CLINICAL STUDY PROTOCOL

ION-01-ALKS 4230

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
Document Date:	29 Oct 2018
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451-1420 USA

PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information

Role in Study	Name	Contact Information
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Abbreviation: ION=Immune Oncology Network

2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 4230	
Name of Active Ingredients: ALKS 4230 and pembrolizumab	
Title of Study: 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	
Investigators: [redacted] **(Coordinating Investigator)**, other investigators at selected study sites	
Study Period (Years): Approximately 2 years Estimated date first patient enrolled: March 2019 Estimated date last patient completed: February 2021	**Phase of Development:** 2

Objectives:

Primary:

- 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 partial 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 progressive disease (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

Secondary:

- 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

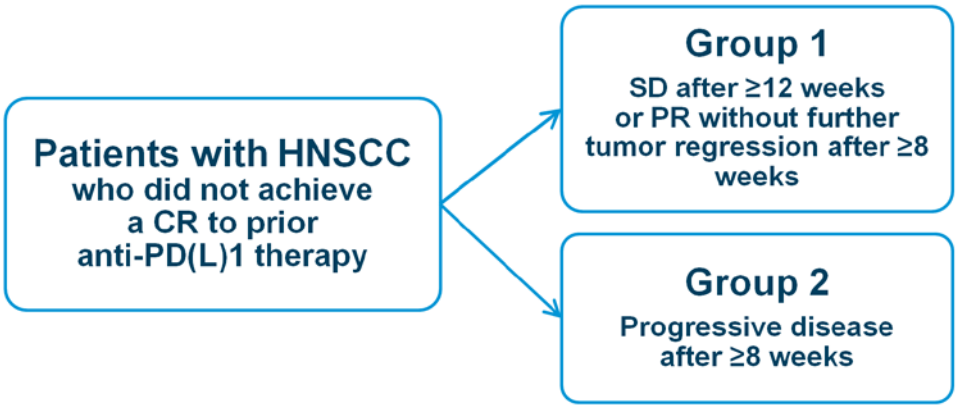
Exploratory:

- 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 that will predict response or failure to the addition of ALKS 4230

- [redacted]

Methodology: This is a multi-center, Phase 2, open-label therapy study to assess the antitumor efficacy of ALKS 4230 in combination with pembrolizumab in patients with advanced, recurrent and/or metastatic HNSCC on treatment with an anti-PD-(L)1 antibody without having achieved a CR.

Study Design Schematic 1



Pembrolizumab regimen: 200 mg once Q3W by IV infusion
ALKS 4230 regimen: 3 µg/kg, given daily on 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.
Abbreviations: CR=complete remission; HNSCC=squamous cell carcinoma of the head and neck; PD-(L)1=programmed cell death ligand-1; PR=partial response; SD=stable disease; Q3W=every 3 weeks

For analysis, patients will be placed into 1 of the 4 cohorts based on their disease status as assessed at screening:

- Cohort 1: SD; defined as ≥12 weeks of SD per RECIST v1.1 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; or
- Cohort 4: Progressive disease after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy

All patients will be administered the combination of ALKS 4230 and pembrolizumab. For analysis, patients in the 4 cohorts will be combined into 2 groups:

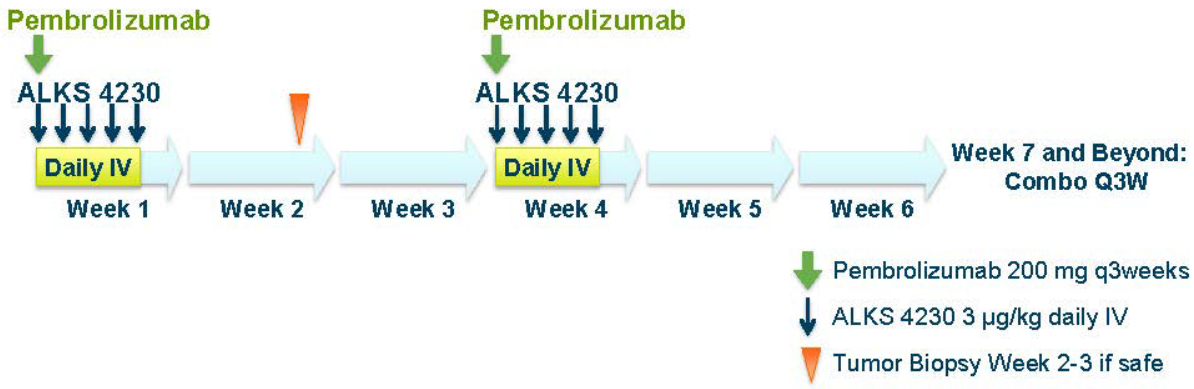
- Group 1 will consist of all patients with current SD or PR (Cohorts 1 and 2) who are not progressing or further demonstrating reductions in tumor size.
- Group 2 will consist of patients with PD (Cohorts 3 and 4).

Patients in both groups (or all cohorts) will receive pembrolizumab 200 mg once every 3 weeks (Q3W) by intravenous (IV) infusion (Keytruda USPI) and ALKS 4230 3 µg/kg, given daily on 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.

Patients will have a pretreatment biopsy within 6 weeks of Cycle (C) 1, Week 1, Day (D) 1 and a post-treatment (second) biopsy at C1D12, or any time from C1D8 through C1D19, to assess whether the addition of ALKS 4230 to the treatment regimen alters the tumor microenvironment and what changes on therapy (immunopharmacodynamics) predispose to responses to the combination.

The study plans to enroll [redacted] patients in total [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 the Immune Oncology Network (ION) to expand a particular cohort of interest.

Study Design Schematic 2



Abbreviations: IV=intravenous; Q3W=every 3 weeks.

Dose delays and modifications for adverse events (AEs) related to the ALKS 4230 + pembrolizumab combination regimen are described in the protocol. After recovery from an AE that meets dose hold criteria, the patient may resume dosing at full dose of pembrolizumab and full or reduced dose of ALKS 4230 in subsequent cycles, with consultation from the ION and Alkermes Medical Monitors, 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.

Number of Patients Planned: [redacted]

Main Criteria for Inclusion:

Inclusion Criteria:

Each patient must meet all of the following inclusion criteria to be qualified to participate in this study:

1. Is ≥18 years of age.
2. Is willing and able to provide informed consent.
3. Is willing and able to follow the study procedures as outlined in the protocol.
4. Must have a histologically or cytopathologically confirmed diagnosis of squamous cell carcinoma of the head and neck region that is locally advanced or recurrent and no longer

amenable to local surgical or radiation therapy and/or with evidence of metastatic disease. Both HPV-positive and -negative patients will be included.

5. Must have had prior PD-1:PD-L1 inhibition therapy with anti-PD-(L)1 therapy as the most recent systemic therapy with
   a. (Group 1, Cohort 1) current SD (for ≥12 weeks by RECIST] criteria v1.1) or
   b. (Group 1, Cohort 2) current PR with no further reduction in tumor size or response for ≥8 weeks (ie, PR and not further improving
   c. (Group 2, Cohort 3) current PD with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-(L)1 or
   d. (Group 2, Cohort 4) current PD after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy.

   Some minimal intervening localized palliative radiotherapy or ablation therapy may be allowed upon review and agreement by the ION and Alkermes Medical Monitors.
6. Must have disease that is measurable by RECIST v1.1 criteria as determined by the treating physician and not confounded by prior treatment such as radiation. Patients with only 1 site of disease must be able to provide adequate tissue samples at the time of biopsy that will not affect the tumor size per RECIST v1.1 criteria.
7. Patients who have received standard or investigational anti-PD-(L)1 agents as the most recent systemic therapy must wait at least 3 weeks (with the exception of an anti-PD-[L]1 inhibitor that is dosed every 2 weeks and in consultation with the ION and Alkermes Medical Monitors, in which case patients must wait at least 2 weeks) before enrollment into the study or 4 weeks if the half-life of the investigational agent is not known. Patients who have received standard or investigational agents other than anti-PD-(L)1 agents (including agents as part of a combination regimen with an anti-PD-[L]1 agent) must wait 8 weeks before enrollment into the study, unless discussed with and approved by the ION and Alkermes Medical Monitors on an individual basis.
8. Patients must be willing to provide tumor tissue adequate for biomarker correlative studies at the time points specified in the protocol.
9. Patients should have readily accessible tumor for biopsy pre- and post-pembrolizumab and ALKS 4230 combination regimen. Biopsy should be excisional, incisional, or core needle and large enough to show tissue architecture.
10. Have a performance status of ≤2 on the Eastern Cooperative Oncology Group Performance Scale.
11. Demonstrate adequate organ function. All screening laboratories should be performed within 10 days of treatment initiation.
12. Female patients of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Is willing to abide by the contraception requirements for the duration of the study. Additional details pertaining to contraception requirements are detailed in the protocol.

Exclusion Criteria:

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

1. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (inhaled or topical steroids are allowable) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
2. Has active tuberculosis (TB; *Bacillus tuberculosis*).
3. Has hypersensitivity to pembrolizumab, ALKS 4230, or any of their excipients.
4. Has prior Grade ≥3 immune-related toxicities requiring systemic immunosuppressant treatment that were attributable or possibly attributable to PD-1 immune checkpoint blockade. Has toxicities deemed reversible from prior therapy, including anti-PD-1, that have not recovered to baseline or Grade ≤1. Patients with persistent Grade ≤2 neuropathy are an exception to this criterion and may qualify for the study.
    a. **Note**: If patient received major surgery, the patient must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Has had a prior dose of anti-PD-(L)1 therapy within 3 weeks of Study Day 1, with the exception of an anti-PD-(L)1 inhibitor that is dosed every 2 weeks and in consultation with the ION and Alkermes Medical Monitors.
6. Has a known history of additional malignancy within 2 years or current additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer, or treated prostate cancer with a prostate-specific antigen value of <0.01 ng/mL.
7. Has known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate, provided that they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study drug. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
8. Has known history of, or any evidence of, non-infectious interstitial pneumonitis that required steroids or current pneumonitis, or oxygen requirement for any reason in the past 28 days.
9. Has an active major infection requiring systemic therapy within 1 week of starting study drug.
10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
11. Has known psychiatric or substance abuse disorders or a social situation that would interfere with cooperation with the requirements of the study.
12. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study drug.

13. Known active infection with hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus HCV RNA [qualitative]) detected.
14. Has any finding that, in the view of the Investigator, would compromise the safety of the patient or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
15. Is Investigator-site personnel, an immediate family of the Investigator-site personnel, employed by Alkermes or ION, or an immediate family member of an Alkermes or ION employee.
16. If, in the opinion of the Investigator (and/or Sponsor), the patient is unsuitable for enrollment in the study.
17. Has significant known cardiovascular impairment (New York Heart Association Congestive Heart Failure >Grade 2, unstable angina, myocardial infarction within the previous 6 months prior to the first dose of investigational drug, or existing serious cardiac arrhythmia).
18. Has chronic or acute gastrointestinal disorders resulting in diarrhea of any severity grade; patient is using chronic anti-diarrheal supportive care (more than 3 days/week) to control diarrhea in the 28 days prior to the first dose of investigational drug.
19. Has known cirrhosis diagnosed with Child-Pugh Class A or higher liver disease.

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

Reconstituted ALKS 4230 is administered via a 30-minute IV infusion once daily for 5 consecutive days during the first week of each treatment cycle.

[redacted]

Pembrolizumab is to be administered as an IV infusion over 30 minutes in a dose of 200 mg Q3W, for up to 1 year for as long as patients are deriving clinical benefit (ie, objective response or SD) and tolerating therapy well.

Reference Therapy, Dosage, Duration, and Mode of Administration: None

Duration of Study: This study consists of a 28-day screening period, treatment period, and 30-day post-treatment follow-up. The treatment period consists of at least five 3-week cycles that can repeat for up to 1 year.

Efficacy Endpoints: The primary efficacy endpoint is the rate of new or improved antitumor response after the addition of ALKS 4230 treatment in patients receiving ongoing anti-PD-1 therapy but who have not achieved a CR.

The secondary efficacy endpoints in this study include:

1. Duration of response, progression-free survival, time to progression, rate of non-progression at 6 months, and OS
2. Antitumor response rate of subsets of patients based on disease status (PR, SD, or PD) at

screening

3. Antitumor activity as measured by radiological assessment compared to screening

Safety Assessments:

- Adverse events
- Physical examination and electrocardiogram findings
- Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature)
- Clinical laboratory parameters (ie, complete blood count with differential, complete serum chemistry, and urinalysis)

Statistical Methods: For all applicable parameters, descriptive statistics will be provided.

Efficacy: Response to treatment will be evaluated using both Response Evaluation Criteria in Solid Tumors v1.1 and immune-related response criteria. For patients with objectively measurable disease, response to therapy, DOR, PFS, and OS will be calculated.

Primary efficacy endpoint will be evaluated in the Efficacy Evaluable population (all patients who received at least 1 dose of both study drugs) for each group separately and overall. The rate of objective improvement after continued anti-PD-1 therapy with ALKS 4230 will be summarized by groups (Group 1 and Group 2) and overall population with descriptive statistics. The analysis of objective response using an exact binomial test will be conducted separately for each group and overall; the 95% confidence interval will be reported.

Secondary efficacy endpoints will be evaluated in the Efficacy Evaluable population (Group 1 and Group 2).

DOR and TTP will be calculated and summarized by group and overall. PFS and OS curves will be plotted by group and overall using the Kaplan-Meier (KM) approach. The median survival time (if applicable) and its 95% CI for PFS and OS will be reported. The PFS and OS rates at 6 and 12 months will be estimated using the KM approach.

The objective response rate will be summarized for each of the 4 cohorts.

The percentage change from baseline in target lesions will be summarized by groups and overall.

Safety: The incidence of TEAEs will be summarized for the Safety Population, defined as all patients who received at least 1 dose of investigational combination, each group and overall, by severity, and by relationship to study drug as assessed by the Investigator. Similar tables will be prepared for SAEs, TEAEs leading to discontinuation, as well as additional categories of AEs as defined in the SAP.

Adverse event severity will be graded according to the CTCAE v5.0 and terms recorded on the CRFs will be mapped to preferred terms using MedDRA version 21.

Results of clinical laboratory tests will be summarized by visit for the absolute value and for change from baseline. Tables showing the shift from baseline will also be presented. ECG findings will be listed.

Concomitant medications will be categorized and presented using the World Health Organization Anatomical Therapeutic Chemical drug classification system.

Sample Size Considerations: This study plans to enroll [redacted] evaluable patients in treatment Groups 1 and 2, [redacted]

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 3
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 10
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 15
5. INTRODUCTION 19
5.1. Disease Overview 19
5.2. Study Rationale 20
5.3. Dose Selection 22
5.3.1. Pembrolizumab 22
5.3.2. ALKS 4230 22
6. STUDY OBJECTIVES 23
6.1. Primary Objective 23
6.2. Secondary Objectives 23
6.3. Exploratory Objectives 23
7. SELECTION AND WITHDRAWAL OF PATIENTS 24
7.1. Patient Inclusion Criteria 24
7.2. Patient Exclusion Criteria 26
7.3. Patient Withdrawal and Discontinuation 27
7.3.1. Discontinuation of Study Drug After Complete Remission 28
7.4. Replacement of Patients 28
8. STUDY DESIGN 30
8.1. Overall Study Design and Plan 30
8.2. Schedule of Assessments 32
8.3. Study Procedures Descriptions 40
8.3.1. Informed Consent 40
8.3.2. Eligibility Review 40
8.3.3. Demographics and Medical History 40
8.3.4. Prior and Concomitant Medication Review 40

8.3.5. Infusion-Type Reactions 40
8.3.6. Vital Signs and Weight 41
8.3.7. Physical Examination 41
8.3.8. 12-Lead Electrocardiogram 41
8.3.9. Eastern Cooperative Oncology Group Performance Status 41
8.3.10. Tumor Imaging and Assessment of Disease 41
8.3.10.1. Definitions 44
8.3.10.2. Disease Parameters 44
8.3.10.3. Methods for Evaluation of Measurable Disease 45
8.3.10.4. Response Criteria 46
8.3.10.5. Evaluation of Best Overall Response 47
8.3.10.6. Duration of Response 48
8.3.11. Laboratory Assessments 48
8.3.11.1. Pregnancy Testing 50
8.3.11.2. Serology Testing 50
8.3.12. Laboratory Correlative Studies 50
8.3.12.1. Correlative Studies With Biopsies 50
8.3.12.2. Correlative Studies with Blood Draws 51
8.3.12.3. Microbiome Analysis 53
8.3.13. Drug Dispensation and Reconciliation 54
8.3.13.1. Collection of Specimens 54
8.3.13.2. Handling and Shipping of Specimens 54
8.3.14. Randomization 55
8.3.15. Adverse Event Monitoring 55
8.4. Study Requirements and Restrictions 55
8.4.1. Contraception and Pregnancy 55
8.4.2. Prohibited Medications and Supportive Care 56
9. TREATMENT OF PATIENTS 59
9.1. Study Drug Dose and Administration 59
9.1.1. ALKS 4230 59
9.1.2. Pembrolizumab 59
9.2. Treatment Adherence 60
9.3. Randomization/Method of Assigning Patients to Treatment 60

9.4. Blinding 60
9.5. Study Drug Dose Delays, Interruptions, and Stopping Rules 60
9.5.1. Dose Delays 60
9.5.2. Dose Interruptions and Stopping Rules 60
9.5.3. Dose Modifications 62
9.5.4. Dose Delays and Modification Guidelines for Events Considered Related to Study Drug 63
9.5.4.1. Events Considered Related to ALKS 4230 63
9.5.4.2. Events Considered Related to Pembrolizumab 66
10. STUDY DRUG MATERIALS AND MANAGEMENT 67
10.1. Study Drug 67
10.1.1. ALKS 4230 67
10.1.2. Pembrolizumab 67
10.2. Packaging and Labeling 67
10.2.1. ALKS 4230 67
10.2.2. Pembrolizumab 67
10.3. Storage 68
10.3.1. ALKS 4230 68
10.3.2. Pembrolizumab 68
10.4. Accountability 68
10.5. Handling and Disposal 68
11. ASSESSMENT OF EFFICACY 70
11.1. Primary Efficacy Endpoint 70
11.2. Secondary Efficacy Endpoints 71
11.3. Exploratory Efficacy Endpoints 71
12. ASSESSMENT OF SAFETY 73
12.1. Definition of Adverse Event 73
12.1.1. Events of Clinical Interest 73
12.2. Definition of Serious Adverse Events 74
12.3. Relationship to Study Drug 74
12.3.1. Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab 75
12.3.2. Toxicity Management for Infusion Reactions Related to Pembrolizumab 79

12.4. Monitoring and Recording of Adverse Events 81
12.5. Reporting of Serious Adverse Events and Pregnancy 82
12.5.1. Protocol-specific Exemptions to Serious Adverse Event Reporting 82
12.5.2. Reporting of Pregnancy Events 83
13. STATISTICS 84
13.1. Sample Size Considerations 84
13.2. General Statistical Methodology 84
13.2.1. Study Populations 84
13.2.1.1. Efficacy Evaluable Population 84
13.2.1.2. Safety Population 85
13.3. Demographics and Baseline Data 85
13.4. Efficacy Analyses 85
13.4.1. Primary Efficacy Endpoints Analysis 85
13.4.2. Secondary Efficacy Analysis 85
[redacted] [redacted] 85
13.5. Safety and Tolerability Analyses 86
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 87
14.1. Study Monitoring 87
14.2. Audits and Inspections 87
14.3. Institutional Review Board/Independent Ethics Committee 87
15. QUALITY CONTROL AND QUALITY ASSURANCE 88
15.1. Case Report Forms 88
15.2. Confidentiality of Data 88
16. ETHICAL CONSIDERATIONS 89
16.1. Ethics Review 89
16.2. Ethical Conduct of the Study 89
16.3. Written Informed Consent 89
17. DATA HANDLING AND RECORDKEEPING 91
17.1. Data Capture 91
17.2. Inspection of Records 91
17.3. Retention of Records 91
18. REFERENCES 92
19. APPENDIX A: LABORATORY CORRELATES 94

20. APPENDIX B: ADDITIONAL INFORMATION FOR MANAGING IMMUNE-RELATED PEMBROLIZUMAB TOXICITIES 96

LIST OF TABLES

Table 1: Study Contact Information 2
Table 2: List of Abbreviations and Definition of Terms 15
Table 3: Laboratory Values Defining Adequate Organ Function....25
Table 4: Schedule of Assessments and Study Visits 33
Table 5: Long-term Follow-up Schedule....39
Table 6: Eastern Cooperative Oncology Group Performance Status....41
Table 7: Tumor Imaging/Assessment for Disease Progression 43
Table 8: Best Overall Response for Patients with Measurable Disease (ie, Target Disease)....47
Table 9: Best Overall Response for Patients with Non-Measurable Disease (ie, Non-Target Disease)....48
Table 10: Clinical Laboratory Assessments 49
Table 11: Study Drug Dose Interruptions and Stopping Rules for ALKS 4230 61
Table 12: Dose Management for Toxicities Related to ALKS 4230....64
Table 13: Adverse Event Causality Guidelines 75
Table 14: Dose Modification and Toxicity Management for Immune-related Toxicities Related to Pembrolizumab....76
Table 15: Dose Modification and Toxicity Management for Infusion Reactions Related to Pembrolizumab....80
Table 16: Laboratory Correlates 94

LIST OF FIGURES

Figure 1: Study Design Schematic 1 32
Figure 2: Study Design Schematic 2 32

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form of Definition
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
AE	Adverse event
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CI	Confidence interval
CIML	Central Immune Monitoring Laboratory
CNS	Central nervous system
CO_2	Carbon dioxide
CR	Complete remission
CrCl	Creatinine clearance
CRO	Contract research organization
CSA	Clinical Study Agreement
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DKA	Diabetic ketoacidosis
DLT	Dose-limiting toxicities
DNA	Deoxyribonucleic acid
DOR	Duration of response
D/C	Discontinuation
ECG	Electrocardiogram

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form of Definition
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOT	End of Treatment
FDG	Fluorodeoxyglucose
FHCRC	Fred Hutchinson Cancer Research Center
FIH	First-in-human
FNA	Fine needle aspiration
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Squamous cell carcinoma of the head and neck
HPV	Human papillomavirus
hsTCRB	Human T-cell receptor beta chain
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ID	Identification
IEC	Independent ethics committee
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IL-2R	Interleukin-2 receptor

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form of Definition
INR	International normalized ratio
ION	Immune Oncology Network
irAE	Immune-related adverse event
IRB	Institutional review board
irRC	Immune-related response criteria
IUD	Intrauterine device
IV	Intravenous, intravenously
Kyn	Kynurenine
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean fluorescence intensity
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-1
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal Investigator
PR	Partial response
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form of Definition
R	Receptor
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOP	Standard operating procedures
SRC	Safety Review Committee
T1DM	Type 1 diabetes mellitus
TB	Tuberculosis
TCR	T-cell receptor
TCRB	T-cell receptor beta chain
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TMB	Tumor mutational burden
TME	Tumor microenvironment
T_{reg}	Regulatory T cell
Trp	Tryptophan
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
USP-NF	United States Pharmacopeia-National Formulary
WGS	Whole genome shotgun
WHO-ATC	World Health Organization-Anatomical Therapeutic Chemical (drug classification system)

5. INTRODUCTION

5.1. Disease Overview

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common cancer worldwide (SEER database). An estimated 61,000 new cases of HNSCC were diagnosed in 2016 in the US alone, with approximately 13,000 patients dying of their disease. Despite advances in the diagnosis and treatment of this disease, the prognosis for patients with HNSCC remains poor (Kamangar et al, 2006; Siegel et al, 2016). Approximately two-thirds of HNSCC cases are diagnosed in advanced stages, although metastatic disease at presentation is uncommon (Argiris et al, 2008; National Comprehensive Cancer Network 2016; Rothenberg and Ellisen 2012). Recurrent and metastatic diseases are often refractory or unable to be treated with further surgery and/or radiation therapy (Colevas 2006; Specenier and Vermorken 2008). The 5-year survival rate for later-stage disease is estimated to be 50% or less (Gregoire et al, 2010; Lefebvre 2005; Rousseau and Badoual 2012). Metastatic and recurrent HNSCC that is no longer amenable to local surgical/radiation therapy is associated with a high mortality rate and a median survival of 6 to 9 months (Lefebvre 2005; Vermorken et al, 2008). First-line therapy with platinum-based therapy in combination with 5FU and cetuximab offers some palliation and efficacy but also high treatment-related toxicity. For patients with disease progression after first-line therapy, or who are platinum intolerant or platinum refractory, the anti-programmed cell death protein-1 (PD-1) antibodies, nivolumab and pembrolizumab, have demonstrated substantial palliative benefits with durable tumor regressions noted.

Pembrolizumab is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy, and this therapy is considered standard of care. Pembrolizumab was granted accelerated approval in 2017 based on an overall response rate (ORR) of 16% (95% confidence interval [CI]: 11, 22) and a complete response rate of 5% in a non-randomized study of 174 patients with recurrent or metastatic HNSCC refractory to platinum-containing chemotherapy (Larkins et al, 2017). Patients received pembrolizumab 10 mg/kg every 2 weeks (Q2W; n=53) or the now standard regimen of 200 mg every 3 weeks (Q3W; n=121) (Keytruda USPI). Among the 28 responding patients, the median duration of response (DOR) had not been reached (range 2.4+ to 27.7+ months), and the ORR and DOR were similar irrespective of dosage regimen (10 mg/kg Q2W or 200 mg Q3W) or human papillomavirus (HPV) status (Keytruda USPI). Subsequently, the efficacy of pembrolizumab was demonstrated in a single-arm study of 177 platinum- and cetuximab-pretreated HNSCC patients who had an ORR of 16% (95% CI: 11, 23) with a median DOR of 8 months (range 2+ to 12+ months) (Bauml et al, 2017). The open-label randomized Phase 3 study, Keynote 040, in platinum-pretreated HNSCC patients demonstrated that pembrolizumab narrowly failed to improve the primary endpoint of overall survival (OS) compared to the Investigator's choice therapy; the study's ORR was 14.6% in the pembrolizumab arm vs 10.1% with the active comparator (hazard ratio 0.81, one-sided P=0.0204) (Cohen et al, 2017).

Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or non-small cell lung cancer (NSCLC), with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3 to 4) and new or worsening hypothyroidism (14.6%) (Larkins et al, 2017; Seiwert et al, 2016).

ALKS 4230 is an engineered fusion protein composed of a circularly permuted interleukin (IL)-2 and IL-2 receptor (R; 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 (aldesleukin).

ALKS 4230 is agonist for IL-2Rβ and the common gamma chains, the two chains that make up the intermediate-affinity IL-2R. This is the same receptor complex stimulated by IL-15:IL-15Rα. Accordingly, ALKS 4230 functions in a fashion similar to IL-15, in that it activates and expands $CD8^+$ T cell and natural killer (NK) cells in preference to other categories of T cells and lymphocytes. In early clinical data, both ALKS 4230 and IL-15 function as T-cell growth factors that both activate and induce expansion of T cells and NK cells. PD-1 blocking antibodies "unleash" T cells, including T cells that can recognize and kill tumor cells. Theoretically, the combination of a T-cell growth factor with an agent that "unleashes" T cells should be synergistic in patients with T cells capable of recognizing and killing cancer cells. The synergy of anti-PD-1 and ALKS 4230 has previously been demonstrated in a murine model. The murine ortholog of ALKS 4230 delayed tumor growth in a subcutaneous B16F10 tumor model when used as monotherapy and in combination with anti-PD-1 (Losey et al, 2017). This study will test whether patients with HNSCC treated with anti-PD-1 therapy (pembrolizumab or nivolumab) who have failed to achieve complete remission (CR) can achieve partial or complete tumor response by the addition of ALKS 4230 in combination with pembrolizumab.

5.2. Study Rationale

Although the clinical studies with nivolumab and pembrolizumab have demonstrated antitumor activity and established the efficacy, activity, and benefits with anti-PD-1 therapy in the recurrent metastatic platinum-experienced HNSCC population, the response rates remain low, and the numbers of patients who relapse or fail to achieve CR remain in the high majority of 85% or more. As patients with HNSCC suffer tremendous morbidity and mortality with this disease, and the efficacy of any single-agent chemotherapy remains low with no proven salvage options in this population that fails anti PD-1 therapy, there is an exceptionally high unmet need to discover new therapies or effective combination immunotherapy to enhance, improve, or restore the responses to anti-PD-1 therapy.

This study (ION-01-ALKS4230) will enroll patients who have received prior anti-PD-1 antibody therapy (pembrolizumab or nivolumab) as their last treatment or those receiving ongoing current anti-PD-1 antibody therapy who have not achieved a CR. Programmed cell death protein-1:programmed cell death ligand-1 (PD-L1) (henceforth referred to as PD-[L]1) inhibitors are effective in small subsets of virtually every histologic type of cancer, yet most treated patients fail to benefit. Moreover, many of the tumors that respond eventually relapse. Therefore, it is highly likely that, in the near future, patients with stable disease (SD) or progressing on anti-PD-(L)1 therapy will likely be the largest single category of patients in the US. In the long-term follow-up analysis of the KEYNOTE-012 study of single agent pembrolizumab conducted in 192 patients with HNSCC, the objective response rate was 18% (95% CI, 13% to 24%) (Mehra et al, 2018). Among the subset of patients achieving a response, the median time to best response

was 2 months (range, 2 to 17 months). [redacted]

Discerning the character of the tumors in patients who are not achieving complete regression on PD-(L)1 inhibition with anti-PD1 or anti-PD-L is essential. Thus, pretreatment biopsies will be mandated. At present, the tumors most likely to respond to anti-PD-1 are those with an increased number of mutations and thus abnormal proteins containing potentially immunogenic epitopes and infiltration of T cells capable of recognizing the abnormal proteins. Mechanisms by which tumors fail to respond to anti-PD-1 are not yet comprehensively defined [redacted] There are likely to be many more redundant and non-redundant mechanisms of failure. Presumably, some mechanisms of failure will be rescued by ALKS 4230 ([redacted]) and some will not.

While it is not currently possible to hypothesize the frequency or proportion of each mechanism, we believe that biopsies from participants prior to and during therapy will provide insight into purported mechanisms of failure or success to generate hypotheses that will provide the foundation for future study design.

Assessment of whether addition of ALKS 4230 can induce remission for patients with tumors that do not respond to anti-PD-1 treatment is the essential goal of the study. Understanding whether ALKS 4230 alters the number of NK cells and T cells within tumors is also critical. Thus, the post-treatment (second) biopsy will be collected during Week 2 (Cycle [C] 1, Day [D] 12 or at any time from C1D8 through C1D19).

The study population designates patients with advanced or recurrent HNSCC who are either refractory and progressive on prior anti-PD-(L)1 therapy or have failed to obtain response or tumor regression to anti-PD-1 therapy for more than 8 weeks to receive ALKS 4230 in combination with pembrolizumab. Patients in this population are as follows:

Group 1 (Cohorts 1 and 2) will consist of all patients with current SD (for at least 12 weeks) or partial response (PR) with no further reduction in tumor size or response for ≥8 weeks (ie, PR and not further improving).

Group 2 (Cohorts 3 and 4) will consist of patients with progressive disease (PD) with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-(L)1 or current PD after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy.

HNSCC was chosen due to the high unmet need in this difficult-to-treat patient population with no effective therapeutic options for a number of reasons: 1) the demonstrated efficacy and recent approval of pembrolizumab for previously platinum-experienced recurrent or metastatic HNSCC, 2) the ease of serial biopsies in easily accessible sites of tumor in a proportion of patients, and 3) the responses to the combination of ALKS 4230 and pembrolizumab being

readily and easily assessable. However, if efficacy or response is observed, the combination could be tested in many different cancers.

This study will be performed in collaboration with the Immune Oncology Network (ION), who will perform activities related to, but not limited to, oversight and management of clinical sites, medical monitoring, and laboratory analysis services.

5.3. Dose Selection

5.3.1. Pembrolizumab

The pembrolizumab dose of 200 mg Q3W is the approved dose for the treatment of patients with HNSCC (Keytruda USPI).

5.3.2. ALKS 4230

All patients in this study will be given ALKS 4230 at a daily dose of 3 µg/kg for 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.

A first-in-human (FIH) clinical study with ALKS 4230 has been initiated and is currently ongoing (ALK4230-A101). This study is being conducted in patients with advanced solid tumors who are refractory or intolerant to therapies known to provide clinical benefit. Patients are administered ALKS 4230 by a 30-minute intravenous (IV) infusion daily for 5 days followed by an off-treatment period (as described in the ALK4230-A101 protocol) in repeating cycles. Dosing is repeated every 21 days, except during the first treatment cycle, which is 14 days.

[redacted] LT definitions were subsequently amended to loosen DLT criteria and allow continued dose escalation.

[redacted]

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of this study is to estimate the response rate to ALKS 4230 in combination with pembrolizumab in patients with 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 Response Evaluation Criteria in Solid Tumors (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.

6.2. Secondary Objectives

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

6.3. 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], can identify changes in tumors that will predict response or failure to the addition of ALKS 4230 [redacted]
- [redacted]

7. SELECTION AND WITHDRAWAL OF PATIENTS

Each patient must meet all of the inclusion and none of the exclusion criteria to be qualified to participate in this study.

7.1. Patient Inclusion Criteria

1. Is ≥18 years of age.
2. Is willing and able to provide informed consent.
3. Is willing and able to follow the study procedures as outlined in the protocol.
4. Must have a histologically or cytopathologically confirmed diagnosis of HNSCC region that is locally advanced or recurrent and no longer amenable to local surgical or radiation therapy and/or with evidence of metastatic disease. Both HPV-positive and -negative patients will be included.
5. Must have had prior PD-1:PD-L1 inhibition therapy with anti-PD-(L)1 therapy as the most recent systemic therapy with
   a. (Group 1, Cohort 1) current SD (for ≥12 weeks by RECIST criteria v1.1) or
   b. (Group 1, Cohort 2) current PR with no further reduction in tumor size or response for ≥8 weeks (ie, PR and not further improving)
   c. (Group 2, Cohort 3) current PD with no prior response to anti-PD-(L)1 therapy after ≥8 weeks on anti-PD-(L)1 or
   d. (Group 2, Cohort 4) current PD after prior achievement of a best response of SD or PR and after ≥8 weeks on anti-PD-(L)1 therapy

   Some minimal intervening localized palliative radiotherapy or ablation therapy may be allowed upon review and agreement by the ION and Alkermes Medical Monitors.
6. Must have disease that is measurable by RECIST v1.1 criteria as determined by the treating physician and not confounded by prior treatment such as radiation. Patients with only 1 site of disease must be able to provide adequate tissue samples at the time of biopsy that will not affect the tumor size per RECIST v1.1 criteria.
7. Patients who have received standard or investigational anti-PD-(L)1 agents as the most recent systemic therapy must wait at least 3 weeks (with the exception of an anti-PD-[L]1 inhibitor that is dosed Q2W and in consultation with the ION and Alkermes Medical Monitors, in which case patients must wait at least 2 weeks) before enrollment into the study or 4 weeks if the half-life of the investigational agent is not known. Patients who have received standard or investigational agents other than anti-PD-(L)1 agents (including agents as part of a combination regimen with an anti-PD-[L]1 agent) must wait 8 weeks before enrollment into the study, unless discussed with and approved by the ION and Alkermes Medical Monitors on an individual basis.
8. Patients must be willing to provide tumor tissue adequate for biomarker correlative studies at the time points specified in the protocol.

9. Patients should have readily accessible tumor for biopsy pre- and post-pembrolizumab and ALKS 4230 combination regimen. Biopsy should be excisional, incisional, or core needle and large enough to show tissue architecture.
10. Have a performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
11. Demonstrate adequate organ function as defined in Table 3. All screening laboratories should be performed within 10 days of treatment initiation.

Table 3: Laboratory Values Defining Adequate Organ Function

System	Laboratory Value
Hematological	
ANC	≥1,000/μL without hematopoietic growth factor support
Platelet count	≥100,000/μL without transfusion support
Hemoglobin	≥9 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] CrCl (glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5×ULN **OR** ≥60 mL/min
Hepatic	
Serum total bilirubin	≤1.5×ULN **OR** Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5×ULN
AST and ALT	≤2.5×ULN **OR** ≤5×ULN for patients with liver metastases
Albumin	>2.5 mg/dL
Coagulation	
INR or PT	≤1.5×ULN unless patient is receiving anticoagulant therapy. If the patient is receiving anticoagulant therapy, the INR or PT needs to be within the therapeutic range of intended use of anticoagulants or deemed a safe level for the proposed biopsies by the biopsy surgeon or interventional radiologist.
aPTT	≤1.5×ULN unless patient is receiving anticoagulant therapy. If the patient is receiving anticoagulant therapy, the aPTT needs to be within the therapeutic range of intended use of anticoagulants or deemed a safe level for the proposed biopsies by the biopsy surgeon or interventional radiologist.

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CrCl=creatinine clearance; INR=international normalized ratio; PT=prothrombin time; ULN=upper limit of normal

[a] CrCl should be calculated per institutional standard.

12. Female patients of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Is willing to abide by the contraception requirements for the duration of the study (additional details regarding contraception requirements are provided in Section 8.4.1).

7.2. Patient Exclusion Criteria

1. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (inhaled or topical steroids are allowable) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
2. Has active tuberculosis (TB; *Bacillus tuberculosis*).
3. Has hypersensitivity to pembrolizumab, ALKS 4230, or any of their excipients.
4. Has prior Grade ≥3 immune-related toxicities requiring systemic immunosuppressant treatment that were attributable or possibly attributable to PD-1 immune checkpoint blockade. Has toxicities deemed reversible from prior therapy, including anti-PD-1, that have not recovered to baseline or Grade ≤1. Patients with persistent Grade ≤2 neuropathy are an exception to this criterion and may qualify for the study.
    a. **Note**: If patient received major surgery, the patient must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Has had a prior dose of anti-PD-(L)1 therapy within 3 weeks of Study Day 1, with the exception of an anti-PD-(L)1 inhibitor that is dosed Q2W and in consultation with the ION and Alkermes Medical Monitors.
6. Has a known history of additional malignancy within 2 years or current additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer, or treated prostate cancer with a prostate-specific antigen value of <0.01 ng/mL.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate, provided that they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study drug. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.
8. Has known history of, or any evidence of, non-infectious interstitial pneumonitis that required steroids or current pneumonitis, or oxygen requirement for any reason in the past 28 days.
9. Has an active major infection requiring systemic therapy within 1 week of starting study drug.

10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
11. Has known psychiatric or substance abuse disorders or a social situation that would interfere with cooperation with the requirements of the study.
12. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 120 days after the last dose of study drug (see Section 8.4.1 for additional details).
13. Known active infection with hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus [HCV] RNA [qualitative]) detected.
14. Has any finding that, in the view of the Investigator, would compromise the safety of the patient or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements.
15. Is Investigator-site personnel, an immediate family of the Investigator-site personnel, employed by Alkermes or ION, or an immediate family member of an Alkermes or ION employee.
16. If, in the opinion of the Investigator (and/or Sponsor), the patient is unsuitable for enrollment in the study.
17. Has significant known cardiovascular impairment (New York Heart Association Congestive Heart Failure >Grade 2, unstable angina, myocardial infarction within the previous 6 months prior to the first dose of investigational drug, or existing serious cardiac arrhythmia).
18. Has chronic or acute gastrointestinal (GI) disorders resulting in diarrhea of any severity grade; patient is using chronic anti-diarrheal supportive care (more than 3 days/week) to control diarrhea in the 28 days prior to the first dose of investigational drug.
19. Has known cirrhosis diagnosed with Child-Pugh Class A or higher liver disease.

7.3. Patient Withdrawal and Discontinuation

A patient may be discontinued from the study at any time if the patient or Investigator determines that it is not in the best interest of the patient to continue participation. Reasons for discontinuation include:

- Adverse event (see Section 12.1.)
- Disease progression
  - For unconfirmed radiographic disease, see Section 8.3.10.
  - A patient may be granted an exception to continue on treatment with confirmed radiographic progression if the patient is clinically stable and upon written agreement from both ION and Alkermes Medical Monitors (see Section 8.3.10).
- Intercurrent illness that prevents further administration of treatment

- The need for administration of an excluded or prohibited medication
- Loss to follow-up
- Withdrawal of consent
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Other

If a patient withdraws from the study for any reason, any ongoing adverse events (AEs) will be followed until resolution, until deemed stable by the Investigator, until initiation of new anticancer therapy, or until the patient is deemed by the Investigator to be lost to follow-up. If, in the opinion of the Investigator, it is necessary to monitor a patient beyond the Safety Follow-up Visit, the follow-up period may be extended as necessary. In such instances, the Sponsor and the Investigator will agree to an acceptable follow-up schedule.

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. If the patient fails or refuses to return to the study center, an attempt must be made to contact the patient by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the patient's study record.

The Investigator must maintain a record of all patients who fail to complete the study. The reason for study discontinuation will be documented and made on the appropriate electronic case report form (eCRF). If a patient is lost to follow-up, a reasonable attempt to contact the patient must be made and documented.

The Sponsor reserves the right to terminate the study at any time for any reason.

7.3.1. Discontinuation of Study Drug After Complete Remission

[redacted]

7.4. Replacement of Patients

Patients who do not receive all doses of ALKS 4230 and pembrolizumab in Cycle 1 will be replaced, unless they missed a dose due to toxicity, as assessed by the Investigator. Patients who miss a dose of ALKS 4230 and pembrolizumab in Cycle 1 due to toxicity will not be replaced.

Patients who do not provide a second biopsy may be replaced at the discretion of the Investigator.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

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, or
- 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

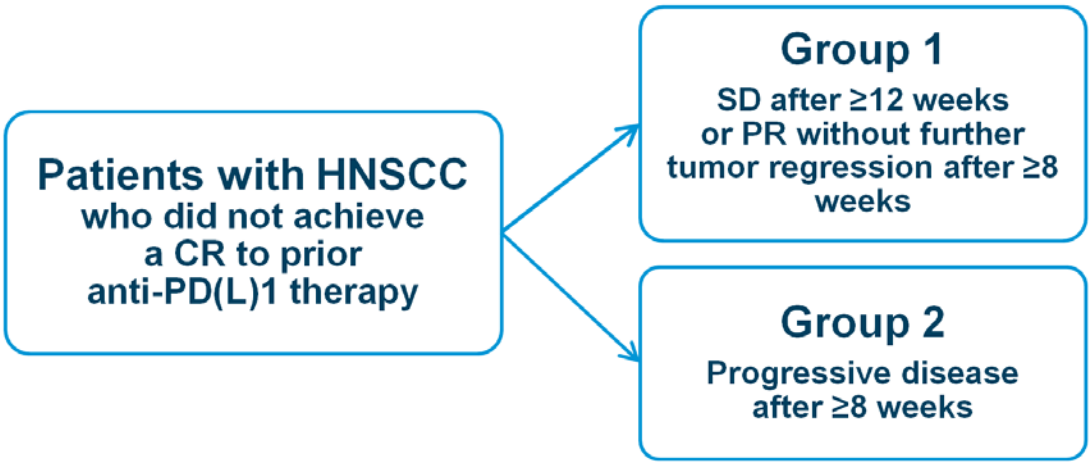
Safety and tolerability will be assessed and reported using standard Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria. Safety will be monitored by the study Principal Investigator (PI), participating site PIs, the ION Coordinating Center PI and staff, and representatives from Alkermes. 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) 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.

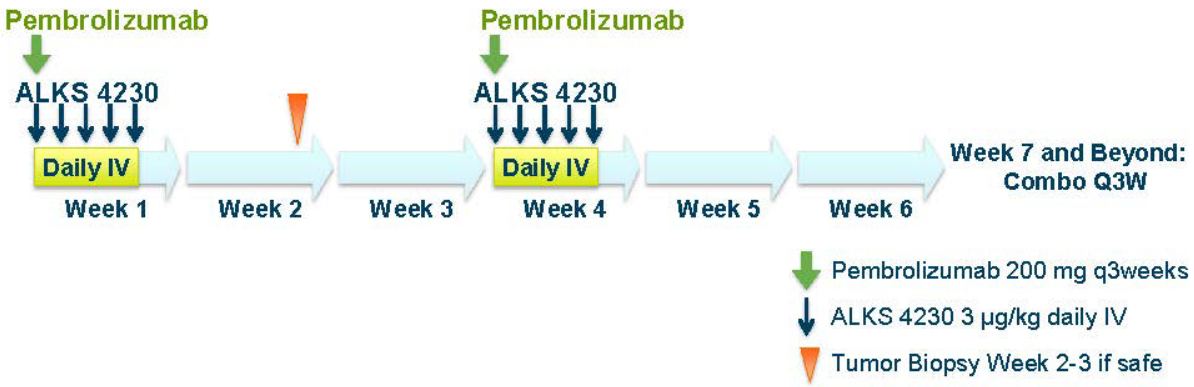
Study design schematics are provided in Figure 1 and Figure 2.

Figure 1: Study Design Schematic 1



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

8.2. Schedule of Assessments

The schedule of assessments for treatment and post-treatment follow-up is shown in Table 4. The schedule of assessments for long-term follow-up is shown in Table 5.

Premature discontinuation procedures are provided in Section 7.3.

Table 4: Schedule of Assessments and Study Visits

Treatment Cycle[a]		**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Subsequent Cycle (Repeat for up to 1 year)**				**Post-treatment Follow-up**		
Weeks	**Screening**	**w 1**	**w 2**	**w 3**	**w 4**	**w 5**	**w 6**	**w 7**	**w 8**	**w 9**	**w 10**	**w 11**	**w 12**	**w 13**	**w 14**	**w 15**	**w 16**	**w 17**	**w 18**	**End of Tx**[a]	**Safety FU**	**Disease Assessment**[b]	**Survival FU**[c]
Scheduling window (days)[d]	-28 to -1 days				-1/ +3			-1/ +3			-1/ +3			-1/ +3			-1/ +3			At time of D/C	30 days ±5 post D/C	Every 8 weeks post D/C for up to 2 years	Every 12 weeks for up to 2 years
Pembrolizumab		P			P			P			P			P			P						
ALKS 4230		A			A			A			A			A			A						
Antipyretics		X			X			X			X			X			X						
Administrative Procedures																							
Informed Consent	X[e]																						
Inclusion/ Exclusion Criteria	X																						
Demographics	X																						
Medical History	X																						
Prior and Concomitant Medications[f]	X	X			X			X			X			X			X				X		

Table 4: Schedule of Assessments and Study Visits (Continued)

Treatment Cycle[a]		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Subsequent Cycle (Repeat for up to 1 year)			End of Tx[a]	Post-treatment Follow-up		
Weeks	**Screening**	**w 1**	**w 2**	**w 3**	**w 4**	**w 5**	**w 6**	**w 7**	**w 8**	**w 9**	**w 10**	**w 11**	**w 12**	**w 13**	**w 14**	**w 15**	**w 16**	**w 17**	**w 18**		**Safety FU**	**Disease Assessment[b]**	**Survival FU[c]**
Clinical Procedures/Assessments																							
Review AEs[g]	X	X	X	X	X			X			X			X			X				X[h]	X[h]	
Full Physical Examination	X																			X			
Directed Physical Examination		X			X			X			X			X			X						
Vital Signs, Weight, and Height[i]	X	X			X			X			X			X			X			X			
ECOG Performance Status[j]	X[j]	X			X			X			X			X			X			X			
12-lead ECG[k]	X	X																		X			
Laboratory Assessments (Safety Labs)																							
HBsAg, anti-HCV, and HIV	X																						
Pregnancy Test – Urine or Serum β-hCG[l]	X	X			X			X			X			X			X			X			
PT/INR and aPTT[m]	X[j]					X																	

Table 4: Schedule of Assessments and Study Visits (Continued)

Treatment Cycle[a]		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Subsequent Cycle (Repeat for up to 1 year)			End of Tx[a]	Post-treatment Follow-up		
Weeks	**Screening**	**w 1**	**w 2**	**w 3**	**w 4**	**w 5**	**w 6**	**w 7**	**w 8**	**w 9**	**w 10**	**w 11**	**w 12**	**w 13**	**w 14**	**w 15**	**w 16**	**w 17**	**w 18**		**Safety FU**	**Disease Assessment[b]**	**Survival FU[c]**
Laboratory Assessments (Safety Labs) (Continued)																							
CBC with Differential[n]	X[j]	X			X			X			X			X			X			X	X[o]		
Complete Serum Chemistry Panel[n]	X[j]	X			X			X			X			X			X			X	X[o]		
Urinalysis[n]	X[j]	X			X			X			X[p]						X				X[o]		
TSH, Cortisol, and ACTH[q]	X							X						X			X						
Efficacy Measurements																							
Tumor Imaging	X[r]						X[s]				X[s]						X[s]			X[b,t]		X[b]	
Tumor Biopsies/Archival Tissue and Microbiota Collection																							
Archival or Newly Obtained Tumor Biopsy (for Tumor T-cell Clonality; GEP studies, and Sequencing and TMB analysis)		X[u]	X[v]																				

Table 4: Schedule of Assessments and Study Visits (Continued)

Treatment Cycle[a]		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Subsequent Cycle (Repeat for up to 1 year)			End of Tx[a]	Post-treatment Follow-up		
Weeks	**Screening**	**w 1**	**w 2**	**w 3**	**w 4**	**w 5**	**w 6**	**w 7**	**w 8**	**w 9**	**w 10**	**w 11**	**w 12**	**w 13**	**w 14**	**w 15**	**w 16**	**w 17**	**w 18**		**Safety FU**	**Disease Assessment[b]**	**Survival FU[c]**
Tumor Biopsies/Archival Tissue and Microbiota Collection (Continued)																							
Stool Sample[w]		X				X																	
Correlative Studies Blood Draws[x]																							
Immunogenicity of ALKS 4230		X			X			X			X			X			X				X (14 days post D/C)		
Immunophenotyping of PBMC		X	X	X	X	X		X			X			X			X			X			
T- and NK-cell Function Analysis		X	X	X	X	X		X			X			X			X			X			
Plasma Cytokine Assays		X			X																		
Kyn/Trp Ratio, Arginine		X			X			X			X			X			X			X			

Abbreviations: A=ALKS 4230: 3 µg/kg, daily for 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.
ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT=activated partial thromboplastin time; C=Cycle; CBC=complete blood count; CIML=Central Immune Monitoring Laboratory; CTCAE=Common Terminology Criteria for Adverse Events; D=Day; D/C=discontinuation; ECG=electrocardiogram; ECI=events of clinical interest; ECOG=Eastern Cooperative Oncology Group; FNA=fine needle aspiration; FU=follow-up; GEP=gene expression profiling; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HPV=human papillomavirus; ID=identification; INR=international normalized ratio; Kyn=kynurenine; NCI=National Cancer Institute; NK=natural killer; P=Pembrolizumab: 200 mg flat dose, once Q3W, starting Cycle 1, Day 1 for up to 1 year; PD=progressive disease; PD-L1=programmed death ligand-1;

PBMC=peripheral blood mononuclear cell; PT=prothrombin time; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TMB=tumor mutational burden; Trp=tryptophan; TSH=thyroid-stimulating hormone; Tx=treatment; w=Week (visit).

[a] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks; however, the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 9.1.1 and Section 9.1.2.

[b] In patients who discontinue study therapy, every effort should be made to continue monitoring their disease status by radiologic imaging per local standard of care or Investigator clinical judgment every 8 weeks for up to 2 years until (1) the initiation of new therapy, (2) death, or (3) the end of the study, whichever occurs first.

[c] After the start of new anticancer treatment or documented disease progression by local imaging review, the patient should be contacted by telephone every 12 weeks (±1 week) to assess for survival status for up to 2 years.

[d] In general, the window for each visit is -1/+3 days unless otherwise noted. Pembrolizumab is given on Day 1 of each cycle with a -1/+3-day window. ALKS 4230 is given daily on 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle. Day 1 of each 5-day dosing period will have a -1/+3-day scheduling window; however, all subsequent days within a cycle (Days 2 to 5) must be administered on their scheduled day. Refer to Section 9.5.2 for management of skipped dosing days.

[e] Written consent must be obtained prior to performing any protocol-specified procedure. Consent should include option to copy relevant imaging for central review by the manufacturer, enabling confirmation of Investigator-determined responses. Results of a test performed prior to the patient signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to the first dose of study drug). A patient ID number will be assigned when the patient is enrolled.

[f] Prior medications – Record all medications taken within 30 days of Screening Visit. Concomitant medications – Enter new medications started within 28 days before the first dose of study drug through the Safety Follow-up Visit. Record all medications taken for AEs.

[g] AEs and laboratory safety measurements will be graded per NCI CTCAE v5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. The Week 3 AE review can be captured via telephone; no visit is required.

[h] Record all AEs occurring within 30 days after the last dose of study drug. Report all SAEs (related and unrelated to study drug) and ECIs occurring up until 90 days after the last dose of study drug or 30 days after the start of new anticancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to study drug.

[i] Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Visit 1 only.

[j] ECOG Performance Status and laboratory tests for screening are to be performed within 10 days prior to the first dose of study drug.

[k] ECGs should be performed on Day 1, Day 3, and Day 5 of each cycle. ECGs should be performed in triplicate approximately 5 minutes apart at each time point assessed. ECGs will be obtained predose of pembrolizumab on Cycle 2 Day 1. ECGs should also be obtained predose of ALKS 4230, at the end of infusion, and 1 hour (±15 minutes) after the completion of administration of ALKS 4230.

[l] 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 Dose 1 of each cycle is administered for all cycles.

[m] Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures and before collection of the post-treatment (second) biopsy for all patients. Any patient receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

[n] After Cycle 1, laboratory samples can be collected up to 72 hours prior to Day 1 (CBC with differential; complete serum chemistry panel, including magnesium, calcium, and phosphorus; and urinalysis). CBC and complete serum chemistry panel should also be done up to 72 hours prior to Day 1 of the ALKS 4230 infusion.

[o] Unresolved abnormal laboratories that are drug-related AEs should be followed until resolution. Laboratories do not need to be repeated after the end of treatment if laboratories are within normal range.

[p] To be repeated every 2 cycles after Cycle 4.

[q] TSH, cortisol, and ACTH should be measured at baseline and every other cycle (every 6 weeks). Cortisol should be measured in the morning.

[r] The initial tumor imaging will be performed within 28 days prior to the first dose of study drug. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of study drug. Local reading (Investigator assessment with site RECIST radiology reading) will be used to determine eligibility and for patient management.

[s] The first on-study imaging time point will be performed at 6 weeks (±7 days) after the first dose of study drug, then within 7 days prior to every second cycle, or more frequently if clinically indicated. The same imaging technique should be used in a patient throughout the study. Local reading (Investigator assessment with site RECIST radiology reading) will be used to determine eligibility and for patient management.

[t] In patients who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (ie, date of discontinue ± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.

[u] Baseline tumor tissue from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) from patients with oropharynx cancer must be tested locally for HPV status (if HPV status not known) prior to enrollment. Baseline tumor tissue from a newly obtained sample must also be provided to the CIML for PD-L1 biomarker testing (see Laboratory Manual for additional details). Newly obtained tissue may be obtained up to 42 days prior to treatment initiation, as long as the patient has provided study consent. Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual. If the patient gives permission for the future use of additional biospecimen materials, then any leftover tissue that would ordinarily be discarded will be stored for future, as-yet-identified testing.

[v] The post-treatment (second) biopsy will be performed on the same or similar tumor site during the first cycle of therapy at C1D12, or at any time from C1D8 through C1D19.

[w] Fecal swab/storage devices and instructions must be given to the patient; sample collection to be performed at home by patient and returned to clinical research site at the next study visit.

[x] Additional information regarding correlative studies is located in Table 16, and additional instructions are provided in the Laboratory Manual.

Table 5: Long-term Follow-up Schedule

Patient Group	Imaging	Follow-up	AE Tracking
Patients with SD/PR who continue on Tx, no progression, for up to 1 year	9 weeks post-treatment start (within 7 days prior to Cycle 4), then within 7 days prior to every 3rd cycle Follow-up: every 12 weeks ±1 week	Safety Follow-up Visit at 30 days after discontinuation Clinic visit every 8 weeks	Until 90 days after discontinuation or 30 days after discontinuation if patient begins new anticancer therapy
Patients who progress on-study before 1 year	Per local standard of care	Safety Follow-up Visit at 30 days after discontinuation or before start of new therapy, if applicable (in-clinic) Safety Follow-up Visit at 90 days after discontinuation (in-clinic preferable, by phone possible) Survival telephone call every 12 weeks for up to 2 years	Until 90 days after discontinuation or 30 days after discontinuation if patient begins new anticancer therapy
Patients who discontinue treatment due to any reason other than progression	Per local standard of care or Investigator clinical judgment	Safety Follow-up Visit at 30 days after discontinuation or before start of new therapy, if applicable Clinic follow-up until toxicity resolves or until death	Until 90 days after discontinuation or 30 days after discontinuation if patient begins new anticancer therapy
Patients who achieve CR on Tx (after at least 24 weeks of Tx + 2 doses post-CR imaging)	After discontinuation of treatment: Follow-up: every 12 weeks ±1 week OR at clinical signs/symptoms of progression	Safety Follow-up Visit at 30 days after discontinuation Clinic visit every 8 weeks	Until 90 days after discontinuation or 30 days after discontinuation if patient begins new anticancer therapy

Abbreviations: AE=adverse event; CR=complete remission; NA=not applicable; PR=partial response; SD=stable disease; Tx=treatment.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 4.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the patient by the Investigator or designated study personnel as outlined in Section 16.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential patient. Consent should include the option to copy relevant imaging for central review by the manufacturer to enable confirmation of Investigator-determined responses.

8.3.2. Eligibility Review

An eligibility review will be conducted by the Investigator at the visits specified in Table 4 using the patient inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

8.3.3. Demographics and Medical History

Patient's demographic data and medical history will be reviewed and documented at the time point(s) specified in Table 4. Tumor measurements should be collected prior to the patient's enrollment on the study. Measurements to collect should include any measurements RECIST made during the patient's previous treatment with an anti-PD-(L)1 agent.

8.3.4. Prior and Concomitant Medication Review

At the time point(s) specified in Table 4, prospective patients will be asked about the medications they have taken in the last 28 days, including prescription and nonprescription medications, vitamins, and supplements.

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

Prohibited medications are described in Section 8.4.2.

8.3.5. Infusion-Type Reactions

ALKS 4230 may be associated with infusion-type reactions. Infusion reactions should be treated at the discretion of the Investigator. The National Cancer Institute CTCAE v5.0 describes multiple types of infusion reactions:

1. Allergic reactions
2. Anaphylaxis
3. Cytokine release syndrome

Patients who experience Grade 3 or 4 infusion reactions should not be rechallenged with ALKS 4230.

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

8.3.6. Vital Signs and Weight

Vital signs (ie, weight, blood pressure, pulse, respiratory rate, and body temperature) will be assessed at the time point(s) specified in Table 4. Height will be measured at screening (Visit 1) only. Blood pressure, pulse, and respiratory rate will be measured after the patient 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 point(s) specified in Table 4. For cycles that do not require a full physical exam per the study flow chart, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study drug administration.

8.3.8. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at the time point(s) specified in Table 4.

8.3.9. Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status assesses the patients' activity status and will be assessed at the time points specified in Table 4. Possible scores are 0 to 5. Descriptions of activity status are presented in Table 6.

Table 6: 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

8.3.10. Tumor Imaging and Assessment of Disease

For the purposes of this study, baseline scans must be done within 28 days before beginning treatment. In addition to a baseline scan, the first on-study imaging time point will be performed

at 6 weeks (± 7 days) after first dose, then within 7 days prior to every second cycle thereafter, or more frequently if clinically indicated while the patient is on study.

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. If the patient continues on study after confirmatory scan, then the patient would receive scan per regular schedule. Thereafter, timing of tumor assessments will depend on whether or not the patient continues with study drug (see Table 5 for additional information).

Accumulating evidence indicates that a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response. Patients will be permitted to continue on treatment beyond initial RECIST v1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and no rapid disease progression.
- Patient continues to meet relevant eligibility criteria, as determined by the ION and Alkermes Medical Monitors (or designee) in discussion with the Investigator.
- Stable performance status.
- Patient is tolerating study treatment.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases).

The decision to continue treatment beyond initial Investigator-assessed progression should be discussed with the ION and Alkermes Medical Monitors (or designee) and documented in the study records. A follow-up scan should be performed at the next scheduled imaging evaluation 6 weeks later to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment. If the Investigator feels that the patient continues to achieve clinical benefit by continuing treatment, then the patient should remain on the study and continue to receive monitoring according to the Schedule of Assessments (Section 8.2), with consultation from the ION and Alkermes Medical Monitors.

[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

Table 7: Tumor Imaging/Assessment for Disease Progression

Disease assessment by RECISTv1.1	**Clinically Stable**		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at approximately 4 to 6 weeks to confirm PD	May continue study drug at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at approximately 4 to 6 weeks to confirm PD if possible	Discontinue treatment if alternative therapy is warranted
Repeat scan confirms PD[a]	No additional imaging required	Discontinue treatment	No additional imaging required	NA
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments prior to every 3rd cycle[b]	Continue study drug at the Investigator's discretion	Continue regularly scheduled imaging assessments prior to every 3rd cycle[b]	May restart study drug if condition has improved and/or clinically stable per Investigator's discretion

Abbreviations: CR=complete remission; NA=not applicable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

[a] Patients who are otherwise clinically stable may be continued on study drug, per Investigator discretion. Even if the patient remains otherwise stable, study drug will be discontinued if tumor burden increases by 25% or more following initial confirmation of progression.

[b] Tumor imaging/assessment will be performed at baseline, at 9 weeks, and prior to every 3rd cycle.

Response and progression for purpose of publication will be evaluated in this study using the new international criteria proposed by the revised RECIST v1.1 guideline. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes will be used in the RECIST criteria.

Often with immunotherapy, tumors appear larger before they decrease in size. [redacted]. Clinicians are encouraged to consider this possibility to avoid stopping potentially effective immunotherapy too soon.

8.3.10.1. Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of consent.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (NOTE: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment will be based on the presence, absence, or unequivocal progression of the lesions.

8.3.10.2. Disease Parameters

Measurable disease: For the purposes of this study, measurable lesions are defined according to RECIST v1.1 criteria. All tumor measurements must be recorded in mm (or decimal fractions of centimeters).

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by computerized tomography (CT) scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or magnetic resonance imaging [MRI]), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions

with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement; in such circumstance, the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or rare cases of unequivocal progression of each should be noted throughout follow-up.

8.3.10.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged and are only assessable by clinical examination. Methods allowable for disease evaluation are as follows:

- Clinical examination: For skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (eg, skin nodules).
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Conventional CT and MRI: A CT scan may be used to measure the lesion if the CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). For both scanning methods, technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- Positron emission tomography (PET)-CT: Combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical

diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Fluorodeoxyglucose (FDG)-PET: FDG-PET scanning is optional and may be used to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
3. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A ‘positive’ FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Cytology and histology techniques can be used to differentiate between PR and CR in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

8.3.10.4. Response Criteria

Evaluation of Target Lesions

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

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

PD: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (NOTE: the appearance of one or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

8.3.10.5. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Best overall response is described in Table 8 for patients with measurable disease and in Table 9 for patients with non-measurable disease.

Table 8: Best Overall Response for Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 weeks confirmation[a]
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation[a]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD[b]	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR=complete remission; SD=stable disease; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.
[a] Only for non-randomized studies with response as primary endpoint.
[b] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.

NOTE: For purposes of this trial, confirmation of response will occur at 6 weeks after the response-defining measurements rather than the 4-week point specified in the RECIST v1.1 criteria.

Table 9: Best Overall Response for Patients with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete remission; PD=progressive disease; SD=stable disease
[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.3.10.6. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented.

Duration of SD: The duration of SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.3.11. Laboratory Assessments

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 4. Specific complete blood count (CBC) with differential, complete serum chemistry, 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 CBC with differential, complete serum chemistry, and urinalysis.

Table 10: Clinical Laboratory Assessments

CBC with Differential	Complete Serum Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell count Total and differential white blood cell count ANC Absolute lymphocyte count	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 only. If urine pregnancy test results cannot be confirmed as negative, a serum pregnancy test will be required.

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing on Day 1 of each cycle. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of study drug.

If a site is unable to collect all specimens due to low hemoglobin or other issues such as vein access, specimens should be collected in the following order if required at the visit:

- Toxicity/safety specimens
- [redacted]

- [redacted]

8.3.11.1. Pregnancy Testing

A urine/serum pregnancy test will be administered to all women of childbearing potential at the time point(s) specified in Table 4. At the Screening Visit, results must be negative for the patient to be eligible for the study.

Section 12.5 provides guidance on the reporting requirements for pregnancies.

8.3.11.2. Serology Testing

A blood sample for serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and human immunodeficiency virus will be performed at screening only.

8.3.12. Laboratory Correlative Studies

Specimens will be collected for several planned correlative studies (summarized in Table 16) at the time points specified in Table 4. Many samples will be processed and stored, to be run in batches. When blood volume is limited, correlative studies will be considered secondary to tests needed to make clinical decisions. Also, testing may be delayed or omitted if collecting the specimens may pose a danger to the patient, if samples cannot be processed or assayed, or if results are determined to be non-essential to achieving the objectives of the study.

8.3.12.1. Correlative Studies With Biopsies

Collection of pretreatment tumor tissue (fresh biopsy via excisional, incisional, or core needle and large enough to show tissue architecture) is mandatory; if collecting pretreatment tissue is not possible (eg, inaccessible or patient safety concern), submission of archived specimen is possible upon agreement from the Sponsor. Obtaining a post-treatment (second) biopsy is mandatory in order to achieve protocol objectives and to study the TME post-treatment but may be bypassed for patient safety reasons only after discussions with the Sponsor. Biopsy-based correlatives are considered exploratory. Prioritization of biopsy specimens will be made based on technical considerations that will be included in the Laboratory Manual, total number of samples acquired, and feasibility of correlative study based on the above considerations.

The pretreatment biopsy will be collected after all screening assessments have been performed and before the first dose of pembrolizumab and ALKS 4230 on Cycle 1, Week 1, Day 1. The pretreatment specimen may be obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1, provided study informed consent has been obtained or the biopsy was performed as part of routine patient care. The post-treatment (second) biopsy will be performed on the same or similar tumor site during the first cycle of therapy at C1D12 or at any time from C1D8 through C1D19. Fine needle aspirates are not allowed for tissue sampling but may be used to localize active disease prior to tissue sampling.

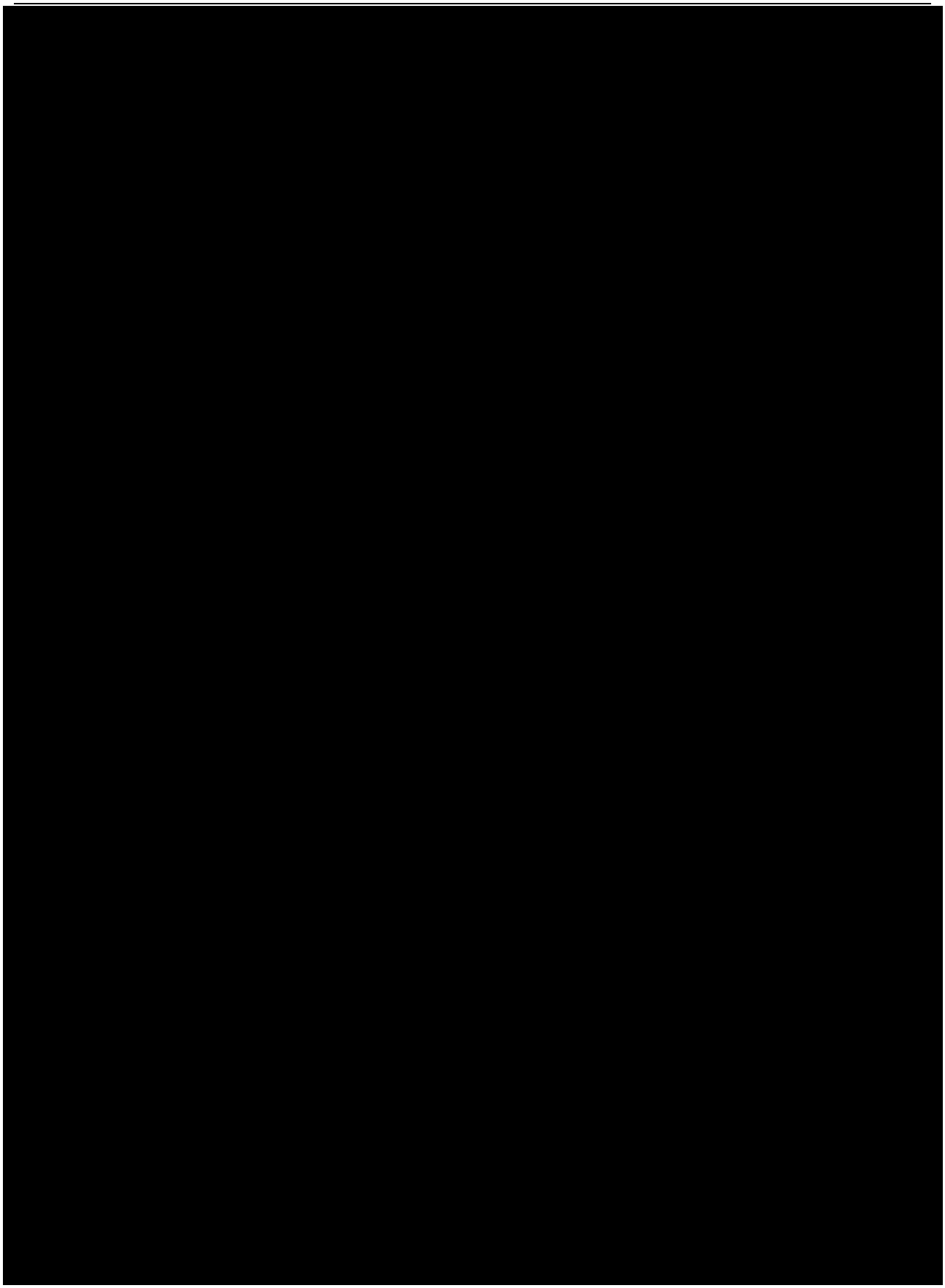
The biopsies will be collected according to clinical site standard operating procedures (SOPs).

[redacted]

[redacted]

8.3.12.2. Correlative Studies with Blood Draws

The timing of sample collection for the following assessments is presented in Table 4.



[redacted]

8.3.12.2.5. Immunogenicity of ALKS 4230

Patients will be monitored for the presence and development of auto-antibodies to ALKS 4230. Serial serum samples will be assessed from baseline, at Day 1 of each cycle, and 14 days after the last treatment.

All patients who met eligibility criteria, had analyzable specimens, and received at least 1 dose of ALKS 4230 will be included in the immunogenicity analyses. Subset analysis will prospectively be analyzed for all patients completing each complete cycle of ALKS 4230. Immune testing will follow a similar scheme with each cycle of ALKS 4230. Serum samples for evaluation of anti-ALKS 4230 antibody induction will be obtained from each patient at predetermined time points. [redacted] Remaining serum samples will be stored for potential analysis of anti-pembrolizumab antibody induction at a future date.

NOTE: Blood collection for all immunogenicity samples required must be drawn before the patient receives the ALKS 4230 on any scheduled day (see Table 16 for specific laboratory tests).

[redacted]

8.3.13. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be dispensed/administered at the time point(s) specified in Table 4.

8.3.13.1. Collection of Specimens

[redacted]

Patients will undergo pretreatment and post-treatment biopsies as part of this protocol. These biopsies will serve as specimens for tumor PD-L1 expression and multi-parameter IHC; [redacted]

8.3.13.2. Handling and Shipping of Specimens

Whole blood samples will be shipped ambient to the CIML for next-day delivery at the same day as the blood draw, so that the sample is received at the CIML within 24 hours of blood draw. [redacted] Specific instructions will be detailed in the Laboratory Manual.

Additionally, [redacted], whole blood will be processed to PBMC [redacted] at the CIML and stored in liquid nitrogen.

For [redacted], plasma and serum samples, respectively, will be collected at room temperature and taken to the local laboratory for processing. Plasma will be obtained and frozen at -80°C at the local laboratory. Samples will be shipped in batches to the CIML and distributed to assay site(s).

Plasma and serum cryovials will be batch shipped at regular intervals to the CIML on dry ice for next-day delivery. The frequency of batch shipments will be determined by the CIML in communication with each site. [redacted] Specific instructions will be detailed in the Laboratory Manual.

Plasma and serum will be stored at -80°C at the CIML until analysis. The CIML will coordinate shipments of plasma and serum to the agreed upon vendor or assay site(s).

For PD-L1 expression and IHC; [redacted] the tissue will be placed in formalin and shipped overnight at ambient temperature to the CIML. [redacted]

[redacted] Specific instruction will be detailed in the Laboratory Manual.

The CIML or designate will prepare FFPE blocks and then prepare slides.

[redacted]

8.3.14. Randomization

This is an open-label study. Randomization is not applicable.

8.3.15. Adverse Event Monitoring

Adverse events will be monitored continuously from the time a patient signs the informed consent document until the completion of the Safety Follow-up Visit or final disease assessment visit during the post-treatment follow-up (Table 4). Adverse events and serious adverse events (SAEs) are defined in Sections 12.1 and 12.2, respectively. Section 9.5.2 provides stopping criteria, and Section 12.4 provides guidance on the monitoring and recording requirements for AEs. Section 12.5 provides guidance on the reporting requirements for SAEs.

8.4. Study Requirements and Restrictions

8.4.1. Contraception and Pregnancy

All male and female patients must agree to use an acceptable method of contraception for the duration of the study and 120 days after the final dose of study drug unless they are surgically sterile or postmenopausal (see below). The following are considered acceptable methods of contraception:

1. Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
2. Intrauterine device (IUD)
3. Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, and contraceptive implant); oral contraceptives should have been initiated at least 30 days prior to Screening

Patients who are abstinent are eligible, provided this is the usual lifestyle and preferred contraception for the patient, and they agree to use an acceptable contraceptive method should they become sexually active.

Patients who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone vasectomy are considered surgically sterile. Partner vasectomy is not considered an approved acceptable method of contraception for a female patient.

Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women who are 45 years of age or older or menopausal levels of follicle-stimulating hormone in the absence of hormone replacement therapy for women less than 45 years of age.

If a patient becomes pregnant while participating in the study, she will be discontinued from study drug immediately. The EOT and Safety Follow-up Visits will be scheduled, and the pregnancy will be reported to Alkermes. Additional follow-up may be required. Pregnancies in female partners of male patients should also be reported following permission from the partner and will be followed in the same manner.

A Pregnancy Report Form must be submitted to Alkermes (per Section 12.5) immediately, 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 a SAE, it should be reported following the SAE procedure (see Section 12.5).

8.4.2. Prohibited Medications and Supportive Care

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 7.2) are not allowed during the ongoing study. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The Investigator should discuss any questions about this with the ION and Alkermes study teams. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. If a necessary supportive therapy or medication is a prohibited concomitant medication, as described in this section, then the patient may continue in the study, coupled with appropriate monitoring by the Investigator and upon review and written permission by the ION and Alkermes Medical Monitors.

Live vaccines are not recommended while on study. If the patient has been on a stable dose of denosumab for at least 3 months, it is acceptable to continue denosumab or switch to zoledronic acid (Zometa®), if possible. Study teams should verify with the local pharmacy that any concomitant medications given do not interact with the ALKS 4230 and pembrolizumab agents.

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.

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- 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 C1D1 of ALKS 4230), or monoclonal antibody therapy.

- Prophylactic hematopoietic growth factors. Continued administration of erythropoietin may be allowed upon agreement with the ION and Alkermes Medical Monitors.
- Pharmacologic doses of glucocorticoids (≥10 mg of prednisone daily, or equivalent). Replacement doses, topical, ophthalmological, and inhalational corticosteroids are permitted. Use of glucocorticoids for the purpose of treating immune-mediated AEs is permitted but may result in discontinuation from study based on consultation between the Investigator and the ION and Alkermes Medical Monitors. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Antineoplastic systemic chemotherapy or biological therapy.
- Chemotherapy not specified in this protocol.
- Investigational devices or agents other than pembrolizumab and ALKS 4230.
- Any radiotherapy, including systemically administered radioisotopes.

NOTE: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.

- Live vaccines within 30 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), intranasal influenza (FluMist®) and typhoid vaccine.

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 [NSAIDs] and/or 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 patient.

Medroxyprogesterone or megestrol acetate may be given to patients without breast cancer as an appetite stimulant, and bisphosphonates or denosumab may be administered to patients with bone metastases if started at least 90 days before study entry.

Additionally, patients may be treated with a histamine type 2 receptor antagonist, acetaminophen, meperidine, diphenhydramine, and/or other agents per the Investigator's discretion.

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

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients may receive other medications that the Investigator deems to be medically necessary.

The exclusion criteria describe other medications that are prohibited in this study (Section 7.2).

There are no prohibited therapies during the post-treatment follow-up phase.

See Section 8.3.4 for details regarding the prior and concomitant medication review.

9. TREATMENT OF PATIENTS

9.1. Study Drug Dose and Administration

9.1.1. ALKS 4230

A patient is considered enrolled after he or she has completed all screening assessments and provided a pretreatment biopsy. Study drug should begin as close as possible to the date of enrollment, but no later than 72 hours afterward. On days when pembrolizumab and ALKS 4230 are both administered, pembrolizumab will be administered first.

ALKS 4230 will be administered IV as a 30-minute infusion 3 µg/kg daily 5 consecutive days on Days 1 through 5 of the first week of each 3-week treatment cycle.

Infusion for each dosing day of each cycle should begin within ±2 hours of the infusion start time for Day 1 of that cycle. [redacted]

Premedication with an antipyretic agent (NSAIDs and/or acetaminophen) is required at least 15 minutes prior to infusion with ALKS 4230 as described in Section 8.4.2. Emergency resuscitation equipment should be available. For the first 3 to 6 patients in this study, the first 2 treatment cycles of ALKS 4230 will be administered in a medical facility with access to medical support measures and to an intensive care unit, if needed.

[redacted]

Amount of drug administered is based on patients' body weight as measured at Day 1 of each cycle.

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

Preparation details and procedures are provided in the Pharmacy Manual.

9.1.2. Pembrolizumab

Pembrolizumab should be administered on Day 1 of each cycle at a dose of 200 mg. Patients will receive 1 dose of pembrolizumab Q3W on an outpatient basis. Patients will receive up to 1 year of pembrolizumab (17 cycles or 1 year of treatment, whichever occurs later) calculated from the date of first dose. There will be no option for retreatment with pembrolizumab alone following the completion of combination regimen (a maximum of 17 cycles).

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion Q3W. 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 of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 minutes/+10 minutes).

Preparation details and procedures are provided in the Pharmacy Manual.

9.2. Treatment Adherence

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 supply and administration records during the study and/or at the end of the study.

9.3. Randomization/Method of Assigning Patients to Treatment

Not applicable. There is no randomization in this study.

9.4. Blinding

Not applicable. The study is open-label.

9.5. Study Drug Dose Delays, Interruptions, and Stopping Rules

9.5.1. Dose Delays

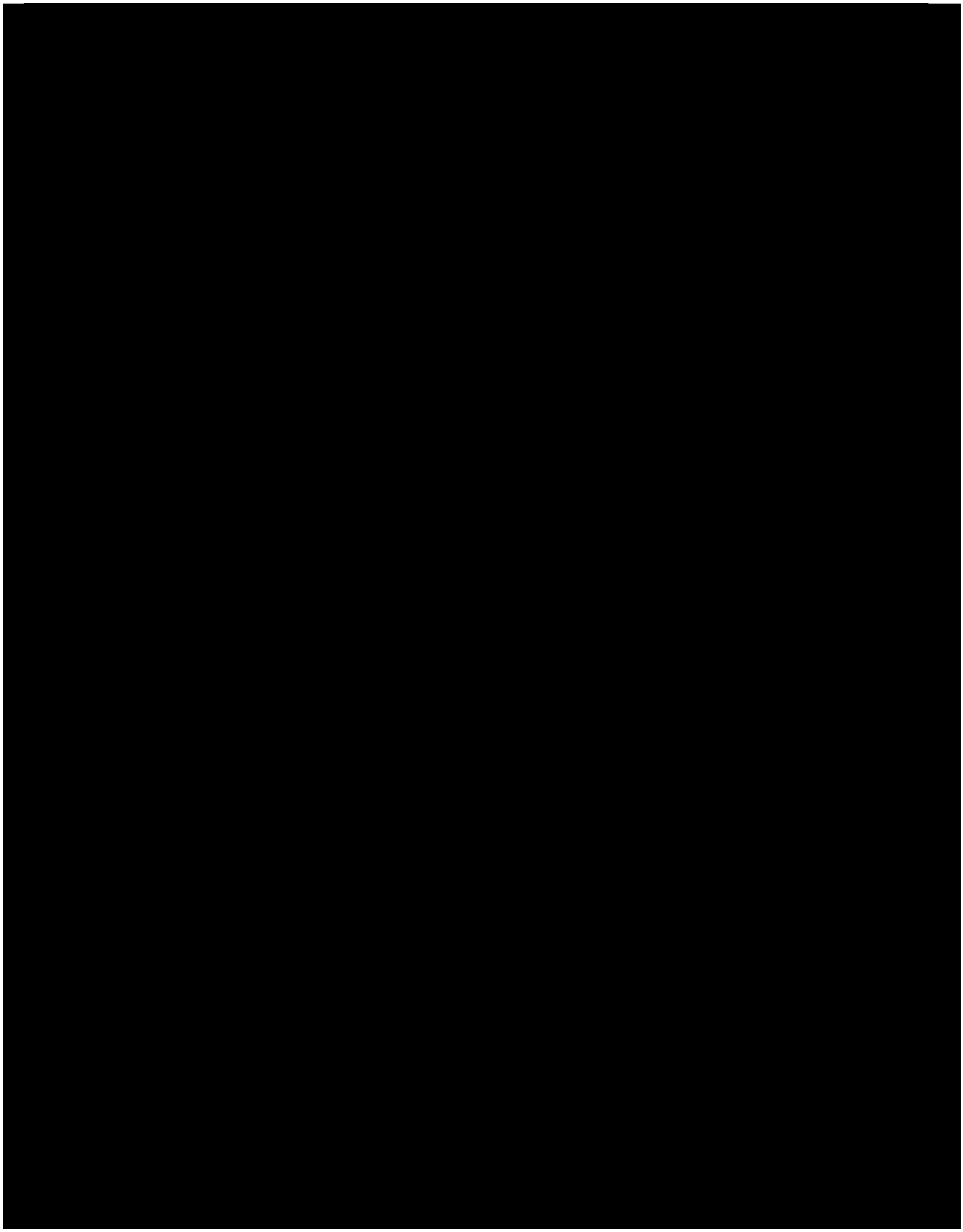
[redacted]

In consideration of the prescribing information for pembrolizumab (Keytruda USPI), follow the label accordingly for pembrolizumab dose adjustments and stopping rules.

9.5.2. Dose Interruptions and Stopping Rules

In consideration of the prescribing information for pembrolizumab (Keytruda USPI), follow the label accordingly for pembrolizumab dose adjustments and stopping rules. If a patient permanently discontinues study therapy, the patient should be discontinued from the study; however, every effort should be made to continue monitoring the patient's disease status by radiologic imaging per local standard of care (Section 8.2).

[redacted]



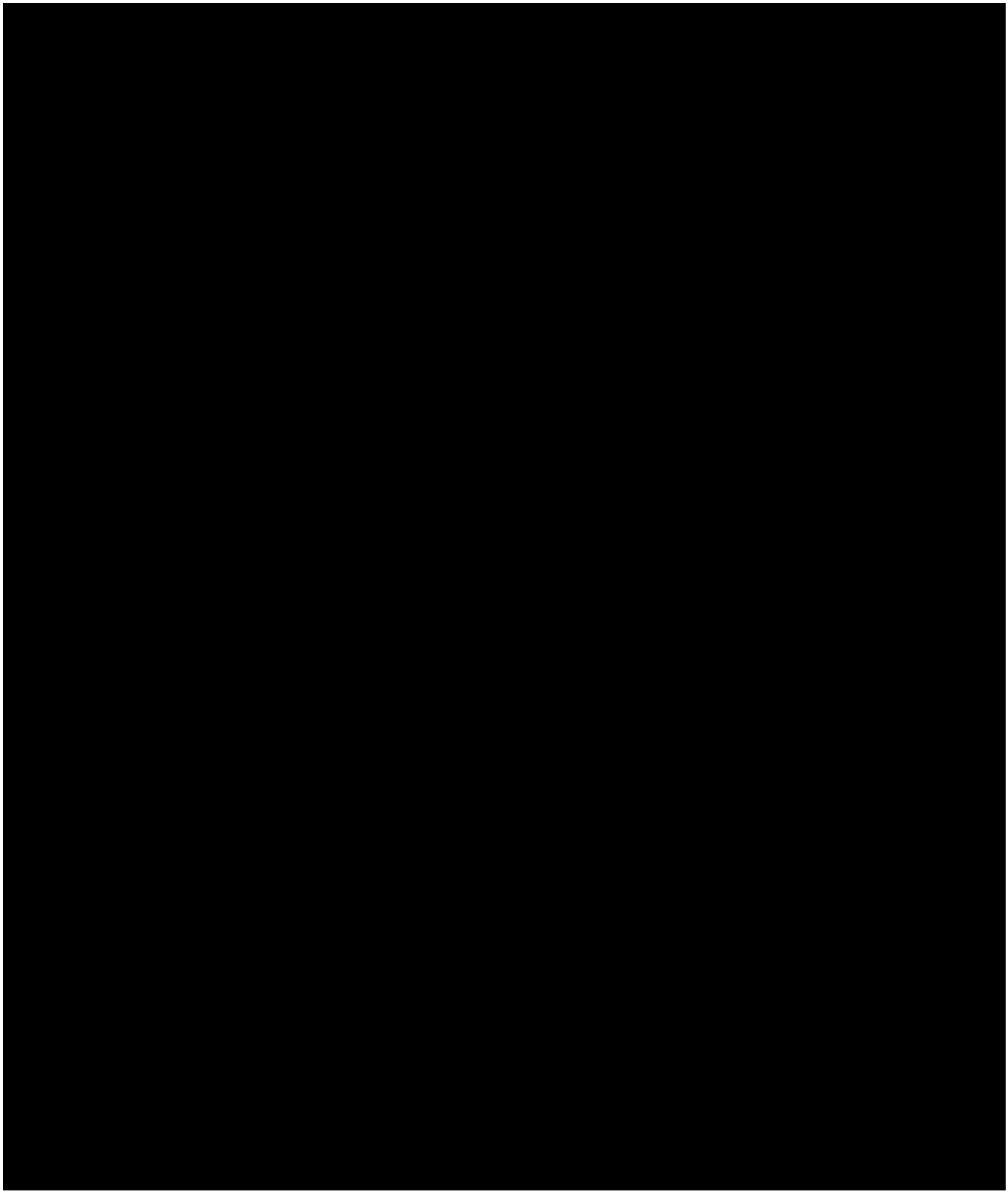
[redacted]

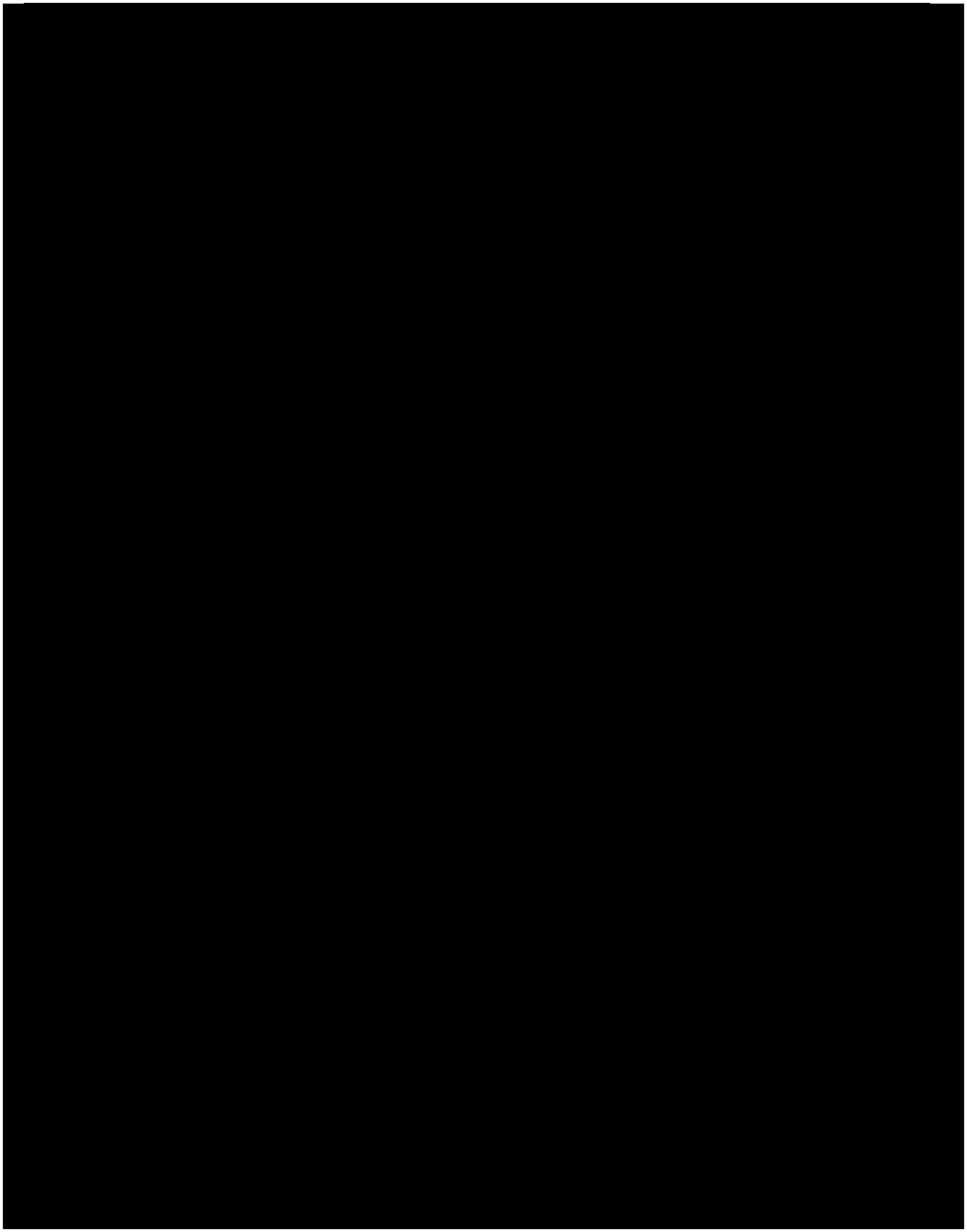
9.5.3. Dose Modifications

[redacted]

Dose reductions of pembrolizumab are not permitted on study. Refer to Section 9.5.1 for guidelines on dose delays.

The decision to continue pembrolizumab or to remove the patient from protocol therapy will be made at the discretion of the Investigator and/or the Sponsor and the SRC.





9.5.4.2. Events Considered Related to Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs. Refer to the Keytruda USPI for dose management of toxicities related to pembrolizumab.

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

10. STUDY DRUG MATERIALS AND MANAGEMENT

All patients will receive ALKS 4230 and pembrolizumab.

[redacted] Pembrolizumab will be externally sourced.

10.1. Study Drug

10.1.1. ALKS 4230

[redacted]

10.1.2. Pembrolizumab

[redacted]

10.2. Packaging and Labeling

This study is open-label; therefore, the patient, the study site personnel, the Sponsor, Alkermes, and other study vendors are not blinded to treatment. Drug identity (name, strength) is included in the label text. Random code/disclosure envelopes or lists are not provided.

10.2.1. ALKS 4230

[redacted]

10.2.2. Pembrolizumab

[redacted]

[redacted]

10.3. Storage

10.3.1. ALKS 4230

[redacted]The Directions for Use will be distributed to the study sites and will provide in-use storage conditions and duration of time within which it should be used.

10.3.2. Pembrolizumab

[redacted]

10.4. Accountability

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

Refer to Section 9 for additional study drug reconciliation procedures.

10.5. Handling and Disposal

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

Following completion and verification of accountability logs, all unused and used vials must be destroyed. Vials may be destroyed on site according to Good Clinical Practice (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 (GMP), as applicable.

Details on ALKS 4230 and pembrolizumab ordering and return/destruction may be found in the Pharmacy Manual.

11. ASSESSMENT OF EFFICACY

11.1. 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). 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 drug.

[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

11.2. 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

11.3. Exploratory Efficacy 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]

[redacted]

12. ASSESSMENT OF SAFETY

Safety will be assessed on the basis of:

- Adverse events
- Physical examination and ECG findings
- Vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature)
- Clinical laboratory parameters (ie, CBC with differential, complete serum chemistry, and urinalysis)

12.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient who has been 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 patient and is considered clinically significant.

Illnesses present prior to the patient signing the informed consent form (ICF) are considered to be preexisting conditions and are documented on the medical history eCRF. Preexisting conditions that worsen during the study are entered on the AE eCRF.

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 will be recorded as such on the eCRFs.

Progressive disease is not considered an AE. Death due to PD is not considered an SAE (see Section 12.5.1). Disease progression and outcome, as assessed by the Investigator, will be recorded on the eCRF.

Pregnancy is not considered an AE, although a patient will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.1, the pregnancy, including a partner's pregnancy, must be reported to Alkermes in an expedited manner similar to an SAE (Section 12.5), and additional follow-up may be required.

12.1.1. Events of Clinical Interest

Selected nonserious and serious adverse events are also known as events of clinical interest (ECI) and must be reported within 24 hours to the ION Coordinating Center/Alkermes within 2 working days.

For the time period beginning when the consent form is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, that occurs to any patient, whether or not related to pembrolizumab or ALKS 4230, must be reported within 24 hours to the ION Coordinating Center/Alkermes within 2 working days.

The ECIs for this study include:

- 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, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

NOTE: These criteria are based upon available regulatory guidance documents. The purpose of these criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

12.2. Definition of Serious Adverse Events

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

- Results in death
- Is life-threatening. The patient 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 or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Death secondary to PD is **not** considered an SAE. Disease progression and outcome, as assessed by the Investigator, will be recorded on the eCRF.

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, may jeopardize the patient or patient 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 captured as an AE.

12.3. Relationship to Study Drug

The assessment of the relationship of study drug 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 sub-Investigator) according to his or her best clinical judgment. The criteria listed in Table 13 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.

Table 13: Adverse Event Causality Guidelines

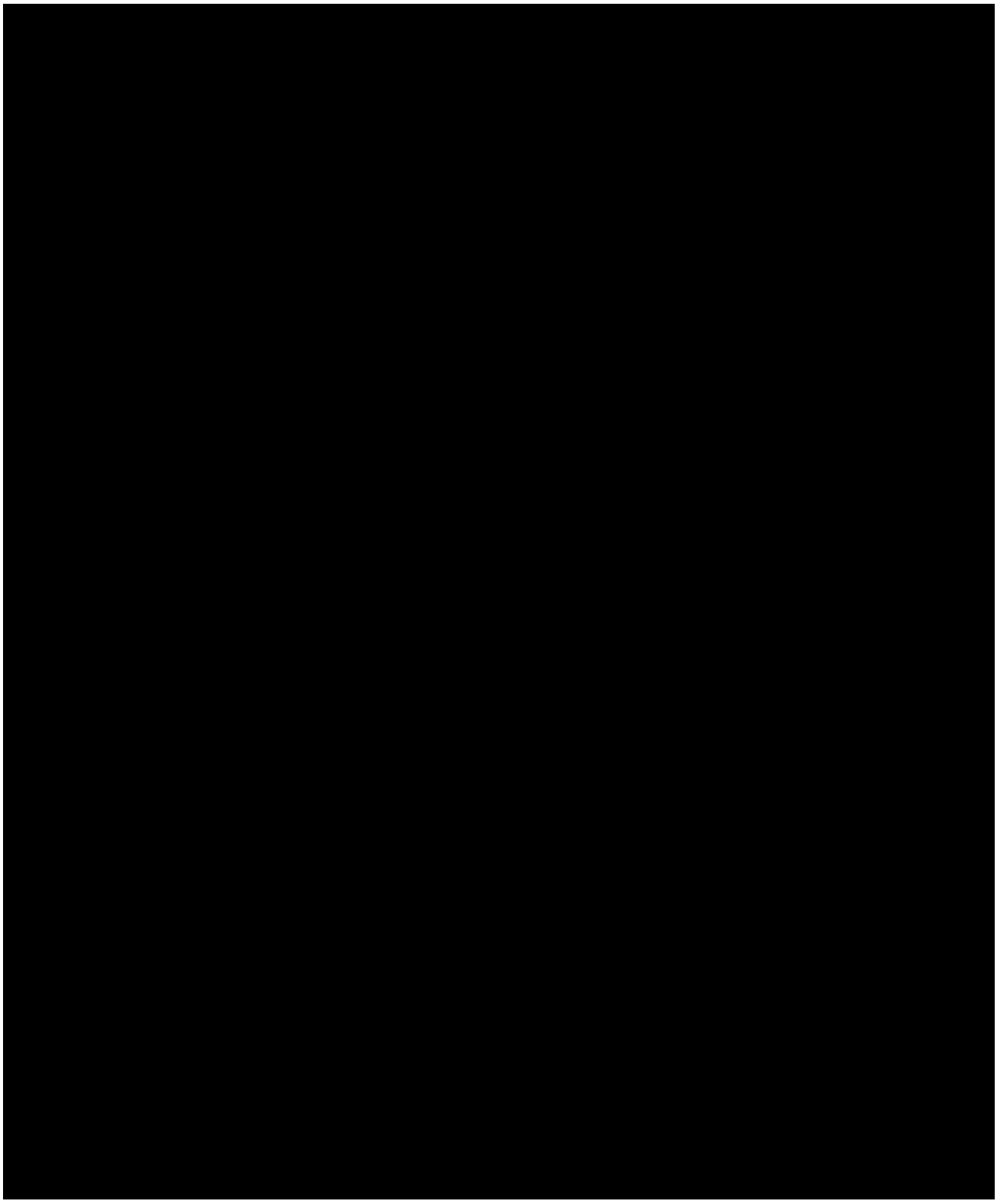
Relationship	Criteria for assessment
Definitely related	There is evidence of exposure to the test drug AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) 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 patient 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

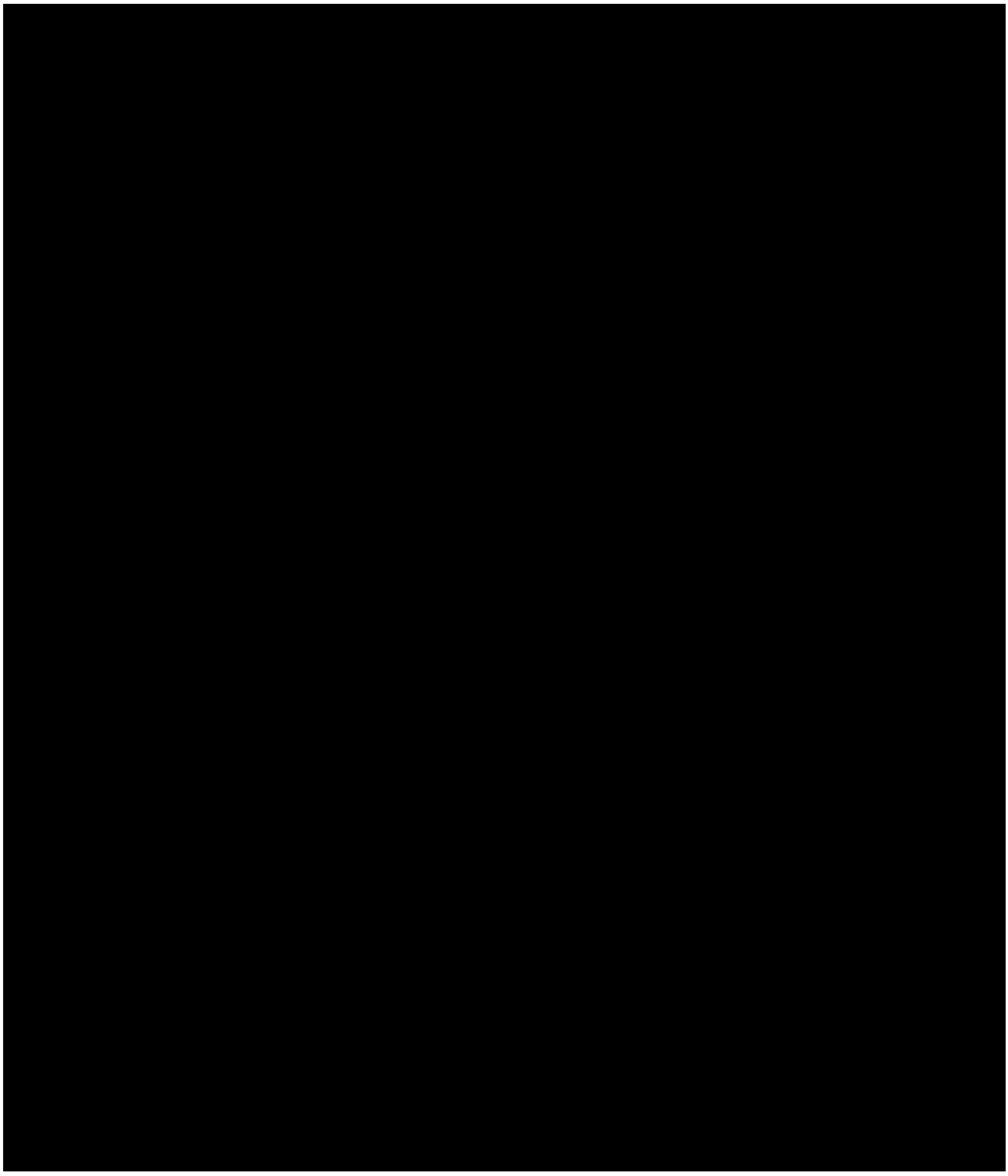
Abbreviation: AE=adverse event.

12.3.1. Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other

supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or discontinue the ALKS 4230 + pembrolizumab combination regimen and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 14.

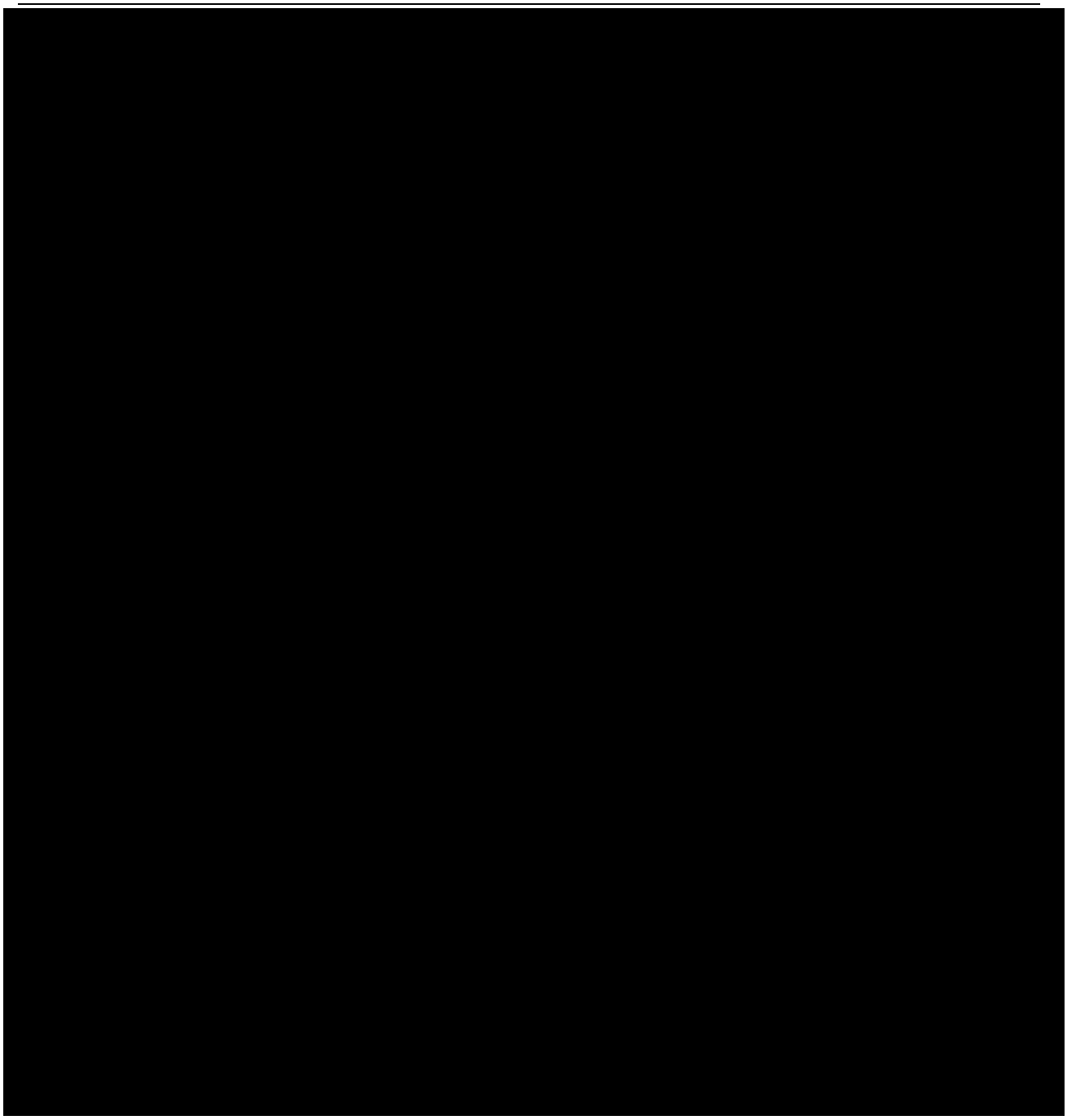




12.3.2. Toxicity Management for Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 15.

On days when patients are given combination treatment, institutions should follow the most conservative therapy intervention/premedication protocol guidelines.



12.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a patient signs the ICF and will continue until completion of the Safety Follow-up Visit for the main part of the study. Long-term collection of AE data is described in Table 5. Any AE or SAE having an onset after the Safety Follow-up Visit will not be collected or reported unless the Investigator feels that the event may be related to the study drug.

The Week 3 AE review can be captured via telephone; no visit is required.

Patients 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(s) (see Section 12.3), the intensity (severity) of the event, action taken, and patient outcome. For AEs not clearly related to either ALKS 4230 or pembrolizumab individually, the most conservative approach to treating the event should be used.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

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

Immune-mediated AEs will be documented as such using the immune-mediated AE eCRF.

For clinical study safety reporting purposes, the most recent version of the ALKS 4230 IB and the Keytruda USPI will be used as the reference document to designate event expectedness.

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 patient withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

12.5. Reporting of Serious Adverse Events and Pregnancy

All SAEs and Pregnancies must be reported to Syneos Drug Safety immediately, within 24 hours of discovery, by emailing or faxing the report to the following:

Attention: Syneos Drug Safety

FAX Number: +1 (877) 464-7787

Phone Number: +1 (877) 462-0134

Email: incdrugsafety@incresearch.com

Attention: Drug Safety and Pharmacovigilance

FAX Number: +1 (617) 494-5202

The written report for SAEs should be submitted on the SAE form provided for this purpose. The SAE 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.

The written report for pregnancies in female patients and in female partners of male patients should be submitted on the Pregnancy Report Form provided for this purpose.

12.5.1. Protocol-specific Exemptions to Serious Adverse Event Reporting

Any event that indicates disease progression will not be reported to Alkermes as described in this section, including death secondary to disease progression, unless there is evidence suggesting a causal relationship between the drug and the event. If there is such a causal relationship, then the event will be submitted to the ION Coordinating Center/Alkermes within 24 hours.

The ION Coordinating Center/Alkermes will monitor aggregated efficacy endpoint events and safety data to ensure the safety of the patients in the study. Any serious suspected events that, upon review, are not determined to be progression of the cancer under study will be forwarded to the ION Coordinating Center/Alkermes within 24 hours.

12.5.2. Reporting of Pregnancy Events

Although pregnancy and lactation are not considered AEs under this protocol, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study.

Pregnancies and lactations that occur from the time the patient is enrolled (including pregnancies in the female partners of male patients) through 120 days following cessation of study product, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies must be followed to the completion or termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the ION Coordinating Center or Alkermes.

13. STATISTICS

13.1. Sample Size Considerations

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). Among the subset of patients achieving a response, the median time to objective improvement was 2 months (range, 2 to 17 months). [redacted]

13.2. 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 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.

13.2.1. Study Populations

13.2.1.1. Efficacy Evaluable Population

All patients who received at least 1 dose of both study drugs will be included in the analysis of efficacy, regardless of the duration of treatment. The Efficacy Evaluable populations will be characterized by groups (Group 1 and Group 2) and overall for analysis of all efficacy endpoints.

13.2.1.2. Safety Population

The Safety population, 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 treatment arm and overall.

13.3. Demographics and Baseline Data

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

Demographics and baseline characteristics such as gender, age, race, weight, vital signs, and clinical laboratory data will be summarized with descriptive statistics.

13.4. Efficacy Analyses

Response to treatment will be evaluated using both RECIST v1.1 and immune-related response criteria (irRC). For patients with objectively measurable disease, response to therapy, DOR, PFS, and OS will be calculated.

13.4.1. Primary Efficacy Endpoints Analysis

Primary efficacy analysis will be evaluated in patients in the Efficacy Evaluable population for each group separately and overall. The objective improvement rate (as defined in Section 11.1) 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. The analysis of objective response rate using an exact binomial test will also be conducted separately for each group.

The 95% CI on the objective improvement rate will be reported. Similar approaches will also be applied to the overall population.

13.4.2. Secondary Efficacy Analysis

Secondary efficacy analysis will be evaluated on the Efficacy Evaluable patients.

DOR and TTP will be calculated and summarized by group and overall. Patients with missing response data will be considered non-responders and excluded from the DOR analysis. PFS and OS curves will be plotted by group and overall using the Kaplan-Meier approach. The median survival time (if applicable) and its 95% CI for PFS and OS will be reported. The PFS and OS rate at 6 and 12 months will be estimated using the Kaplan-Meier approach.

The objective response rate will be summarized for each of the 4 cohorts.

The percentage change from baseline in target lesions will be summarized by group and overall.

13.5. Safety and Tolerability Analyses

Safety will be evaluated based on the occurrence of AEs, vital signs, results of clinical laboratory tests, and ECG findings. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 21 preferred terms and system organ classes.

Treatment-emergent AEs (TEAEs) are defined as any AE that begins on or after the first administration of the study drug. Adverse event severity will be graded according to the CTCAE v5.0 and terms recorded on the CRFs will be mapped to preferred terms using the most recent version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

All AEs will be listed. The incidence of TEAEs will be summarized for each group and overall, by severity, and by relationship to study drug as assessed by the Investigator. The summary tables will include the number and percentage of patients with TEAEs overall, by system organ class, and by preferred terms within each system organ class. Similar tables will be prepared for SAEs, TEAEs leading to discontinuation, as well as additional categories of AEs as defined in the SAP.

Results of clinical laboratory tests will be summarized by visit for the absolute value and for change from baseline. Tables showing the shift from baseline will also be presented.

ECG findings will be listed.

Concomitant medications will be categorized and presented using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) drug classification system.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

14.2. 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, or an institutional review board (IRB)/independent ethics committee (IEC) may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, patient 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 study-related activities and documents (eg, laboratory reports, X-rays, workbooks, patients' medical records) to determine whether these activities were conducted, and data recorded, analyzed and accurately reported, according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements.

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

14.3. Institutional Review Board/Independent Ethics Committee

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

15. 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 site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 14.2 for details regarding the audit process.

15.1. 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 prior to review by the Alkermes Monitor or designated representative.

The Alkermes Monitor or designated representative will review all source records on-site and compare them to the data collected on the eCRF.

15.2. 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 or IEC under an appropriate understanding of confidentiality with such board. Please refer to the Clinical Study Agreement (CSA) for details.

16. ETHICAL CONSIDERATIONS

16.1. Ethics Review

The clinical site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB/IEC prior to enrolling patients into the study; written approval from the committee must be received by Alkermes before study drug will be released to the Investigator. The protocol must be reapproved by the IRB/IEC 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/IEC 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/IEC will be forwarded by the respective study site to the Sponsor in a timely fashion.

16.2. 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. Good Clinical Practice is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human patients. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study patients will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

16.3. Written Informed Consent

The Investigator (or authorized designee) at each center will ensure that the patient (or the patient's legal representative) is given full and adequate oral and written information about the nature, purpose, and potential risks and benefits of the study. Each prospective patient 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 patient and must not include any language that waives the patient's legal rights. Prospective patients must also be informed of their right to withdraw consent without prejudice at any time during the study. If the patient chooses to participate, he or she must sign the ICF before any study-specific procedures are conducted.

All patients will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, ION, the IRB, the contract research organization (CRO), 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 patient's source documents. A copy of the signed ICF must be given to the patient.

17. DATA HANDLING AND RECORDKEEPING

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

17.1. Data Capture

As stated in Section 15.1, 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 (EDC) system maintains a full audit trail.

A copy of all laboratory reports will remain with the source documents at the study site. All electronic source data collected outside of the eCRF, such as e-diaries or centrally reviewed patient data will be transferred directly to the EDC or to Alkermes for incorporation into the final datasets. 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 will be recorded as such on the eCRFs.

Adverse events will be coded using MedDRA version 21. Concomitant medications will be categorized using the WHO-ATC drug classification system.

17.2. 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, patient charts or electronic medical records and source documents, and other records relative to study conduct.

17.3. Retention of Records

Retention and storage of all essential clinical study documents 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.

Patients' 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.

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