at the following time points: 0.5 hour (±15 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), 3 hours (±15 minutes), 4 hours (±15 minutes), 6 hours (±15 minutes), 8 hours (±15 minutes), 12 hours (±15 minutes), and 16 hours (±15 minutes). For Cycle 3 and beyond, vital signs are to be collected during the following time points: pretreatment, middle of infusion, end of infusion; and after the infusion at the following time points: 0.5 hour (±15 minutes), 1 hour (±15 minutes), and 2 hours (±15 minutes). Blood pressure, pulse, and respiratory rate should be measured after the subject has been resting in a seated or supine position for at least 5 minutes. Section 8.3.6 for further details.

[e] These assessments are performed if the subject is hospitalized for monitoring due to neutropenia as per protocol. Subjects who are being monitored for neutropenia may be discharged from the hospital when they have recovered per guidance in protocol Section 9.7.

[f] Height is to be done only at screening. For the Day 1 visit, weight may be recorded up to 72 hours prior to Day 1.

[g] Triplicate ECG to be obtained on Cycle 1 Day 1, Day 5, and Day 8. Timing for ECG assessments is provided in Section 8.3.8.

[h] Single ECGs to be obtained at screening, on Day 1 of each subsequent cycle (Cycle 2 and beyond), and at EOT visit. Timing for ECG assessments is provided in Section 8.3.8.

[i] Blood and urine samples for laboratory assessment will be collected. On dosing days, samples must be collected prior to dosing. For Cycle 1 Day 1, blood and urine assessment does not need to be repeated if performed at screening within 7 days of Cycle 1 Day 1. Samples for laboratory assessments may be drawn up to 72 hours prior to dosing on Day 1. See Section 8.3.10, Table 10 for assessments.

[j] Serum tumor markers as appropriate. After Cycle 2, done only for even-numbered treatment cycles (eg, Cycles 4, 6, etc). See Section 8.3.10 for assessments.

[k] A pregnancy test (urine or serum) must be given to all women of childbearing potential before each treatment cycle begins. Pregnancy test results must be confirmed as negative before the first dose of each cycle is administered for all cycles. Pregnancy testing may be performed up to 72 hours prior to dosing on Day 1.

[l] Tumor imaging should include all appropriate radiographic procedures to document the full extent of the subject's known disease according to RECIST and iRECIST guidelines. Assessments are to be done at the end of Cycle 2 but before the next treatment cycle. For subsequent cycles, assessments are to be done at the end of each even-numbered treatment cycle (eg, Cycles 4, 6) but before the next treatment cycle. Tumor imaging should be done during the last week of the cycle.

[m] Subjects will have tumor imaging scans every 9 weeks during the Follow-up Assessment Period (until the subject discontinues from the study or starts a new therapy).

[n] ALKS 4230 will be given daily for Day 1 to 5 for each treatment cycle. For Cycles 1 and 2 for all dosing levels, all doses will be administered to subjects as inpatients at a medical facility with access to medical support measures and to the intensive care unit, if needed. Discharge is typically on Day 6 for Cycles 1 and 2. Dosing in subsequent cycles may be done as an outpatient. Anytime ALKS 4230 is administered, antipyretics should be administered prior (at least 15 minutes) to the infusion and should only be withheld at the discretion of the Investigator.

[o] PK samples will be collected on Day 1 and Day 5 of Cycle 1 and Cycle 2 at predose, at the completion of the infusion, and 1, 2, 4, 8, and 16 hours after the start of the infusion. Additional samples will be collected at predose on Days 2 through 4 and on Day 6 (24 hours post Day 5 dosing), Day 8 (Cycle 1 and Cycle 2), and Day 15 (Cycle 2 only). All 16-hour samples and the Day 6 (ie, Day 5, 24 hour) sample are optional. For Cycle 3 and beyond, all PK samples will be collected at predose and at the end of the infusion on Days 1, 3, and 5. All PK samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take PK samples from a central line used to infuse study drug. Details regarding PK sample draw windows are provided in Table 11 in Section 8.3.10.3.

[p] For Cycle 1 and Cycle 2, immunophenotyping samples (quantification of T cell, NK cell, and regulatory T cell counts in peripheral blood) will be collected on Day 1 and Day 5 predose and 4 hours (± 15 minutes) after the start of the ALKS 4230 infusion. Additional samples will be collected predose ALKS 4230 on

Day 2 through Day 4, Day 8 (Cycle 1 and 2), and Day 15 (Cycle 2 only). For Cycle 3 and beyond, Immunophenotype samples will be collected predose on Day 1 and Day 5. Immunophenotype draw windows are provided in Section 8.3.10.3.

[q] In Cycle 1 and Cycle 2, cytokine samples (for analysis of serum IFN-γ, TNF-α, IL-1, IL-6, and IL-10 levels) will be collected on Day 1 and Day 5 at predose and 1, 4, 8, and 16 hours after the start of the infusion. All 16-hour samples are optional. Additional samples will be collected at predose on Days 2 through 4 and on Day 6, Day 8 (Cycle 1 and Cycle 2), and Day 15 (Cycle 2 only). Details regarding cytokine sample draw windows are provided in Table 11 in Section 8.3.10.3.

[r] Immunogenicity will be collected predose on Day 1 of each dosing cycle. Immunogenicity draw windows are provided in Section 8.3.10.3.

[s] Archival tumor specimen at baseline in subjects with available paraffin-embedded tissue blocks and/or slides. Refer to Section 12.3.2.2 for further details.

[t] Tumor biopsy in subjects with accessible lesions (optional, not a study requirement). Refer to Section 12.3.2.1 for further details.

[u] Collection of concomitant medication and adverse events can be done by phone if no other assessments are scheduled for the designated day.

[v] In the event of Grade 4 neutropenia (where ANC <100/µL) or Grade 3 or higher febrile neutropenia the subject should be hospitalized for monitoring and assessments, managed as described in Section 9.7.

[w] Subjects will be contacted by the Investigator for phone visits during the Safety Follow-up Period to review any AEs at 30 days after the end of treatment and SAEs at 90 days after the end of treatment. SAEs considered by the Investigator to be related to the study drug or study procedures should be recorded.

Table 6: Schedule of Assessments and Study Visits - Part B

Procedure	Screen-ing	CYCLE 1 (14 DAYS/CYCLE)						CYCLE 2 (21 DAYS/CYCLE)							CYCLE 3 TO START OF EXTENSION PHASE * (21 DAYS/CYCLE)							EOT[a]	Safety Follow-up Period	Follow-Up Assess-ments
Day	(D-21 to D1)	1	2	3	4	5	8	1	2	3	4	5	8	15	1	2	3	4	5	8	15			
Window (days)							+2						+2	+1						+2	+1			
Informed consent	X																							
Eligibility criteria review	X																							
Demographics and medical history	X																							
Physical examination[b]	X	X						X							X							X		
Vital signs[c]	X	X	X	X	X	X		X	X	X	X	X	X[d]		X	X	X	X	X			X		
Weight and height[e]	X	X						X							X									
ECOG performance score	X	X					X	X						X	X							X		
12-lead ECG[f]	X	X						X							X							X		
Hematology[g,h]	X	X		X		X	X	X		X		X	X[d]	X	X				X			X		
Biochemistry[g]	X	X		X		X	X	X		X		X	X[d]	X	X				X			X		
TSH[g]	X							X							X							X		
Coagulation panel[g]	X	X					X	X							X							X		
Pregnancy test[i]	X	X						X							X							X		
Urinalysis[g]	X	X					X	X							X							X		
Tumor imaging[j]	X													X							X			X[k]
Administration of ALKS 4230[l]		X	X	X	X	X		X	X	X	X	X			X	X	X	X	X					
PK sampling[m]		X	X	X	X	X		X	X	X	X	X			X		X		X					

Table 6: Schedule of Assessments and Study Visits - Part B (Continued)

Procedure	Screening (D-21 to D1)	CYCLE 1 (14 DAYS/CYCLE)						CYCLE 2 (21 DAYS/CYCLE)							CYCLE 3 TO START OF EXTENSION PHASE * (21 DAYS/CYCLE)							EOT[a]	Safety Follow-up Period	Follow-Up Assessments
Immunophenotype sampling[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				X						
Cytokine sampling[o]		X	X	X	X	X		X	X	X	X	X		X											
Immunogenicity sample[p]		X						X							X							X			
Archival tumor tissue sample[q]	X																								
Tumor biopsy[r]	X												X												
ctDNA[s]	X						X	X							X							X			
Prior and concomitant medications[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events[t, h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[u]		

Abbreviations: ANC=absolute neutrophil count, ECG=standard 12-lead electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, IFN=interferon, IL=interleukin, iRECIST=Immune Response Evaluation Criteria in Solid Tumors, NK=natural killer, PK=pharmacokinetic, RECIST=Response Evaluation Criteria in Solid Tumors, TNF=tumor necrosis factor, TSH=thyroid-stimulating hormone.

* For procedures beyond 1 year of treatment (ie, after Cycle 18) please refer to the Schedule of Assessments of the Extension Phase (Table 8). 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.

[a] End-of-treatment assessments must be completed for all subjects. Once subjects have completed the EOT visit, subjects will be followed for the Safety Follow-up Period.

[b] Comprehensive physical examination to be done at screening and EOT. Brief physical examination focused on areas of disease or adverse events to be done on Day 1 of all treatment cycles.

[c] During dosing, vital signs are to be collected during the following time points: pretreatment, middle of infusion, end of infusion; and after the infusion at the following time points: 0.5 hour (±15 minutes), 1 hour (±15 minutes), and 2 hours (±15 minutes). Blood pressure, pulse, and respiratory rate should be measured after the subject has been resting in a seated or supine position for at least 5 minutes. See Section 8.3.6 for further details.

[d] Only required if biopsy is collected.

[e] Height is to be done only at screening. For the Day 1 visit, weight may be recorded up to 72 hours prior to Day 1.

[f] Single ECG to be obtained. Timing for ECG assessments is provided in Section 8.3.8.

[g] Blood and urine samples for laboratory assessment will be collected. On dosing days, samples must be collected prior to dosing. For Cycle 1 Day 1, blood and urine assessment does not need to be repeated if performed at screening within 7 days of Cycle 1 Day 1. Samples for laboratory assessments may be drawn up to 72 hours prior to dosing on Day 1. See Section 8.3.10, Table 10 for assessments.

[h] In the event of Grade 4 neutropenia (where ANC <100/µL) or Grade 3 or higher febrile neutropenia the subject should be hospitalized for monitoring and assessments, managed as described in Section 9.7.

[i] A pregnancy test (urine or serum) must be given to all women of childbearing potential before each treatment cycle begins. Pregnancy test results must be confirmed as negative before the first dose of each cycle is administered for all cycles. Pregnancy testing may be performed up to 72 hours prior to dosing on Day 1.

[j] Tumor imaging should include all appropriate radiographic procedures to document the full extent of the subject's known disease according to RECIST and iRECIST guidelines. Assessments are to be done at the end of Cycle 2 but before the next treatment cycle. For subsequent cycles, assessments are to be done at the end of each even-numbered treatment cycle (eg, Cycles 4, 6) but before the next treatment cycle. Tumor imaging should be done during the last week of the cycle.

[k] Subjects will have tumor imaging scans every 9 weeks during the Follow-up Assessment Period (until the subject discontinues from the study or starts a new therapy).

[l] Anytime ALKS 4230 is administered, antipyretics should be administered prior (at least 15 minutes) to the infusion and should only be withheld at the discretion of the Investigator.

[m] PK samples will be collected on Day 1 and Day 5 of Cycle 1 and Cycle 2 at predose, at the completion of the ALKS 4230 infusion, and 1, 2, 4, 8, and 16 hours after the start of the infusion. Additional samples will be collected at predose on Days 2 through 4 and on Day 6 (24 hours post Day 5 dosing). All 16-hour samples, the 8-hour sample on Day 5, and the Day 6 (ie, Day 5, 24 hour) sample are optional. For Cycle 3 and beyond, all PK samples will be collected at predose and at the end of the infusion on Days 1, 3, and 5. All PK samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take PK samples from a central line used to infuse study drug. Details regarding PK sample draw windows are provided in Table 11 in Section 8.3.10.3.

[n] For Cycle 1 and Cycle 2, immunophenotyping samples (quantification of T cell, NK cell, and regulatory T cell counts in peripheral blood) will be collected on Day 1 and Day 5 predose and 4 hours (± 15 minutes) after the start of the ALKS4230 infusion. Additional samples will be collected predose ALKS 4230 on Day 2 through Day 4, Day 8 (Cycle 1 and 2), and Day 15 (Cycle 2 only). For Cycle 3 and beyond, immunophenotype samples will be collected predose on Day 1 and Day 5.

[o] Cytokine samples (for analysis of serum IFN-γ, TNF-α, IL-1, IL-6, and IL-10 levels) will be collected on Day 1 and Day 5 at predose and 1, 4, 8, and 16 hours after the start of the ALKS 4230 infusion. All 16-hour samples are optional. Additional samples will be collected at predose on Days 2 through 4 and on Day 15 (Cycle 2 only). Details regarding cytokine sample draw windows are provided in Table 11 in Section 8.3.10.3.

[p] Immunogenicity will be collected predose on Day 1 of each dosing cycle. Immunogenicity draw windows are provided in Section 8.3.10.3.

[q] Archival tumor specimen at baseline in subjects with available paraffin-embedded tissue blocks and/or slides. Refer to Section 12.3.2.2 for further details.

[r] Tumor biopsy in subjects with accessible lesions (optional, not a study requirement). Refer to Section 12.3.2.1 for further details.

[s] ctDNA to be collected at screening, Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, and EOT. On dosing days, ctDNA to be collected prior to dosing.

[t] Collection of concomitant medication and adverse events can be done by phone if no other assessments are scheduled for the designated day.

[u] Subjects will be contacted by the Investigator for phone visits during the Safety Follow-up Period to review any AEs at 30 days after the end of treatment and SAEs at 90 days after the end of treatment. SAEs considered by the Investigator to be related to the study drug or study procedures should be recorded.

Table 7: Schedule of Assessments and Study Visits - Part C

Procedure	Screen-ing	CYCLE 1 (21 DAYS/CYCLE)							CYCLE 2 (21 DAYS/CYCLE)							CYCLE 3 TO START OF EXTENSION PHASE * (21 DAYS/CYCLE)							EOT[a]	Safety Follow-up Period	Follow-Up Assess-ments
Day	(D-21 to D1)	1	2	3	4	5	8	15	1	2	3	4	5	8	15	1	2	3	4	5	8	15			
Window (days)							+2	+1						+2	+1						+2	+1			
Informed consent	X																								
Eligibility criteria review	X																								
Demographics and medical history	X																								
Physical examination[b]	X	X							X							X							X		
Airway evaluation[c]	X	X							X							X							X		
Vital signs[d]	X	X	X	X	X	X	X		X	X	X	X	X	X[e]		X	X	X	X	X			X		
Weight and height[f]	X	X							X							X									
ECOG performance score	X	X					X		X						X	X							X		
12-lead ECG[g]	X	X				X			X							X							X		
Hematology[h,i]	X	X		X		X	X		X		X		X	X[e]	X	X				X			X		
Biochemistry[h]	X	X		X		X	X		X		X		X	X[e]	X	X				X			X		
TSH[h]	X								X							X							X		
Serum tumor markers[j]	X								X							X									
Coagulation panel[h]	X	X					X		X							X							X		
Pregnancy test[k]	X	X							X							X							X		
Urinalysis[h]	X	X					X		X							X							X		
Tumor imaging[l]	X														X							X			X[m]
Administration of ALKS 4230[n]		X	X	X	X	X			X	X	X	X	X			X	X	X	X	X					

Table 7: Schedule of Assessments and Study Visits - Part C (Continued)

Procedure	Screening (D-21 to D1)	CYCLE 1 (21 DAYS/CYCLE)							CYCLE 2 (21 DAYS/CYCLE)							CYCLE 3 TO START OF EXTENSION PHASE * (21 DAYS/CYCLE)							EOT[a]	Safety Follow-up Period	Follow-Up Assessments
Administration of Pembrolizumab		X							X							X									
PK sampling[o]		X	X	X	X	X			X	X	X	X	X			X		X		X					
Immunophenotype sampling[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X						
Cytokine sampling[q]		X	X	X	X	X			X	X	X	X	X													
Immunogenicity sample[r]		X							X							X							X		
Archival tumor tissue sample[s]	X																								
Tumor biopsy[t]	X													X											
ctDNA[u]	X						X		X							X							X		
Prior and concomitant medications[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[u,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[w]	

Abbreviations: ANC=absolute neutrophil count, ECG=standard 12-lead electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, IFN=interferon, IL=interleukin, INR=international normalized ratio, iRECIST=Immune Response Evaluation Criteria in Solid Tumors, NK=natural killer, PK=pharmacokinetic, RECIST=Response Evaluation Criteria in Solid Tumors, TNF=tumor necrosis factor, TSH=thyroid-stimulating hormone.

* For procedures beyond 1 year of treatment (ie, after Cycle 18) please refer to the Schedule of Assessments of the Extension Phase (Table 8). 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.

[a] End-of-treatment assessments must be completed for all subjects. Once subjects have completed the EOT visit, subjects will be followed for the Safety Follow-up Period.

[b] Comprehensive physical examination to be done at screening and EOT. Brief physical examination focused on areas of disease or adverse events to be done on Day 1 of all treatment cycles.

[c] Airway evaluation to be done at times of the physical exam. Subjects with head and neck cancer only. See Section 8.3.7.1 for details of the Screening Airway Evaluation and Section 8.3.7.2 for details of the On Study Airway Evaluation.

[d] In Cycle 1 and Cycle 2, Day 1 vital signs should be collected before pembrolizumab infusion, during pembrolizumab infusion and at end of pembrolizumab infusion. Vital signs should also be collected before ALKS 4230 infusion; during the infusion; at end of infusion; and 0.5, 1, 2, 3, 4, and 6 hours (±15 minutes) after ALKS 4230 infusion. During all other dosing days of Cycle 1 and Cycle 2, vital signs should be collected before ALKS 4230 infusion; during the

infusion; at end of infusion; and 0.5, 1, 2, 3, 4, and 6 hours (±15 minutes) after ALKS 4230 infusion. On dosing days in Cycles 3 and beyond, vital signs are to be collected before pembrolizumab infusion; middle of ALKS 4230 infusion; end of ALKS 4230 infusion; and 0.5, 1, and 2 hours (±15 minutes) after ALKS 4230 infusion. Blood pressure, pulse, and respiratory rate should be measured after the subject has been resting in a seated or supine position for at least 5 minutes. Section 8.3.6 for further details.

[e] Only required if biopsy is collected.

[f] Height is to be done only at screening. For the Day 1 visit, weight may be recorded up to 72 hours prior to Day 1.

[g] Single ECG to be obtained. Timing for ECG assessments is provided in Section 8.3.8.

[h] Blood and urine samples for laboratory assessment will be collected. On dosing days, samples must be collected prior to dosing (predose samples should be collected prior to first administration of any study drug, either pembrolizumab or ALKS 4230). For Cycle 1 Day 1, blood and urine assessments do not need to be repeated if performed at screening within 7 days of Cycle 1 Day 1. Samples for laboratory assessments may be drawn up to 72 hours prior to dosing on Day 1. See Section 8.3.10, Table 10 for assessments.

[i] In the event of Grade 4 neutropenia (where ANC <100/µL) or Grade 3 or higher febrile neutropenia the subject should be hospitalized for monitoring and assessments, managed as described in Section 9.7.

[j] After Cycle 2, done only for even-numbered treatment cycle (eg, Cycles 4, 6, etc).

[k] A pregnancy test (urine or serum) must be given to all women of childbearing potential before each treatment cycle begins. Pregnancy test results must be confirmed as negative before the first dose of each cycle is administered for all cycles. Pregnancy testing may be performed up to 72 hours prior to dosing on Day 1.

[l] Tumor imaging should include all appropriate radiographic procedures to document the full extent of the subject's known disease according to RECIST and iRECIST guidelines. For those subjects in the Part C rollover cohort (Cohort 4), who were initially enrolled into study Part A or Part B, the baseline tumor image is reset to for Part C will be the screening scan for Part C (not the previous screening scan from Part A or Part B). Assessments are to be done at the end of Cycle 2 but before the next treatment cycle. For subsequent cycles, assessments are to be done at the end of each even-numbered treatment cycle (eg, Cycles 4, 6) but before the next treatment cycle. Tumor imaging should be done during the last week of the cycle.

[m] Subjects will have tumor imaging scans every 9 weeks during the Follow-up Assessment Period (until the subject discontinues from the study or starts a new therapy).

[n] Anytime ALKS 4230 is administered, antipyretics should be administered prior (at least 15 minutes) to the infusion and should only be withheld at the discretion of the Investigator.

[o] PK samples will be collected on Day 1 and Day 5 of Cycle 1 and Cycle 2 at predose (predose samples should be collected prior to first administration of any study drug, either pembrolizumab or ALKS 4230), at the completion of the ALKS 4230 infusion, and 1, 2, 4, and 8 hours after the start of the ALKS 4230 infusion. Additional samples will be collected at predose on Days 2 through 4. For Cycle 3 and beyond, PK samples will be collected at predose and at the end of the ALKS 4230 infusion on Days 1, 3, and 5. All PK samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take PK samples from a central line used to infuse study drug. Details regarding PK sample draw windows are provided in Table 11 in Section 8.3.10.3. The 8-hour PK sample on Day 5 is optional.

[p] For Cycle 1 and Cycle 2, Immunophenotype samples (quantification of T cell, NK cell, and regulatory T cell counts in peripheral blood) will be collected on Day 1 and Day 5 predose (predose samples should be collected prior to first administration of any study drug, either pembrolizumab or ALKS 4230), and 4 hours (±15 minutes) after the start of the ALKS 4230 infusion. Additional samples will be collected predose on Days 2 through 4 and on Days 8 and 15. For Cycle 3 and beyond, immunophenotype samples will be collected predose on Day 1 and Day 5.

[q] For Cycle 1 and Cycle 2, Cytokine samples (for analysis of serum IFN-γ, TNF-α, IL-1, IL-6, and IL-10 levels) will be collected on Day 1 and Day 5 at predose (predose samples should be collected prior to first administration of any study drug, either pembrolizumab or ALKS 4230), and at 1, 4, and 8 hours after the

start of the ALKS 4230 infusion. Additional samples will be collected at predose on Days 2 through 4. Details regarding cytokine sample draw windows are provided in Table 11 in Section 8.3.10.3.

[r] Immunogenicity will be collected predose (predose samples should be collected prior to first administration of any study drug, either pembrolizumab or ALKS 4230) on Day 1 of each dosing cycle. Immunogenicity draw windows are provided in Section 8.3.10.3.

[s] Archival tumor specimen at baseline in subjects with available paraffin-embedded tissue blocks and/or slides. Refer to Section 12.3.2.2 for further details.

[t] Tumor biopsy in subjects with accessible lesions (optional, not a study requirement). Refer to Section 12.3.2.1 for further details.

[u] ctDNA to be collected at screening, Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, and EOT. On dosing days, ctDNA to be collected prior to dosing.

[v] Collection of concomitant medication and adverse events can be done by phone if no other assessments are scheduled for the designated day.

[w] Subjects will be contacted by the Investigator for phone visits during the Safety Follow-up Period to review any AEs at 30 days after the end of treatment and SAEs at 90 days after the end of treatment. SAEs considered by the Investigator to be related to the study drug or study procedures should be recorded.

Table 8: Schedule of Assessments and Study Visits - Extension Phase (Part B and Part C)

Procedure	CYCLES IN EXTENSION PHASE (21 DAYS/CYCLE) X=Every Cycle; (X)=Every 3 Cycles						EOT[a]	Safety Follow-up Period	Follow-Up Assessments
Day	1	2	3	4	5	21			
Window (days)						-7			
Physical examination[b]	(X)						X		
Vital signs[c]	(X)						X		
Weight[d]	X								
ECOG performance score	(X)						X		
Single ECG	(X)						X		
Hematology[e f,]	(X)						X		
Biochemistry[e]	(X)						X		
Thyroid-stimulating hormone[e]	(X)						X		
Coagulation panel[e]	(X)						X		
Pregnancy test[g]	X						X		
Urinalysis[e]	(X)						X		
Tumor imaging[h]						(X)			X[h]
Administration of ALKS 4230[i]	X	X	X	X	X				
PK sampling[j]	(X)								
Immunogenicity sample[k]	X						X		
ctDNA[l]	(X)						X		
Prior and concomitant medications[m]	X	X	X	X	X		X		
Adverse events[m f]	X	X	X	X	X		X	X[n]	
PART C EXTENSION ONLY									
Airway evaluation[o]	(X)						X		
Administration of Pembrolizumab	X								
Serum tumor markers[p]						(X)			

Abbreviations: ECG=standard 12-lead electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=end of treatment, iRECIST=Immune Response Evaluation Criteria in Solid Tumors, PK=pharmacokinetic, RECIST=Response Evaluation Criteria in Solid Tumors, Tx=treatment, X=Every Cycle, (X)=Every 3 Cycles.

[a] End-of-treatment assessments must be completed for all subjects. Once subjects have completed the EOT visit, subjects will be followed for the Safety Follow up Period.

[b] Brief physical examination focused on areas of disease or adverse events.

[c] In Part B Extension, vital signs are to be collected every 3 cycles: before ALKS 4230 infusion; middle of infusion; end of infusion; and 0.5, 1, and 2 hours (±15 minutes) after ALKS 4230 infusion. In Part C Extension, vital signs

are to be collected every 3 cycles: before pembrolizumab infusion; middle of ALKS 4230 infusion; end of ALKS 4230 infusion; and 0.5, 1, and 2 hours (±15 minutes) after ALKS 4230 infusion. Blood pressure, pulse, and respiratory rate should be measured after the subject has been resting in a seated or supine position for at least 5 minutes. See Section 8.3.6 for further details. Only clinically significant results are to be collected in the eCRF.

[d] For dose calculation, only clinically significant weight changes are to be collected in the eCRF.

[e] Blood and urine samples for laboratory assessment will be collected only if clinically indicated. On dosing days, samples must be collected prior to dosing. Samples for laboratory assessments may be drawn up to 72 hours prior to dosing on Day 1. See Section 8.3.10 and Table 10 for assessments. Only clinically significant results are to be collected in the eCRF.

[f] In the event of Grade 4 neutropenia (where absolute neutrophil count <100/µL) or Grade 3 or higher febrile neutropenia the subject should be hospitalized for monitoring and assessments, managed as described in Section 9.7.

[g] A pregnancy test (urine or serum) must be performed and must be negative for all women of childbearing potential at the beginning of each cycle prior to dosing on Day 1. Pregnancy testing may be performed up to 72 hours prior to dosing on Day 1. Pregnancy test results during the Extension Phase must be recorded in source documentation for monitoring purposes and are not required to be collected in the eCRF.

[h] Tumor imaging should include all appropriate radiographic procedures to document the full extent of the subject's known disease according to RECIST and iRECIST guidelines. Assessments are to be done every 3 cycles during the last week of the cycle (before the next treatment cycle). Subjects will have tumor imaging scans every 12 weeks during the Follow-up Assessment Period (until the subject discontinues from the study or starts a new therapy).

[i] Anytime ALKS 4230 is administered, antipyretics should be administered prior (at least 15 minutes) to the infusion and should only be withheld at the discretion of the Investigator.

[j] PK samples will be collected every 3 cycles. In the first cycle of the Extension Phase, samples will be collected on Day 1 at predose (prior to first administration of any study drug, either pembrolizumab or ALKS 4230) and at completion of the ALKS 4230 infusion. For other cycles, PK samples will be collected only at the completion of the ALKS 4230 infusion.

[k] Immunogenicity samples will be collected every 3 cycles at predose (prior to first administration of any study drug, either pembrolizumab or ALKS 4230).

[l] Every 3 Cycles, on dosing days, ctDNA to be collected prior to dosing.

[m] Collection of concomitant medication and adverse events for the remaining cycle days (Days 6 to 21) can be done on Day 1 of the next cycle or EOT (as applicable).

[n] Subjects will be contacted by the Investigator for phone visits during the Safety Follow-up Period to review any adverse events at 30 days after the end of treatment and serious adverse events at 90 days after the end of treatment. Serious adverse events considered by the Investigator to be related to the study drug or study procedures should be recorded.

[o] Airway evaluation to be done at times of the physical exam. Subjects with head and neck cancer only. See Section 8.3.7.2 for details of the On Study Airway Evaluation.

[p] Serum tumor markers as appropriate; in the same day of tumor imaging.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedules of assessments are provided in Table 5, Table 6, Table 7, and Table 8. This study will be conducted in 3 parts: Part A, Part B, and Part C. The procedures described in this section will be carried out separately for each part. Data cleaning and database lock may occur separately for each part.

8.3.1. Informed Consent

The nature of the study and its risks and potential benefits will be explained to the subject by the Principal Investigator or designated study personnel as outlined in Section 17.3.

Before the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential subject.

8.3.2. Eligibility Review

An eligibility review will be conducted by the Investigator at the visits specified in Table 5, Table 6, and Table 7 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

8.3.3. Demographics and Medical History

Subject's demographic data and medical history will be reviewed and documented at the time point specified in Table 5, Table 6, and Table 7.

The following will be documented for cancer history, if available

- Primary cancer diagnosis
- Date of first diagnosis
- Mutational status if known (eg, MSI/MSS, BRCA1, BRCA2)
- PD-L1 status if known
- HPV status if known (subjects with head and neck cancer)

8.3.4. Prior Medication Review

At the time point(s) specified in Table 5, Table 6, Table 7, and Table 8, prospective subjects are to provide a history of all anticancer medications, and a history of all other types of medications taken in the last 30 days, including prescription and nonprescription medications, vitamins, and supplements.

The Investigator will record the following data on all medications used by the subject: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

Information collected on prior anticancer medications will be:

- Information on prior neoadjuvant/adjuvant treatment, if applicable:
  - Agents used in treatment
- Information on previous anticancer treatments (eg, radiation, systemic therapy, surgery):
  - Agents used in all treatments
- Best response for each line of therapy

8.3.5. Concomitant Medication Review

Subjects will be asked about all concomitant medications at the time points specified in Table 5, Table 6, Table 7, and Table 8, including prescription and nonprescription medications, vitamins, and supplements.

The following data on all medications used by the subject: name, dose, start and stop dates, and the indication for use will be recorded.

8.3.6. Vital Signs, Height, and Weight

Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature), weight, and height will be assessed at the time points specified in Table 5, Table 6, Table 7, and Table 8.

Blood pressure, pulse, and respiratory rate will be measured after the subject has been resting in a seated or supine position for at least 5 minutes.

8.3.7. Physical Examination

A physical examination will be performed at the time points specified in Table 5, Table 6, Table 7, and Table 8.

8.3.7.1. Screening Airway Evaluation for Subjects With Head and Neck Cancer Only

All subjects whose primary oncologic diagnosis is "head and neck cancer" (regardless of histology, ie, whether squamous cell carcinoma of the upper aerodigestive tract, salivary gland cancer, sarcoma, etc) and who manifest active loco-regional disease and/or have had a prior tracheostomy shall undergo flexible fiberoptic laryngoscopy (FFL) by an appropriately trained practitioner at the time of screening, for the purposes of determining airway stability. (FFL reports shall be recorded in the respective subject's chart as a source document.) Subjects whose airways are deemed unstable or potentially unstable (threatened) on FFL shall be referred to a qualified ear, nose, and throat or head and neck surgeon for further evaluation and clearance or definitive management, prior to receiving investigational product(s).

Subjects with an existing tracheostomy shall be exempted from the above.

8.3.7.2. On Study Airway Evaluation for Subjects With Head and Neck Cancer Only

While receiving investigational product(s), at the time of each scheduled physical exam (per protocol), all subjects whose primary diagnosis is "head and neck cancer" shall undergo pulse oximetry and assessment for subjective dyspnea, stridor, tachypnea, and use of accessory respiratory muscles. Subjects whose pulse oximetry is less than baseline by 5% or more and/or who are deemed to be stridorous, tachypneic and/or dyspneic shall have investigational product administration temporarily withheld and shall be referred for emergent formal airway evaluation.

Tracheostomy removal (decannulation), except for regular cleaning and/or replacement, shall not be undertaken during any subject's (regardless of whether the active oncologic diagnosis is head and neck cancer or a different malignancy) time on investigational product(s) unless specifically cleared by the Sponsor's Medical Monitor.

8.3.8. Standard 12-Lead Electrocardiogram

Part A:

Triplicate (5 minutes apart) electrocardiograms (ECGs) will be obtained in Cycle 1 at predose, at the end of infusion (+15 minutes), and 4 hours (±15 minutes) after the start of the infusion on Day 1 and Day 5, and at a single timepoint on Day 8.

Single ECGs will be obtained at screening, predose on Day 1 of all subsequent cycles (Cycle 2 and beyond), and at the EOT visit.

Part B:

Single ECGs will be obtained at screening, predose on Day 1 of every dosing cycle, and at the EOT visit.

Part C:

Single ECGs will be obtained at screening, predose (predose assessment is prior to first administration of any study drug, either pembrolizumab or ALKS 4230), at the end of ALKS 4230 infusion (+15 minutes), and 4 hours (±15 minutes) after the start of ALKS 4230 infusion on Day 1 and Day 5 of Cycle 1, and predose (predose assessment is prior to first administration of any study drug, either pembrolizumab or ALKS 4230) on Day 1 of all subsequent cycles (Cycle 2 and beyond), and at the EOT visit.

8.3.9. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status assesses the subjects' activity status and will be assessed at the time points specified in Table 5, Table 6, Table 7, and Table 8. Possible scores are 0 to 5. Descriptions of activity status are presented in Table 9.

Table 9: 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).

8.3.10. Laboratory Assessments

8.3.10.1. Hematology, Biochemistry, Microbiology, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 5, Table 6, Table 7, and Table 8. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 10. Samples will be collected in accordance with the site's usual procedures and analyzed by the site's local laboratory for hematology, biochemistry, and urinalysis.

Fasting is not required prior to sample collection for laboratory assessments.

In the event that any microbiology specimens are obtained for culture, results should be recorded in the eCRF.

Table 10: Clinical Laboratory Assessments

<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
<u>Thyroid Test</u>
• Thyroid-stimulating hormone
<u>Serum Tumor Marker</u>
• 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>

8.3.10.2. Pregnancy Testing

A serum or urine pregnancy test will be administered to all WOCBP at the time points specified in Table 5, Table 6, Table 7 and Table 8. At the screening visit, results must be negative for the subject to be eligible for the study. Pregnancy test results must be confirmed as negative before the first dose of each cycle is administered for all cycles.

8.3.10.3. Pharmacokinetic, Pharmacodynamic, Immunogenicity, and Immunophenotype Testing

Samples for PK, pharmacodynamic, and immunogenicity testing will be obtained at the time points specified in Table 5, Table 6, Table 7, and Table 8. All PK and immunogenicity samples should be drawn from the arm opposite of the arm used to infuse study drug. Do not take PK samples from a central line used to infuse study drug. Time point draw windows (minutes) are summarized in Table 11.

Table 11: Blood Draw Time Windows

Draw Window	+5 Minutes	±5 Minutes	±15 Minutes	±60 Minutes	+2 Days (Day 8-10)	±24 Hours
Draw time	End of Infusion	1 hour after infusion	2, 4, 8, and 16 hours after start of infusion*	Day 6 (Day 5 + 24 hours)*	Day 8	Day 15

* Denotes an optional sample

Samples will be collected in accordance with the site's usual procedures. A Laboratory Manual is provided to the sites by the central laboratory with details regarding the collection, handling, and shipping of samples for PK, pharmacodynamics, and immunogenicity testing.

8.3.11. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be administered at the time point(s) specified in Table 5, Table 6, Table 7, and Table 8.

8.3.12. Tumor Imaging and Disease Assessments

Disease assessments will be made at the time point(s) specified in Table 5, Table 6, Table 7, and Table 8. Assessments will be based on Investigator review of the radiographic or photographic images as defined by RECIST and iRECIST. Tumor images will be collected and stored centrally. Centralized readings may be used to assess scans beginning in the second stage (N2) of Part B cohorts and Part C C5, C6, and C7 cohorts.

8.3.13. Adverse Event Monitoring

Adverse events will be collected from the time a subject signs the informed consent document until the completion of the final study visit (see Table 5, Table 6, Table 7, and Table 8). Adverse events and serious AEs (SAEs) are defined in Section 13.1 and Section 13.2, respectively.

Section 13.4 provides guidance on the monitoring and reporting requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

See Section 8.1 for the monitoring and definitions of DLTs.

8.3.14. Tumor Tissue Assessments (Optional)

Biopsies of tumors in subjects with accessible lesions are taken at baseline and at time points specified in Table 5, Table 6, and Table 7. This is optional for subjects.

The on-treatment biopsy should be taken at the same site as the baseline biopsy if feasible.

8.4. Study Requirements and Restrictions

8.4.1. Inpatient Treatment

All subjects participating in the dose-escalation (Part A) portion of the study will stay at a medical facility with immediate access to intensive care unit and medical support measures for the dosing days of the first 2 cycles of therapy and will be discharged 24 hours after the last dose if medically stable. This will apply to all subjects at each dose level in the dose-escalation portion of the protocol. If a subject experiences an AE/SAE of concern to the Investigator or a DLT in any cycle, the Investigator may choose to administer the next dose or next cycle of doses in an inpatient setting, if continued dosing is deemed appropriate for that subject. In the absence of any of the events that define a DLT, subjects may receive subsequent cycles after Cycle 2 of ALKS 4230 in an outpatient setting. Dosing in subsequent cycles may also be administered to subjects as inpatients, if necessary based on the opinion of the Investigator.

Inpatient treatment and observation are not mandatory for Part B or Part C of the study.

Subjects should be hospitalized for monitoring (for either Part A, Part B, or Part C) in the event of Grade 4 neutropenia (where ANC <100/μL) or Grade 3 or higher febrile neutropenia, as outlined in Section 9.7.

Any subject in any part of the study may be admitted to the hospital for observation and safety monitoring at any time during the study if the Investigator believes it to be in the best interest of the subject.

8.4.2. Contraception and Pregnancy

All WOCBP and all men (if their sexual partners are WOCBP) must use at least two methods of contraception, at least one of which is considered highly effective, during the study and 90 days after the final dose of study drug (for subjects in Part A and Part B) or 4 months after the final dose of study drug (for subjects in Part C), if heterosexually active. A woman is considered as a WOCBP (fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include total hysterectomy and/or bilateral salpingectomy and/or bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

Highly effective methods of contraception include the following:

- Combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation. Delivery may be oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation. Delivery may be oral, injectable, or implantable.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or occlusion
- Bilateral vasectomy (provided that the male has a medical assessment of surgical success)
- True sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk, in line with the preferred and usual lifestyle of the subject)

All female subjects of childbearing potential will receive a pregnancy test (serum or urine) at screening and a negative result must be confirmed before the first dose in each cycle of treatment. If a subject becomes pregnant while participating in the study, she will be discontinued from study drug immediately. The early termination and safety follow-up visits will be scheduled and the pregnancy will be reported to Alkermes. Pregnancies in female partners of male subjects should also be reported and will be followed in the same manner. Additional follow-up may be required.

In the event of a pregnancy, a Pregnancy Report Form must be submitted to Alkermes (fax number in Section 13.5) within 24 hours of awareness of the pregnancy, irrespective of whether an AE has occurred. The pregnancy will be followed until completion or termination. If the outcome of the pregnancy meets the criteria for classification as an SAE it should be reported following the SAE procedure (see Section 13.5).

8.4.3. Concomitant and Prohibited Medications

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care. All concomitant medications and treatments will be documented on the eCRF.

The following treatments are not permitted during the study:

- Any other investigational treatment
- Any other systemic antineoplastic therapy including, but not limited to, cytotoxic chemotherapy, immunotherapy, targeted agents, hormonal therapy (except luteinizing hormone-releasing hormone antagonists or agonists for prostate cancer started at least 3 months before Cycle 1, Day 1 of ALKS 4230) or monoclonal antibody therapy
- Radiotherapy, including systemically administered radioisotopes; only palliative radiotherapy to a nontarget lesion is allowed at the discretion of the Medical Monitor

- Hematopoietic growth factors. In Part A, hematopoietic growth factors are prohibited during the DLT evaluation period. At all other times in Part A, and at all time in Parts B and C, hematopoietic growth factors may be used as clinically indicated.
- Pharmacologic doses of corticosteroids (greater than 10 mg of prednisone daily, or equivalent); topical, ophthalmological, and inhalational corticosteroids are permitted. Use of glucocorticoids for the purpose of treating immune-mediated AEs is permitted (see Section 9.8) but may result in discontinuation from study based on consultation between the Investigator and the Medical Monitor.

Medroxyprogesterone or megestrol acetate may be given to subjects without breast cancer as an appetite stimulant and bisphosphonates or denosumab may be administered to subjects with bone metastases if started 60 days before study entry.

As ALKS 4230 is a protein, there are no anticipated metabolic drug-drug interactions.

8.4.3.1. Premedication

Antipyretics are required throughout the ALKS 4230 treatment period. To reduce the potential for infusion-related fever or chills, premedication with an antipyretic agent (nonsteroidal anti-inflammatory drugs and acetaminophen) is required at least 15 minutes prior to ALKS 4230 administration and should continue for at least 12 hours after the last dose of ALKS 4230 unless the Investigator has a rationale to withhold it from the subject.

8.5. Definition of End of the Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the Safety Follow-up Period and Follow-up Assessments or the last scheduled visit as indicated in the Schedule of Assessments (Table 5, Table 6, Table 7, and Table 8).

The end of the study will be the last subject's last visit (if applicable, the last phone call with the Investigator during the Safety Follow-up Period and Follow-up Assessments) as indicated in the Schedule of Assessments (Table 5, Table 6, Table 7, and Table 8).

8.6. Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the Institutional Review Board (IRB) or independent ethics committee and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

9.1.1. ALKS 4230 Dosing and Administration

ALKS 4230 will be administered IV as a 30-minute infusion through a 0.22 µm in-line filter 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 3 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 dose may be reduced by one dose level as needed at the discretion of the Investigator. Study drug dose adjustments for all subjects are described in Section 9.6.

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 (ie, 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 judgment. All subjects 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.

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.

9.1.2. 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, for up to 2 years as long as subjects are deriving clinical benefit (ie, objective response or SD), 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, as described in Section 9.1.1.

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 (ie, 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]

9.2. Infusion-Related Reactions

ALKS 4230 may be associated with infusion-related reactions, including pyrexia, tachycardia, and chills with onset 3-6 hours postinfusion. Infusion-related reactions should be treated at the discretion of the Investigator. [redacted]

Refer to Section 8.4.3.1 for guidance around medications used for pretreatment.

Infusion-related reactions associated with the use of pembrolizumab should be managed in accordance with the prescribing information for pembrolizumab (Keytruda [pembrolizumab] USPI).

9.3. Treatment Adherence

ALKS 4230 and pembrolizumab will be administered at a medical facility or study center by study staff; therefore, compliance is ensured. The clinical research associates will confirm study drug was administered and documented in subject's eCRFs during site visits.

9.4. Method of Assigning Subjects to Treatment

Randomization is not planned for this open-label study.

9.5. Blinding

Not applicable for this open-label study.

9.6. Study Drug Dose Adjustments and Stopping Rules

9.6.1. Adverse Events Observed After Dose-Limiting Toxicity Observation Period

Subjects who are part of the first dose cohort who experience an event that meets the definition of a DLT during Cycle 1 or Cycle 2 will be removed from the study. Beyond C2D15, if a subject experiences a DLT, a dose reduction of one level (Table 1) may be allowed and treatment continued at this reduced dose for all subsequent cycles. If a subject has another DLT at the reduced level, another dose reduction may be allowed if, in the Investigator's opinion, benefit-risk assessment warrants continuing ALKS 4230. The Investigator should consult with the Medical Monitor for approval to continue to treat at reduced dose. A subject who experiences a third DLT after 2 dose reductions should be discontinued from study treatment.

9.6.2. Management of Missed Doses

[redacted]

9.6.3. Intrapatient Dose Escalation

Under the circumstances described below, an individual subject may be permitted to have his/her dose escalated (ie, intrapatient dose escalation) upon the mutual agreement of the Investigator and the Medical Monitor. Such escalations would increase the subject's dose to the protocol-defined dose level that is one level higher than the subject's current dose level. For such escalation to be considered for a subject, the following criteria must be met:

- The subject must have tolerated his/her current dose level without experiencing a DLT;
- The higher dose level being considered for the subject must have had its cohort enrolled and determined by the SRC to not exceed the MTD and;
- The Investigator must believe that the dose escalation is in the best interest of the subject.

A subject may have more than one dose escalation. The above criteria must be met for each escalation.

For subjects in Part C Cohorts C1, C2, C3, or C4, intrapatient dose escalation may be considered for subjects who had been assigned to the 1 µg/kg/day dose level or the 3 µg/kg/day dose level and adequately tolerated combination therapy. Escalation to a dose of 6 µg/kg/day or above may be considered after the SRC has determined the dose level to be adequately tolerated.

9.6.4. Cycle Delays

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted].

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]		[redacted]

[redacted]

9.7. Treatment of Toxicities of ALKS 4230

CCI

[redacted]

CCI

[redacted]

9.8. Treatment of Immune-mediated Adverse Events

For AEs that the Investigator believes may be attributable to pembrolizumab, the prescribing information for pembrolizumab (Keytruda [pembrolizumab] USPI) can be reviewed for additional information.

[redacted]

9.9. Guidance for Measures to Address Hypotension

Hypotension has been reported in subjects receiving ALKS 4230 and preventive measures to reduce hypotension may be used as indicated. These include:

- Oral intake of up to 2L per day of electrolyte-containing fluid for Days 1-5 of every cycle
- Antihypertensive medications held 24-48 hours prior to dosing
- IV fluids during clinic visits
- Avoid fasting in advance of coming for study visits

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

[redacted]

ALKS 4230 is to be administered as an IV infusion as described in Section 9.1.1.

The Directions for Use will be distributed to the study centers and will provide detailed dose preparation, handling, and administration instructions.

Pembrolizumab is to be administered as an IV infusion over 30 minutes in a dose of 200 mg every 3 weeks for as long as subjects are deriving clinical benefit. Pembrolizumab is to be administered as described in Section 9.1.2.

Pembrolizumab is to be obtained from the study sites' pharmacies, from commercial supplies, or provided by Sponsor. [redacted]

10.2. Packaging and Labeling

[redacted]

10.3. Storage

[redacted]

10.4. Handling and Disposal

Following completion and verification of accountability logs, all vials must be destroyed. Vials may be destroyed on site according to GCP and site practice. Alternatively, the Sponsor may

arrange for destruction with a third-party vendor operating in accordance with GCP and/or Good Manufacturing Practice, as applicable.

10.5. Accountability

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug transport records during the study and/or at the end of the study.

11. ASSESSMENT OF ANTITUMOR ACTIVITY

Tumor Assessments

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 scanning, magnetic resonance imaging, 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 and iRECIST criteria for Parts A, B, and C.

Refer to the guidelines for RECIST, tumors are assessed as CR, PR, SD, or PD.

Refer to the guidelines for iRECIST, tumors are assessed as immune CR (iCR), immune PR (iPR), immune SD (iSD), or immune PD (iPD).

For purposes of this study, subjects must meet the definition for SD/iSD for a minimum of 12 weeks before this assessment can be determined.

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.

The ORR/iORR is the number of subjects exhibiting a CR/iCR or PR or iPR divided by the number of subjects evaluable for antitumor activity. Duration of response will also be determined. The ORR/iORR will be calculated separately for subjects in the dose-escalation portion of the study (Part A), in the dose-expansion part of the study (Part B), and in the combination therapy part of the study (Part C). Tumor images will be collected and stored centrally. Centralized readings may be used to assess scans beginning in the second stage (N2) of Part B cohorts and Part C C5, C6, and C7 cohorts.

Antitumor activity will be expressed as the following:

- ORR based on RECIST
- iORR based on iRECIST
- DCR per RECIST
- iDCR per iRECIST
- DOR per RECIST
- iDOR per iRECIST
- PFS per RECIST
- Immune PFS (iPFS) per iRECIST
- DRR per RECIST (Part B and Part C5, C6, C7)
- iDRR per iRECIST (Part B and Part C5, C6, C7)

12. ASSESSMENT OF PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY

12.1. Pharmacokinetics

Serum samples for evaluation of ALKS 4230 PK will be obtained from each subject at predetermined time points. A validated electrochemiluminescence method using the Meso Scale Discovery platform will be used for the quantitation of ALKS 4230 in human serum.

Noncompartmental PK analysis will be performed to estimate the PK parameters for ALKS 4230.

Remaining serum PK samples obtained during scheduled PK blood draws in Part C, as noted in Table 7, may be analyzed for pembrolizumab concentrations at a future date.

12.2. Immunogenicity

Serum samples for evaluation of anti-ALKS 4230 antibody induction will be obtained from each subject at predetermined time points. A validated electrochemiluminescence method using the Meso Scale Discovery platform will be used for the detection of antidrug antibodies to ALKS 4230 in human serum. The assessment of immune-response induction for each study subject will be based on the comparison of the predose and postdose sample results.

12.3. Pharmacodynamics and Biomarkers

The pharmacodynamic response of various biomarkers will be assessed in blood and serum samples collected from all subjects in the study. Additional biomarker analyses may be performed on tumor tissue samples, which are optional for study subjects.

12.3.1. Blood-Based Biomarkers

The pharmacodynamic effect of ALKS 4230 is assessed by measuring circulating CD8+ T cells, T_{regs}, and NK cells in peripheral blood by flow cytometry from each subject at predetermined time points.

In addition, serum samples will be obtained from each subject at predetermined time points. Concentration of multiple proinflammatory cytokines including interferon-γ, tumor necrosis factor-α, IL-1β, IL-6, and IL-10 will be determined.

Circulating tumor DNA (ctDNA) will also be measured at predetermined time points.

12.3.2. Tumor Tissue Biomarkers

12.3.2.1. Tumor Biopsies

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 subjects.

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. Comparison of on-treatment versus baseline results can be used to demonstrate the pharmacologic impact to tumor microenvironment. The analysis of the baseline tumor tissues will be used for correlative analysis. Refer to the Laboratory Manual for tumor sample handling and processing information.

12.3.2.2. Archived Tumor

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), if available. 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. For subjects who have available samples of formalin-fixed, paraffin-embedded tumor tissue, 15 unstained glass slides of tissue sections will be provided, to be analyzed. 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. Comparison of on-treatment versus baseline results can be used to demonstrate the pharmacologic impact to tumor microenvironment. The analysis of the baseline tumor tissues will be used for correlative analysis. Refer to the Laboratory Manual for tumor sample handling and processing information.

13. ASSESSMENT OF SAFETY

Safety will be assessed on the basis of:

- Reporting of AEs
- Collection of vital signs (ie, systolic and diastolic blood pressure, pulse, respiratory rate, and body temperature) and weight
- Clinical laboratory parameters (ie, hematology, chemistry, and urinalysis; see Section 8.3.10)
- ECG parameters (overall assessment; heart rate; RR, PR, QRS, and QTc intervals)

13.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that subject and is considered clinically significant. Thus, an AE can be any unintended and unfavorable physical sign, laboratory parameter, or symptom that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, regardless of relationship to investigational treatment.

Illnesses present before the subject signing the informed consent form (ICF) are considered to be preexisting conditions and are documented on the medical history eCRF. Any new or preexisting conditions that worsen during the study are entered on the AE eCRF. Disease progression is not considered as an AE or SAE. Death resulting from disease progression should not be reported as an SAE.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator, and may or may not be an AE. An abnormal lab value may be considered an AE under the following conditions:

- It is clinically significant
- It is an SAE (eg, it requires hospitalization)
- It requires medical intervention
- It requires a change or delay in the administration of study drug or permanent discontinuation of study drug

Clinically significant values will be considered AEs and recorded as such on the eCRFs. Laboratory values that do not meet one of the above criteria are not required to be reported as AEs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.2, the pregnancy must be reported to Alkermes and additional follow-up may be required.

13.2. Definition of Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent and significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require intervention to prevent one of the other outcomes listed above.

Admission to a hospital or an inpatient unit for a nonmedical reason (ie, social stay admission) during the study in the absence of untoward medical occurrence will not be considered as an SAE, but will be reported as an AE.

Hospitalization due to worsening of behavioral health related issues should be reported as an SAE.

13.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated subinvestigator) according to his/her best clinical judgment. The criteria listed in Table 14 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

For subjects participating in Part C of the study, AE causality relationships will be attributed to both pembrolizumab and ALKS 4230 unless it is explicitly stated otherwise by the Investigator (eg, if the AE occurs immediately after pembrolizumab is administered and prior to ALKS 4230 administration).

Table 14: Adverse Event Causality Guidelines

Relationship	Criteria for Assessment
Definitely related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
Probably not related	There is evidence of exposure to the test drug. AND There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
Definitely not related	The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

13.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a subject signs the ICF and will continue until 30 days after the final dose of study drug. Any SAE that the Investigator attributes to study drug with onset any time after the 30-day period must be reported. Subjects with ongoing AEs will be followed by the Investigator until the AE has resolved or returned to the baseline level.

The Investigator, Medical Monitor, and Sponsor will review the collected data regularly for evidence of AEs. All subjects will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using NCI CTCAE version 4.03 or higher. Refer to the NCI CTCAE website for descriptions of Grades 1 through 5 for AEs.

Subjects will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will assess all AEs regarding any causal relationship to the study drug (see Section 13.3), the intensity (severity) of the event, action taken, and subject outcome. Refer to the NCI CTCAE website for descriptions of AE severities.

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure will be used as the reference document to designate event expectedness. For AEs associated with pembrolizumab, the prescribing information for pembrolizumab should be used as the reference document to designate event expectedness (Keytruda [pembrolizumab] USPI).

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the Investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

13.5. Reporting of Serious Adverse Events

All SAEs and pregnancies must be reported within 24 hours of discovery, by emailing or faxing the report to the following:

Before 14 Nov 2022	From 14 Nov 2022 00:00 EST Onwards
Attention: Syneos Health Safety and Pharmacovigilance **FAX Number**: +1 (877) 464-7787 **Email: safetyreporting@syneoshealth.com**	**Attention:** PPD Safety **Toll Free Fax:** +1 (888) 488 9697 **Direct Dial Fax:** +1 (919) 654 3849 **Email: WILSafety@ppd.com**

The written report should be submitted on the SAE form provided for this purpose. The report must include the Investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

14. STATISTICS

14.1. 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 (Table 15).

Table 15: 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 Table 1. 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 below. Response assessments will be based on the RECIST and iRECIST guidelines.

Table 16: Simon's Two-stage Design Enrollment for 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.

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 Part C cohorts have closed early due to insufficient antitumor activity.

Table 17: Simon's Two-stage Design Enrollment for 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.

14.2. General Statistical Methodology

The statistical analysis methods are described below. Additional details will be provided in the Statistical Analysis Plan (SAP) to be finalized before database lock.

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables and number and percentage of subjects in each category for categorical variables) will be provided for evaluated variables. All individual subject level data will be presented as data listings.

No inferential testing procedures are planned in this study.

Data will be summarized for Part A, Part B, and Part C separately. In addition, data regarding antitumor activity for subjects in Part A who are treated at the RP2D dose may be summarized with subjects from Part B. The cumulative tumor response and AE data will be summarized for subjects who enter into the Extension Phase; additional details will be specified in the SAP.

Baseline is defined as the last value prior to the first dose of study treatment administration for each part separately.

14.3. Study Populations

14.3.1. Safety Population

In Part A and Part B, the safety population will include all subjects who received ALKS 4230. In Part C, all subjects exposed to ALKS 4230 or pembrolizumab will be included in the safety population. This population will be used for all safety analyses.

14.3.2. Pharmacokinetic and Pharmacodynamic Population

The PK population will consist of all subjects who received at least 1 dose of ALKS 4230 and have at least 1 measurable serum concentration of ALKS 4230 at any scheduled PK time point.

The PD population will consist of all subjects who received at least 1 dose of ALKS 4230 and have at least one available postbaseline pharmacodynamics measurement.

14.3.3. Antitumor Evaluable Population

The antitumor evaluable population will consist of subjects who complete 2 cycles of therapy and have at least one follow-up scan.

14.4. Statistical Analysis

14.4.1. Subject Disposition, Baseline Demographics, and Treatment Characteristics

14.4.1.1. Subject Disposition

The number of subjects in the safety population from each study part and the reasons for discontinuation will be summarized. In addition, subjects' status with regard to study treatment and follow-up will also be summarized in the Final Study Report.

14.4.1.2. Demographics and Baseline Characteristics

Subject disease and baseline characteristics will be summarized using frequency distribution or descriptive statistics as appropriate.

14.4.1.3. Study Treatment

The ALKS 4230 administration profile will be summarized with respect to number of cycles taken, the dose intensity, dose modifications, and reasons for deviations from the planned regimen.

14.4.2. Antitumor Activity Analyses

Antitumor activity analyses will be based on the antitumor population.

14.4.2.1. Overall Response Rate

The evaluation of ORR will be based on Investigator review of the radiographic or photographic images, as defined according to RECIST 1.1. In addition, central review may be assessed for select cohorts (N2 of Part B cohorts and N2 of Part C C5, C6, and C7 cohorts). Overall response

rate is defined as the proportion of subjects with objective evidence of CR or PR among the number of subjects evaluable for antitumor activity.

At the analysis stage, the best ORR will be assigned for each subject as the best response recorded after initiation of study treatment, taking into account any requirement for confirmation. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded.

The ORR 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 ORR will be presented by frequency, percentage, and 95% confidence interval (CI). The CI will be obtained using an exact approach given the small sample size.

Sum of the Diameters of all lesions reported at each visit will be graphed by spider plot (% change over time) and waterfall plot (best % change). The swimmer plot will be used to display the characteristics of the responses in subjects.

14.4.2.2. Immune Overall Response Rate

The Investigator is asked to consult Seymour et al 2017 for full description of iRECIST. iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (ie, immune) to differentiate them from responses assigned using RECIST 1.1. The principles used to establish objective tumor 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 tumor shrinkage.

iRECIST defines iUPD (immune unconfirmed progressive disease) on the basis of RECIST 1.1 principles. If the criteria for iUPD have never been met, principles follow RECIST 1.1. However, if the criteria for iUPD have been met, the next timepoint response could be iUPD, iSD, iPR, or iCR, or iCPD (immune confirmed progressive disease).

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of the study treatment, taking into account any requirement for confirmation. Immune overall response rate will be based on iBOR.

The iBOR 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). A spider plot, waterfall plot, and swimmer plot will be used to display the characteristics of the responses in subjects.

14.4.2.3. Disease Control Rate

Disease control rate is defined as the proportion of subjects with objective evidence of CR, PR, or SD 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, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

14.4.2.4. Immune Disease Control Rate

Immune disease control rate is defined as the proportion of subjects with objective evidence of iCR, iPR, or iSD at Cycle 4 or later.

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

14.4.2.5. Duration of Response (Part B and Part C)

Duration of response, 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. 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 anticancer treatment at a lesion site will be excluded from the analysis.

The rate of response will be calculated for RECIST responders.

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 based on the antitumor evaluable population with subjects who experienced CR or PR. Kaplan-Meier curves will be provided.

14.4.2.6. Immune Duration of Response (Part B and Part C)

Immune duration of response, defined as the time from the first documentation of response (iCR or iPR) to the first documentation of objective tumor progression or death due to any cause. 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 iCR or iPR prior to starting any new anticancer treatment at a lesion site will be excluded from the analysis.

The rate of response will be calculated for iRECIST responders.

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

(date of iPD/death in Part B – date of first response (iCR or iPR) in Part B + 1)/7

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

(date of iPD/death in Part C – date of first response (iCR or iPR) in Part C + 1)/7

The distribution of iDOR will be estimated for Part B and Part C using Kaplan-Meier methodology. The median point estimate iDOR will be provided along with the two-sided 95% CIs based on the antitumor evaluable population with subjects who experienced iCR or iPR. Kaplan-Meier curves will be provided.

14.4.2.7. Durable Response Rate (Part B and Part C)

Durable response rate is defined as the percentage of subjects 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. Summary of DRR will be presented by frequency, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

Immune durable response rate (iDRR) is defined as the percentage of subjects with an objective response (complete or partial response per iRECIST) lasting continuously for 6 months and starting any time within 12 months of initiating the study drug. The iDRR will be summarized by each tumor type. Summary of iDRR will be presented by frequency, percentage, and 95% CI. The CI will be obtained using an exact approach given the small sample size.

14.4.2.8. Progression-free Survival (Part B and Part C)

Progression-free survival, defined as the time from the first dose of ALKS 4230 to the first documentation of objective tumor progression or death due to any cause. 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. 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.

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 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.

14.4.2.9. Immune Progression-free Survival (Part B and Part C)

Immune progression-free survival, defined as the time from the first dose to the first documentation of objective tumor progression or death due to any cause. 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. 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.

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

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

The survival distribution of iPFS will be estimated using Kaplan-Meier methodology. The median iPFS 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 iPFS rate will be estimated using the Kaplan-Meier estimate.

Details of the analysis will be specified in the SAP.

14.4.3. Pharmacokinetic Analyses

Individual serum concentrations and concentration-time data will be presented and summarized both graphically and in tabular form using descriptive statistics. Pharmacokinetic parameters will be summarized using descriptive statistics. A subject listing of individual PK concentration will be provided. Concentration data will be summarized according to nominal (protocol-specified) sampling times. Pharmacokinetic parameters will be calculated by noncompartmental analysis method using Phoenix WinNonlin Professional (version 6.1 or later, Pharsight Corporation); actual elapsed time from dosing will be used to estimate individual serum PK parameters. Dose proportionality and additional PK analyses may be performed, as appropriate.

Details of the analysis will be specified in the SAP.

14.4.4. Pharmacodynamic Analyses

Pharmacodynamic data will be summarized descriptively. Where possible, the relationship between serum PK parameters or concentration of ALKS 4230 and pharmacodynamic responses will be evaluated by correlation analysis or visual inspections. The detailed analytical method will be specified in the SAP.

14.4.5. Immunogenicity Analysis

The presence of anti-ALKS 4230 antibodies will be determined and the data will be summarized by cohort/dose level.

14.4.6. Tissue Biomarker Analysis

The baseline values, post-treatment values, and the changes in density of TILs, ratio of cytotoxic TILs, immunosuppressive TILs, and density of signals of immune-cell–mediated killing will be summarized.

The correlation between antitumor efficacy endpoints (best overall response, progression free survival) and baseline status (or values) for endpoints derived from tumor tissues will be estimated. The efficacy endpoints will be summarized separately based on baseline status, or low and high values.

The correlation between antitumor efficacy endpoints (best overall response, progression free survival) and the change from baseline in post-treatment for endpoints derived from tumor tissues will be estimated.

14.4.7. Safety Analyses

The safety population will be used for safety analysis.

Treatment-emergent AEs 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 Medical Dictionary for Regulatory Activities terminology, and the severity of the toxicities will be graded according to the NCI CTCAE (version 4.03 or higher) where applicable.

The number and percentage of subjects with treatment-emergent AEs will be summarized by dosing group and overall, by severity, by toxicity/severity grade, and by relationship to study drug. Serious AEs, Grade 3 or 4 AEs, and AEs contributing to discontinuation from the study will be summarized.

Observed values and change from baseline in vital signs, ECG, and laboratory parameters will be summarized by dosing group. Shift table and number (percentage) of subjects with potentially clinically significant values at any postbaseline visit will also be summarized as appropriate. In addition, hematological and chemistry laboratory parameters will be graded according to the NCI CTCAE (version 4.03 or higher) where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

Concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical drug classification system. The number and percentage of subjects using concomitant medications will be summarized.

14.5. Interim Analysis

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

A review of safety data will be done at the conclusion of Part A to inform the dose selection for Part B. An additional review of safety data will be done after the run-in phases (after 3 subjects are treated at the 1 μg/kg/day dose of ALKS 4230 and again after 6 subjects are treated at the 3 μg/kg/day dose of ALKS 4230) of Part C to assess the safety of ALKS 4230 in combination with pembrolizumab.

Responses in each N1 stage will be assessed to determine whether progression to the N2 stage is warranted, based on criteria defined in Section 14.1.

14.6. Independent Data Monitoring Committee

An IDMC will be established by the Sponsor to review accumulating safety and efficacy data at regular intervals and monitor overall study conduct beginning in the second stage (N2) of Part B cohorts and Part C C5, C6, and C7 cohorts. Members will include experts in oncology and biostatistics, who are not participating in this study and do not have affiliation with the investigators or the Sponsor. The IDMC's specific duties, as well as statistical monitoring guidelines and procedures, will be fully described in an IDMC charter.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Monitoring of the study center (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes designee.

15.2. Audits and Inspections

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a Regulatory Authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, computed tomography scans/magnetic resonance imaging scans, workbooks, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of ICH, and any applicable regulatory requirements.

The Investigator should contact the Alkermes Study Team immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB approval for the investigation. Initial IRB approval as well as all materials approved by the IRB for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness, and compliance, the study center should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs. All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff before review by the Alkermes monitor or designated representative. Each staff member will obtain a unique user name and password to access the electronic data capture database.

The Alkermes designated representative will review all source records and compare them to the data collected on the eCRF for processing of source data review and source data verification according to specifications noted in the clinical monitoring plan. The treating Investigator is expected to review and sign off on laboratory reports for clinical significance.

16.2. Confidentiality of Data

By signing this protocol, the Investigator affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Study Agreement (CSA) for details.

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

The clinical site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB before enrolling subjects into the study; written approval from the committee must be received by Alkermes before drug will be released to the Investigator.

The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulatory requirements require.

The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

All relevant correspondence from the IRB will be forwarded by the respective study center to the Sponsor in a timely fashion.

17.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. GCP is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

The Investigator (or authorized designee) at each center will ensure that the subject (or the subject's legal representative) is given full and adequate oral and written information about the nature, purpose, and potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he or she must sign and date the ICF before any study-specific procedures are conducted.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the contract research organization if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing, or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORD-KEEPING

An overview of study data handling and record-keeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

18.1. Data Capture

As stated in Section 16.1, this study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

A copy of all images (computed tomography scan, magnetic resonance imaging scan, or photographs) will be stored with the source documents at the study site.

A copy of all laboratory reports will remain with the source documents at the study center. All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Adverse events will be coded using Medical Dictionary for Regulatory Activities. Concomitant medications will be categorized using the World Health Organization Anatomical Therapeutic Chemical classification system.

18.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct.

18.3. Retention of Records

Retention and storage of essential clinical study documents (eg, worksheets, drug accountability forms, and other administrative documentation) shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

18.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that is the sole property of Alkermes. Results of the study are to be held in confidence by both the investigators and the Sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

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