STATISTICAL ANALYSIS PLAN

ION-01-ALKS 4230

NCT04144517

Study Title:	A Phase 2 Study of ALKS 4230 in Combination With Anti-PD-1(Pembrolizumab) in Patients With Advanced or Recurrent Head and Neck Squamous Cell Cancer Currently on Treatment With Anti-PD-(L)1 Without Having Achieved a Complete Remission
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
AC	Absolute Counts
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{∞}	Area Under the Curve from Time Zero to Infinity
AUC_{24H}	Area Under the Curve from Time Zero to 24 Hours Post dose
AUC_{LAST}	Area Under the Curve from Time Zero to the Last Observed Quantifiable Concentration
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C1D1	Cycle 1, Day 1
C#D#	Cycle #, Day #
CBC	Complete Blood Count
CD	Cluster of Differentiation
CI	Confidence Interval
CL	Serum Drug Clearance
C_{last}	The Last Observed Quantifiable Concentration
CM	Concomitant Medication
C_{max}	Maximum Observed Concentration
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Concentrations
DLT	Dose-Limiting Toxicity
DCR	Disease Control Rate

Abbreviation	Definition
DOR	Duration of Response
ECG	Standard 12-Lead Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
ET	Early Termination
ECG	Electrocardiogram
F	Fold Expansion of Circulating Cd8 T Cells, Tregs, And Nk Cells (Day 1 Pre-Infusion as Baseline Levels)
FCB_{max}	Maximum Observed Fold Change from Baseline in Serum Concentration (Day 1 Pre-Infusion As Baseline Levels)
GCP	Good Clinical Practice
HNSCC	Squamous Cell Carcinoma of the Head and Neck
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IFN	Interferon
IL-2	Interleukin-2
IL-2R	Interleukin-2 Receptor
INR	International Normalized Ratio
ir	Immune-Related
irORR	Immune-Response Overall Response Rate
irRC	Immune-Related Response Criteria
IV	Intravenous or Intravenously
LDH	Lactate Dehydrogenase
λ_z	Terminal Elimination Rate Constant
MAX	Maximum
MEDDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
MTD	Maximum Tolerated Dose

Abbreviation	Definition
NCI	National Cancer Institute
NK	Natural Killer [Cells]
N/A	Not Applicable
ORR	Overall Response Rate
PCS	Potentially Clinically Significant
PD	Progressive Disease
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death Ligand-1
PFS	Progression-Free Survival
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
Q3W	Every 3 Weeks
QTCF	QT Interval Corrected by The Fridericia Correction Formula
RCC	Renal Cell Carcinoma
R_{CD8}	Ratio of Cd8 Cells To T_{regs} (Day 1 Pre-Infusion As Baseline Levels)
$R_{CD8, max}$	Maximum R_{CD8}
RECIST	Response Evaluation Criteria in Solid Tumors
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
R_{NK}	Ratio of Nk Cells to T_{regs} (Day 1 Pre-Infusion As Baseline Levels)
$R_{NK, max}$	Maximum R_{NK}
RP	Relative Percentage
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure

Abbreviation	Definition
$T_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
TLF	Table, Listing and Figure
T_{MAX}	Time to C_{max}
TNF	Tumor Necrosis Factor
$T_{CD8, MAX}$	Time to Maximum R_{CD8}
$T_{NK, MAX}$	Time to Maximum R_{NK}
TT_{REGS}	Regulatory T Cells
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
VS	Versus
V_{SS}	Steady-State Volume of Distribution
V_Z	Terminal Volume of Distribution
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data presentation to be used for analyzing and reporting efficacy and safety data for study ION-01-ALKS 4230. This document has been prepared based on the Alkermes ION-01-ALKS 4230 study protocol (dated 29 Oct 2018).

1.1. Study Objectives

1.1.1. Primary Objective

The primary objective of this study is to estimate the response rate to ALKS 4230 in combination with pembrolizumab in patients with Squamous Cell Carcinoma of the Head and Neck (HNSCC) who have previously received anti-programmed cell death protein 1 (anti-PD-1) or anti-programmed cell death ligand-1 (anti-PD-L1) (henceforth referred to as PD-[L]1) therapy but who have not achieved a complete remission (CR). The primary objective will be assessed for the following 2 groups:

- Group 1: Patients with stable disease (SD), defined as ≥12 weeks of SD per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, or patients with partical response (PR) with no further reduction in tumor size or response (ie, PR and not improving further) for ≥8 weeks on prior anti-PD-(L)1 therapy
- Group 2: Patients with PD (progressive disease) with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-1 therapy or patients currently with PD after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy

1.1.2. Secondary Objectives

- To evaluate the duration of response (DOR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS) of patients with advanced or recurrent HNSCC receiving pembrolizumab plus ALKS 4230
- To evaluate the safety and tolerability of pembrolizumab plus ALKS 4230

1.1.3. Exploratory Objectives

- To evaluate whether assessment of pretreatment biopsies from patients who have failed to achieve a CR on therapy with anti-PD-(L)1 can identify a subset of patients who are likely to respond to the addition of ALKS 4230 [redacted]
- To evaluate whether a second biopsy, [redacted] will predict response or failure to the addition of ALKS 4230 [redacted]

[redacted]

1.2. Summary of the Study Design

The study will assess the antitumor efficacy of ALKS 4230 in combination with pembrolizumab in patients with advanced, recurrent, and/or HNSCC on treatment with an anti-PD-(L)1 antibody (pembrolizumab or nivolumab) without having achieved a CR.

The study is a multi-center, Phase 2, open-label therapy study in collaboration with ION. Patients must have received anti-PD-(L)1 therapy prior to enrollment into the study. After enrollment in the study, ALKS 4230 with pembrolizumab will be administered to 4 cohorts of patients with advanced, recurrent, and/or metastatic HNSCC who have received anti-PD-(L)1 therapy whose current response is as follows:

- Cohort 1: SD, defined as ≥12 weeks of SD per RECIST criteria
- Cohort 2: PR with no further reduction in tumor size or response for ≥8 weeks (ie, PR and not improving further)
- Cohort 3: PD with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-(L)1
- Cohort 4: Current PD after prior achievement of best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy

Patients will be administered the combination of ALKS 4230 and pembrolizumab. For simplification, the 4 cohorts of patients will be combined into 2 arms:

- Group 1 will consist of all patients with current SD or PR (Cohorts 1 and 2) who are not progressing or further demonstrating reductions in tumor size.
- Group 2 will consist of patients with PD (Cohorts 3 and 4).

Baseline tumor biopsy will be required at the time of study entry after screening procedures have been completed and prior to first administration of combination regimen to assess each patient's tumor characteristics in an effort to identify patients with tumors that may have limited pembrolizumab efficacy or potential response to anti-PD-1/ALKS 4230 combination. Tumors will be assessed for quantity and character of tumor-infiltrating T cells and other leukocytes, and for quantitative assessment of PD-L1 expression, gene signatures that correlate with response or lack of response [redacted]

Patients will also have a post-treatment (second) biopsy at C1D12, or at any time from C1D8 through C1D19, to assess whether the addition of ALKS 4230 to the treatment regimen alters the TME and what changes on therapy (immunopharmacodynamics) predispose to responses to the combination.

The study plans to enroll [redacted] evaluable patients for Groups 1 and 2, [redacted] The number of patients enrolled into each cohort within each group will be determined at the time of enrollment, based on the patient's response to previous treatment. It will be at the discretion of Alkermes and ION to expand a particular cohort of interest [redacted].

Pembrolizumab will be administered according to the standard regimen of 200 mg flat dose IV Q3W. ALKS 4230 will be administered IV at a daily dose of 3 µg/kg, given daily on 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.

ALKS 4230 may be continued until toxicity develops. If a toxicity attributed to ALKS 4230 occurs, dosing for both pembrolizumab and ALKS 4230 will be held. After recovery from an AE that meets dose hold criteria, the patient may resume at full dose of pembrolizumab and full or reduced dose of ALKS 4230 in subsequent cycles with consultation from the Medical Monitor or may discontinue from the study. [redacted]

Patients with tumors who respond to treatment will continue until the following:

- Confirmed progression occurs (upon agreement with the ION and Alkermes Medical Monitors, patients tolerating therapy and receiving clinical benefit may be allowed to stay on study for up to 1 year)
- Until unacceptable toxicity occurs
- Other criteria for discontinuation occur

Safety and tolerability will be assessed and reported using standard Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria. Safety will be monitored by the study Principal Investigator (PI), participating site PIs, the ION Coordinating Center PI and staff, and representatives from Alkermes. Details pertaining to the Safety Review Committee (SRC), including participants, frequency of meetings, and criteria that would trigger ad hoc meetings, are described in the SRC Charter.

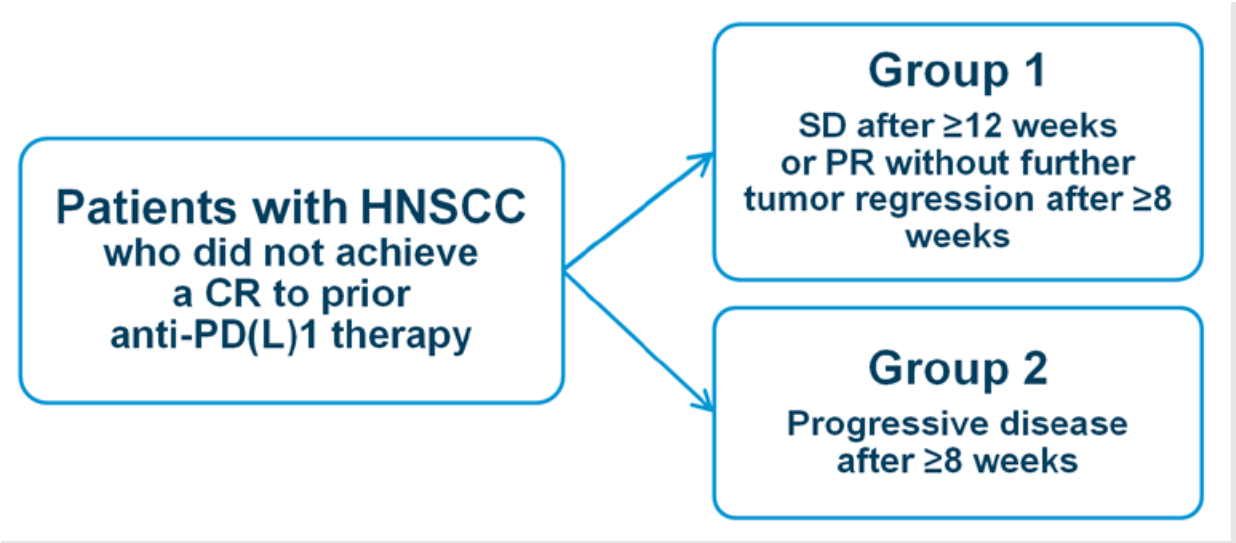
If the unacceptable AEs (defined in Section 12.2 of protocol) observed are typical of known pembrolizumab and/or ALKS 4230 toxicities, the following will be considered: (1) revising the protocol eligibility requirements to decrease the likelihood of toxicities, (2) modifying the dose or schedule, or (3) allowing the study to proceed as designed assuming that patients in this study will have fatal diseases and few other treatment options. The risk/benefit ratio will need to be evaluated in this situation.

If unexpected, unacceptable AEs are considered to be related to concurrent administration of ALKS 4230 and pembrolizumab, the PI, participating site PIs, the ION Coordinating Center PI and staff, and representatives from Alkermes will consider revising the protocol eligibility

requirements to decrease the likelihood of toxicities or may consider allowing the study to proceed as designed given the risk/benefit ratio for this population.

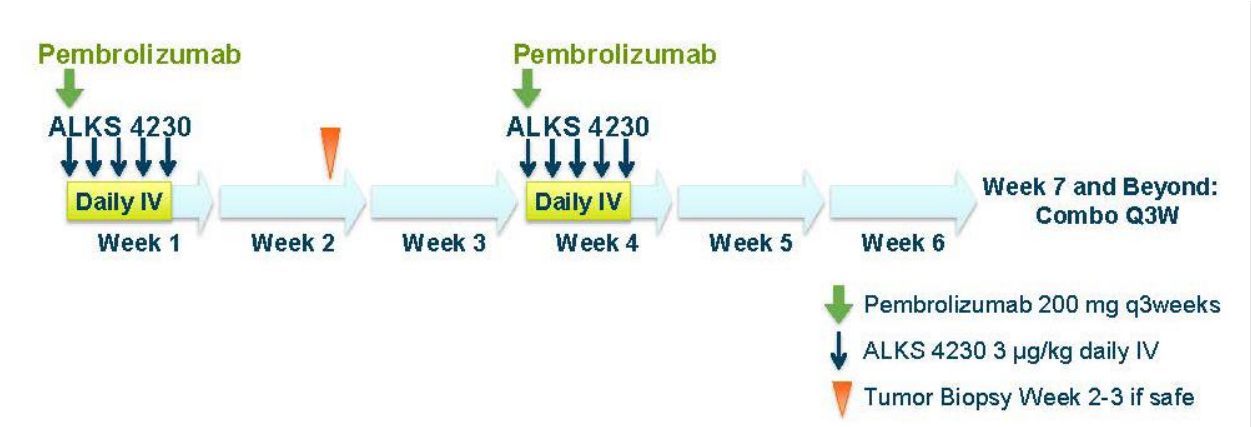
Study design schematics are provided in Figure 1 and Figure 2.

Figure 1: Study Design Schematic 1



Abbreviations: CR=complete remission; HNSCC=squamous cell carcinoma of the head and neck; PD=progressive disease; PD-(L)1=programmed cell death ligand-1; PR=partial response; SD=stable disease; Q3W=every 3 weeks

Figure 2: Study Design Schematic 2



Abbreviations: IV=intravenous; Q3W=every 3 weeks

Note: Pembrolizumab regimen is as follows: 200 mg once Q3W by IV infusion; ALKS 4230 regimen is as follows: 3 µg/kg, given daily on 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.

1.3. Study Endpoints

1.3.1. Primary Efficacy Endpoint

The primary objective of this study is to estimate the response rate to ALKS 4230 in combination with pembrolizumab in patients with HNSCC who have previously received anti-PD-(L)1 therapy but who have not achieved a CR. The primary objective will be assessed for the following 2 groups:

- Group 1: Patients with SD, defined as ≥12 weeks of SD per RECIST v1.1 criteria, or patients with PR with no further reduction in tumor size or response (ie, PR and not improving further) for ≥8 weeks on prior anti-PD-(L)1 therapy
- Group 2: Patients with PD with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-1 therapy or patients currently with PD after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy.

The primary efficacy endpoint is the rate of new or improved antitumor response (hereafter referred to as objective improvement) after the addition of ALKS 4230 treatment in patients receiving ongoing anti-PD-1 therapy but who have not achieved a CR.
Antitumor activity will be measured by radiological assessment compared to screening.
Antitumor response rate of subsets of patients will be based on disease status (defined by PR, SD, or PD based on RECIST v1.1, determined by tumor imaging scans) at screening.

An objective improvement for patients within Group 1 (Cohorts 1 and 2) is defined as:

- SD at screening that improves to PR or CR
- PR at screening that improves to CR

An objective improvement for patients within Group 2 (Cohorts 3 and 4) is defined as:

- PD at screening that improves to PR or CR

Baseline scans must be completed within 28 days before the start of treatment. Scans are to be completed according to the time points indicated in the Schedule of Assessments (Table 4 in the protocol). Patients whose response converts from PD or SD to PR or from PR to CR will have a confirmatory scan for tumor assessments 6 weeks after the response-defining scan. Thereafter, timing of tumor assessments will depend on whether or not the patient continues with study drugs.

[redacted]

Patients may receive study drug while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG Performance Status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

1.3.2. Secondary Efficacy Endpoints

The secondary objectives are to evaluate the DOR, PFS, TTP, rate of non-progression at 6 months, and OS of patients with advanced or recurrent HNSCC receiving pembrolizumab plus ALKS 4230 and to evaluate the safety and tolerability of pembrolizumab plus ALKS 4230. Secondary efficacy endpoints in this study include:

- DOR, PFS, TTP, rate of non-progression at 6 months, and OS
- Antitumor response rate of subsets of patients based on disease status (PR, SD, or PD) at screening
- Antitumor activity as measured by radiological assessment compared to screening

1.3.3. Exploratory Endpoints

The exploratory objectives are:

- To evaluate whether assessment of pretreatment biopsies from patients who have failed to achieve a CR on therapy with anti-PD-(L)1 can identify a subset of patients who are likely to respond to the addition of ALKS 4230
- To evaluate whether a second biopsy, [redacted], can identify changes in tumors predicting response or failure to the addition of ALKS 4230

[redacted]

2. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

This study plans to enroll [redacted] efficacy evaluable patients in Groups 1 and 2, [redacted].

In the long-term follow-up analysis of the KEYNOTE-012 trial of single agent pembrolizumab, which was conducted in 192 patients with HNSCC, the objective improvement rate was 18% (95% CI, 13% to 24%) (Mehra et al, 2018[i]). Among the subset of patients achieving a response, the median time to objective improvement was 2 months (range: 2 to 17 months). [redacted]

3. DATA ANALYSIS

3.1. General Statistical Methodology

Baseline for efficacy or safety analysis is defined as the last non-missing assessment before the first dose of study drug in ION-01-ALKS 4230 study on Day 1, and it will be used for all efficacy and safety analysis unless specified otherwise.

In general, summary statistics (n, mean, standard deviation, median, minimum and maximum for continuous variables, and number [%] of patients in each category for categorical variables) will be provided by group for all variables. Time-to-event variables will be summarized by Kaplan-Meier plots, medians, and ranges. The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. Source data for the summary tables and statistical analyses will be presented as patient data listings. All statistical tests and CIs, unless stated otherwise, will be 2-sided and will be set at α=0.05.

3.2. Definitions of Analysis Populations

3.2.1. Efficacy Evaluable Population

The Efficacy Evaluable Population will include all patients who have received at least 1 dose of both study drugs and have minimum of one post-baseline scan. The Efficacy Evaluable Population will be characterized by groups (Group 1 and Group 2) and overall for analysis of all efficacy endpoints.

3.2.2. Safety Population

The Safety Population is defined as all patients who receive at least 1 dose of investigational combination treatment regimen, will be used in the safety analyses, regardless of the duration of treatment. The data will be presented by groups and overall. The Safety Population will be used for safety analyses as well as for demographics, and baseline characteristics.

3.3. Disposition

The number and percentage of patients in the efficacy evaluable population, patients in the safety population, patients who completed the study, and patients who were prematurely terminated from the study will be summarized.

According to study protocol Section 7.3, a patient may be discontinued from the study at any time if the patient or Investigatory determines that it is not in the best interest of the patient to continue participation.

For patients who discontinued from the study, the reasons for discontinuation will be summarized for the following categories:

- Adverse event
- Disease progression
- Loss to follow-up
- Withdrawal of consent
- Non-Compliance with study drug
- Physician Decision
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Other

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

3.4. Protocol Deviations

Major protocol deviations will be summarized and listed by each category. All protocol deviations identified according to study entry criteria and during treatment will be listed.

3.5. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the Safety Population. Age (years), height (cm), weight (kg), and BMI (kg/m^2) at baseline will be summarized descriptively. Sex, race, ethnicity, BMI category (underweight: < 18.5 kg/m^2; normal: 18.5 to <25 kg/m^2 ; overweight: 25 to <30 kg/m^2; obese: ≥30 kg/m^2), and ECOG performance status (0, 1, 2, 3, 4, or 5) will be summarized by frequency counts. Body mass index is calculated based on weight and height at baseline.

Demographic data and baseline characteristics (as detailed above) as well as informed consent date will be provided in listings.

3.6. Cancer Disease History

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

- Method of Initial Diagnosis
- Primary Origin of Tumor Type

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

Cancer disease history will be listed for the Safety Population.

3.7. Medical History

Reported medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. General medical history information will be summarized by category of medical history being collected. Medical history will be listed for the Safety Population.

3.8. Prior Cancer Related Therapies

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

3.9. Prior and Concomitant Medications

A prior medication is defined as any medication taken with an end date prior to the first dose of study drug. A prior regimen can contain more than one prior medications. A concomitant medication is defined as any medication (1) that started before the first dose of study drug and was continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug and continued up to 30 days after the patient's last dose of study drug.

The number and percentage of patients who have taken prior or concomitant medications will be summarized using the WHO-ATC generic drug name dictionary (version: March 2016 or higher) for the Safety population.

For the summary table, if a subject has taken a concomitant medication more than once, the subject will be counted only once for that medication. A patient who reports the use of two or more medications with same start date will be counted only once in the summary of "Any Concomitant Medication." Similar rules will apply to prior medications as well.

The concomitant medication will be reviewed by medical team to identify the anti-cancer therapy treatment during the study.

All reported medications (including prior medications and concomitant medication) will be included in listing.

3.10. Extent of Exposure

For each study drug, the ALKS 4230 and the pembrolizumab administration profile will be summarized with respect to treatment duration, total number of ALKS 4230 and pembrolizumab infusions, cumulative dose (µg/kg) of ALKS 4230 and pembrolizumab (mg) administered, and number of cycles.

The following items will be summarized for both ALKS 4230 and pembrolizumab:

Duration of Exposure (Days) = min (Last date of exposure, death) – Date of first dose

Last date of exposure = Initial dose date of the last cycle + 21 – 1

Duration of Treatment (Days) = Date of last dose – Date of first dose + 1

Number of Cycles received (Cycles) = Number of cycles with at least one study drug

Total Dose Received during a Cycle= Sum of Doses received during that cycle

Cumulative Dose = Sum of (Total Dose Administreated during a Cycle)

Number of patients with dose reductions, dose interruptions will be summarized by counts and percentages.

3.11. Efficacy Analyses

3.11.1. General Considerations

All statistical analyses will be performed at the 5% significance level. All confidence intervals will be 2-sided 95% confidence intervals. Efficacy analyses will be carried out using the Efficacy Evaluable Population. Response to treatment will be evaluated using RECIST v1.1.

Summary statistics (n, mean, standard deviation, median, minimum and maximum for continuous variables, and number [%] of patients in each category for categorical variables) will be provided for all variables. Time-to-event variables will be summarized by Kaplan-Meier plots, medians, and ranges. Data from all study centers will be combined for analysis. No adjustments for multiple comparisons will be applied.

3.11.2. Efficacy Analysis for the Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of new or improved antitumor response (hereafter referred to as objective improvement) after the addition of ALKS 4230 treatment in patients receiving ongoing anti-PD-1 therapy but who have not achieved a CR.

An objective improvement for patients within Group 1 (Cohorts 1 and 2) is defined as:

- SD at screening that improves to PR or CR,
- PR at screening that improves to CR

An objective improvement for patients within Group 2 (Cohorts 3 and 4) is defined as:

- PD at screening that improves to PR or CR

Primary efficacy analysis will be evaluated in patients in the Efficacy Evaluable population for each group separately and overall. The objective improvement rate after continued anti-PD-1 therapy with ALKS 4230 will be summarized by group (Group 1 and Group 2) separately and overall with descriptive statistics.

$$\text{Objective improvement rate for Group 1} = \frac{\text{number of patients who achieved CR or PR}}{\text{number of patients in Group 1}}$$

$$\text{Objective improvement rate for Group 2} = \frac{\text{number of patients who achieved CR or PR}}{\text{number of patients in Group 2}}$$

The analysis of objective improvement rate using an exact binomial test will be conducted separately for each group. The two-sided 95% confidence interval (CI) on objective improvement rate will be estimated by Clopper-Pearson method.

3.11.3. Efficacy Analysis for the Secondary Efficacy Endpoints

Secondary efficacy endpoints in this study include:

- DOR, PFS, TTP, rate of non-progression at 6 months, and OS
- Antitumor response rate of subsets of patients based on disease status (PR, SD, or PD) at screening
- Antitumor activity as measured by radiological assessment compared to screening

The efficacy analysis for the secondary endpoints will be performed for the following endpoints.

- **Duration of Response:**

  Duration of response (DOR) is defined as the time from the first documentation of response CR or PR (whichever is first recorded) to the first documentation of objective tumor progression or death due to any cause. Patients who are alive and progression free on the analysis cut-off date will be censored at their last evaluable tumor response assessment before initiation of any new anticancer treatment.

  Patients with 2 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 patient was documented to be progression free. The detailed censoring rules for DOR is in section 6.2.3.

DOR will be calculated as follows (in weeks):

(date of disease progression/death – date of first response (CR or PR) + 1)/7

The distribution of DOR will be estimated using Kaplan-Meier methodology. The median point estimate DOR will be provided along with the two-sided 95% CIs based on the Efficacy Evaluable population. Kaplan-Meier curves will be provided.

- **Progression-Free Survival:**

Progression-free survival (PFS) is defined as the time from the first dose to the first documentation of objective tumor progression, start of alternate therapy or death due to any cause. Patients who do not have disease progression or have not died will be censored at the last known time that the patient was progression free. If a patient begins a new anticancer treatment (either systemic or local) prior to documented progression or death, or if a patient is removed from the study due to undocumented clinical disease progression, then the patient will be censored at the last assessment where the patient was documented as progression free prior to the intervention. Patients with 2 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 patient was documented to be progression free. The detailed censoring rules for PFS is in section 6.2.2.

Progression-free survival will be calculated as follows (in weeks):

(date of disease progression/death – first dose date + 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 Efficacy Evaluable population. In addition, Kaplan-Meier curves will be provided. The 6-month PFS rate will be estimated using the Kaplan-Meier estimate.

- **Time to Progression:**

Time to progression (TTP) is defined as the time from the first dose to the confirmed tumor progression. All events of disease progression will be included regardless of whether the patient discontinued the study drug. If the patient has not experienced disease progression, the patient's data will be censored at the date of last disease assessment. Data for patients without any disease assessments performed after the first dose will be censored at the date of first study drug.

The TTP will be calculated as follows (in weeks):

(date of disease progression – date of first dose + 1)/7

TTP will be analyzed by Kaplan-Meier methodology. Median TTP will be calculated and 95% confidence interval for median TTP will be presented.

- **Overall Survival:**

Overall survival (OS) is defined as the time from the first dose to death due to any cause. For patients without documentation of death, patients will be censored at the date that the patient was last known to be alive or the date of study cutoff, whichever comes earlier. The detailed censoring rules for OS is in section 6.2.1.

OS will be calculated as follows (in weeks):

(date of death/censoring – date of first dose date + 1)/7

OS will be analyzed by Kaplan-Meier methodology. Median OS will be calculated and 95% confidence interval for median OS will be presented. In addition, Kaplan-Meier curves will be provided. The one-year OS rate will be estimated using the Kaplan-Meier estimate.

In addition, the objective response rate will be summarized for each of the 4 cohorts, and the percentage change from baseline in target lesions will be summarized by group and overall.

3.13. Safety Analysis

3.13.1. General Considerations

All safety endpoints will be summarized for the Safety Population.

3.13.2. Adverse Events

Analyses of AEs will include only "treatment-emergent" AEs (TEAEs). TEAEs are defined as any AE that begins on or after the first administration of the study drug. Events where the onset date was the same as the study drug start date will be assumed to be treatment-emergent, unless the study drug start time and the AE start time are collected, and the AE start time is prior to the study drug start time. If an incomplete onset date is collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (eg, the AE end date is prior to the date of the first dose of study drug). No imputation will be performed for partial dates for AE. Analyses will not include those that have an onset greater than 30 days after study drug discontinuation.

Treatment-related AEs reported beyond 30 days after study drug discontinuation will be summarized separately during post treatment discontinuation period.

TEAEs will be summarized by Preferred Term (PT) within a System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher.

Patients reporting more than one AE within a SOC will be counted only once for that SOC. Patients reporting the same AE more than once will be counted only once for that PT. For summaries of TEAEs by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5.0) grade, at each level of summation each patient is counted

only once at the maximum grade level. The possible grade levels are 1 to 5, and unknown. If a patient had an AE with unknown grade, then the patient will be counted in the grade category of "unknown," even if the patient had another occurrence of the same event with a grade of 1 or 2. If the patient had another occurrence of the same AE with a grade of 3, 4 or 5, the patient will be counted under the grade 3, 4 or 5 categories based on the maximum grade level reported.

The number and percentage of patients experiencing at least one TEAE will be further summarized as follows.

- Any TEAE
- Any TEAE experienced by ≥ 10% of patients
- Any TEAE with NCI CTCAE toxicity ≥ Grade 3
- Any TEAE broken down by maximum NCI CTCAE toxicity grade (severity)
- Any TEAE related to ALKS 4230 as assessed by the Investigator
- Any TEAE related to pembrolizumab as assessed by the Investigator
- Any TEAE with NCI CTCAE toxicity ≥Grade 3 and related to ALKS 4230 as assessed by the Investigator
- Any TEAE with NCI CTCAE toxicity ≥Grade 3 and related to pembrolizumab as assessed by the Investigator
- Any Treatment Emergent Serious Adverse Event (SAE)
- Any SAE related to ALKS 4230 as assessed by the Investigator
- Any SAE related to pembrolizumab as assessed by the Investigator
- Any SAE related to ALKS 4230 with NCI CTCAE ≥ Grade 3 as assessed by the Investigator
- Any SAE related to pembrolizumab with NCI CTCAE ≥ Grade 3 as assessed by the Investigator
- Any TEAE leading to discontinuation of ALKS 4230
- Any TEAE leading to dose interruption of ALKS 4230
- Any TEAE leading to dose reduction of ALKS 4230
- Any TEAE leading to discontinuation of pembrolizumab
- Any TEAE leading to death

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

The original date and time will be shown on all listings of AEs. Listings will be provided for all TEAEs, serious TEAEs, and TEAEs leading to study treatment discontinuation. The data listings will be provided for dose reductions, and dose interruptions along with the AE/SAE that was associated with the change in dosing for ALKS 4230 and pembrolizumab separately.

3.13.3. Death

Listings will be provided for patients who died during the study for any reason, and for patients who had died due to AE.

3.13.4. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional (ie, US) units. Only scheduled laboratory parameters, as specified in Table 1, will be included in the laboratory results summaries, unless specified otherwise. All laboratory data, including those collected at unscheduled visits, will be included in the listings.
For all quantitative parameters listed in Table 1, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Only data collected as scheduled will be included in the summaries. For each parameter, the mean (+/- SE) at each scheduled visit will be plotted for its actual value and its change from baseline. Data collected at the EOS/ET visit will be included as one time point regardless of subjects' EOS status.

In addition, where applicable, hematology and chemistry laboratory determinations will be categorized according to NCI CTCAE (version 5) grades and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug.

The maximum NCI CTCAE toxicity grade value will be the value with the highest NCI CTCAE toxicity grade collected after the first dose of study drug and within 30 days following study drug discontinuation. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day.

The number and percentage of patients with baseline grades versus maximum post-baseline grades of and baseline grades versus final post-baseline grades will be summarized.

Detailed listings of data for subjects experiencing NCI CTCAE grade ≥3 hematology and chemistry values will be provided. All measurements collected, regardless of the number of days after study drug discontinuation will be included in these listings.

Pregnancy test data will be listed.

Number of subjects who meet protocol defined event of clinical interest criteria (Section 12.1.1 of protocol) as below will be summarized and corresponding listing will be presented.

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

For urinalysis, the number of abnormalities at any post-baseline visit will be summarized.

Table 1: Clinical Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

• Haematocrit
• Haemoglobin
• Red blood cell count (RBC)
• Total white blood cell count (WBC)
• Platelet count
• Differential blood count including:
  ○ Basophils
  ○ Eosinophils
  ○ Neutrophils
  ○ Lymphocytes
  ○ Monocyte
	• Sodium
	• Potassium
	• Phosphorus
	• Glucose
	• Total protein
	• BUN
	• Serum creatinine
	• CrCl
	• Albumin
	• Total bilirubin
	• ALT
	• AST
	• LDH
	• ALK-P
	• CO_2 or bicarbonate[a]
	• Uric acid
	• Calcium
	• Chloride
	• Magnesium
	• Direct bilirubin, *if total bilirubin is elevated above the upper limit of normal*
		• Specific gravity
		• Protein
		• pH
		• Glucose
		• Ketones
		• Blood
		• Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal (2+ or higher)*
		• Urine pregnancy test[b]
			• Serum β-hCG[b]
			• PT (INR)
			• aPTT
			• TSH
			• Cortisol (morning)
			• ACTH

Abbreviations: ACTH=adrenocorticotropic hormone; ALK-P=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; CO_2=carbon dioxide; CrCl=creatinine clearance; hCG=human chorionic gonadotropin; INR=international normalized ratio; LDH=lactic dehydrogenase; PT=prothrombin time; TSH=thyroid-stimulating hormone.

[a] If considered standard of care in local region.

[b] Perform on women of childbearing potential

3.13.5. Vital Signs

Vital signs assessments include respiratory rate, temperature, blood pressure, and heart rate. The observed values at each visit and change from baseline to post-baseline visits will be summarized with descriptive statistics. All vital sign data will be presented in the patient data listings.

[redacted] Patients who meet PCS criteria will be summarized for vital signs parameters.

The figure of mean (+/- SE) of the change from baseline will be summarized by visit for systolic blood pressure, diastolic blood pressure, heart rate and temperature.

3.13.6. Electrocardiograms (ECG)

ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval will be summarized for each visit during the study. QT interval changes from baseline will also be descriptively summarized for each visit. The baseline value will be taken as the average of the triplicate ECG measurements taken prior to the first dose on Cycle 1 Day 1.

The number and percent of patients with abnormal ECG findings at any postbaseline visit will be summarized.

Individual ECG evaluation results will be provided in data listings. A supportive listing will present all values for a parameter for patients with abnormal ECG results.

3.13.7. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG Performance Status assesses the patients' activity status. Descriptions of activity status are presented in Table 2. Possible scores are 0 to 5. The number and percentage of patients with baseline score versus post-baseline scores will be summarized in a shift table. The data will be presented in the patient data listings.

Table 2: Eastern Cooperative Oncology Group Performance Status

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

4. INTERIM ANALYSES

No interim analyses are planned for this study.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

There are no changes made to the statistical methods specified in the ION-01-ALKS 4230 study protocol (dated 29 Dec 2018).

5.1. Revisions and/or clarification of definitions in SAP

Protocol Definition	SAP definition
Efficay Evaluable Population All patients who received at least 1 dose of both study drugs	Efficacy Evaluable Population All patients who received at least 1 dose of both study drugs and have minimum of one post-baseline scan

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF THE DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

Scheduled analysis visits are visits at scheduled timepoints as specified in the protocol (Table 1 Schedule of Assessments and Study Visits).

Scheduled analysis visits during the study period will be the same as the nominal visits collected in the eCRF. There will be one valid value of assessment kept for each scheduled analysis visit in summary/analysis statistics.

In the event that a patient chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the patient's rights. Enrolled patients are to be asked to return to the clinic for an End of Treatment (EOT) Visit. The EOT Visit should be scheduled as close as possible to the patient's last dose, and early termination assessments will follow the assessments scheduled to be conducted at the EOT Visit.

Unscheduled visits are visits with data collected outside of scheduled time points. Unscheduled visits will not be used for by-visit summary/analysis statistics, unless specified otherwise.

All unscheduled visits as collected in the eCRF will be included in listings.

Visit Day is calculated as (date of visit) – (date of the first dose of study drug) +1 day.

6.2. Efficacy Data Handling

The Censoring Rules for Overall Survival, Progression Free Survival and Duration of Response are defined according to the FDA guidance[2].

6.2.1 Censoring Rules for Overall Survival (OS)

The overall survival censoring date for a patient is listed in Table 3. The start date is the first dose date of the study drug.

Table 3: Censoring Rules for Overall Survival (OS)

Situation	Date of Death or Censoring	Outcome
Death during study	Date of death	Death
Patient still alive at data cut-off/death occurred after data cut-off	Date of cut-off	Censored
Patient lost to follow-up before data cut-off	Date last known to be alive	Censored

6.2.1. Censoring Rules for Duration of Response (DOR)

The Duration of Response censoring dates for a patient is in Table 4. The Start date: the date of first documentation of response (CR or PR).

Table 4: Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No baseline or unreadable baseline assessment, but readable post-baseline assessments	Date of the 1st dose of the study drug	Censored
Progression documented between scheduled visits	Earliest of • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Treatment discontinuation for undocumented progression	Date of last tumor assessment with no documented progression	Censored
Treatment discontinuation for toxicity of other reason	Date of last tumor assessment with no documented progression	Censored
Patients still on treatment without PD as of data cut-off	Date of last tumor assessment	Censored
Treatment discontinuation for other than PD or death with post-baseline tumor assessments	Date of last tumor assessment	Censored
New anticancer treatment started before PD or death	Date of last tumor assessment before start of new treatment	Censored
Death or PD after two or more missed tumor assessments	Date of the last tumor assessment before missed assessments	Censored
Only NE assessments after CR, PR, SD	Date of last tumor assessment before NE assessments	Censored

6.2.2. Censoring Rules for Progression Free Survival (PFS)

The Progression Free Survival censoring dates for a patient is listed in Table 5. The start date is the first dose date of the study drug.

Table 5: Censoring Rules for Progression Free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline or unreadable baseline assessment, but readable post-baseline assessments	Date of the 1st dose of the study drug	Censored
Progression documented between scheduled visits	Earliest of • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Treatment discontinuation for undocumented progression	Date of last tumor assessment with no documented progression	Censored
Treatment discontinuation for toxicity of other reason	Date of last tumor assessment with no documented progression	Censored
Patients still on treatment without PD as of data cut-off	Date of last tumor assessment	Censored
Treatment discontinuation for other than PD or death with post-baseline tumor assessments	Date of last tumor assessment	Censored
New anticancer treatment started before PD or death	Date of last tumor assessment before start of new treatment	Censored
Death or PD after two or more missed tumor assessments	Date of the last tumor assessment before missed assessments	Censored
Only NE assessments after CR, PR, SD	Date of last tumor assessment before NE assessments	Censored

6.3. Safety Data Handling

All effort should be made to obtain missing information from the Investigator. For vital signs, laboratory testing (chemistry, hematology, urinalysis), and 12-lead ECGs, only observed data will be used for analyses, and missing data will not be imputed.

6.4. Handling of Partial Dates of Concomitant Medication

Partial start dates of prior and concomitant medication will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing.

For summaries of prior medications, if an incomplete start date is collected for a medication, the medication will be assumed to be a concomitant medication unless there is evidence that confirms that the medication was not a concomitant medication (eg, the medication end date is prior to the first dose of study drug)

If both the start and end date of medication are missing, then these will be excluded from summary statistics but included in the patient data listings.

7. GENERAL STATISTICAL METHODOLOGY

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of patients in each category for categorical variables) will be provided. All summary tables will be based on observed data, and missing values will not be imputed unless otherwise indicated. Measurements collected from unscheduled visits or repeated assessments will not be included in the by-visit summary tables or figures but will be included in the derivation of the last post-baseline value during treatment, the analyses for the PCS post-baseline values, and patient listings. Source data for the summary tables and statistical analyses will be presented as patient data listings.

7.1. Reporting Precision

Summary statistics will be presented to the degree of precision in Table 6, unless otherwise specified:

Table 6: Degree of Precision

Statistics	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One more than the raw data, up to 3 decimal places.
Standard deviation, Standard error	One more than the mean, up to 3 decimal places
Minimum, Maximum	The same as the raw data, up to 2 decimal places
p-value	Rounded to 3 decimal places and therefore presented as 0.xxx; p-values smaller than 0.001 as '<0.001'; p-values greater than 0.999 as '>0.999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12–0.30).

For weight, height, and body mass index (BMI), one decimal place will be used for summary statistics.

8. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

9. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock-up tables and listings will be provided in a separate document.

10. REFERENCES

[1] Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer.* 2018;119(2):153-159. doi: 10.1038/s41416-018-0131-9.

[2] Clinical Trial Endpoints for Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry. April 2015; 14-16.