A Phase 1/2 Study of ALKS 4230 Administered Subcutaneously as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors - ARTISTRY-2 (001)

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Primary Objectives:• To characterize the safety and tolerability and to identify the recommended Phase 2 dose (RP2D) of ALKS 4230 administered subcutaneously (SC) as lead-in monotherapy and in combination with pembrolizumab in subjects with advanced...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55159

Source
ToetsingOnline

Brief title
A phase 1/2 Study of ALKS 4230 in Subjects with Solid Tumors.

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors

Health condition

Advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Alkermes, Inc.
Source(s) of monetary or material Support: Alkermes;Inc.

Intervention

Keyword: ALKS 4320, ARTISTRY-2, Pembrolizumab

Outcome measures

Primary outcome

Primary Endpoints:

• The incidence and severity of treatment-emergent adverse events (AEs) (Phase

1 and Phase 2)

• ORR based on RECIST 1.1 (Phase 2)

Secondary outcome

Secondary Endpoints:

-The incidence of DLTs from the beginning of first dose of investigational

agent(s) through the end of the DLT observation period (Phase 1)

-Serum concentrations of ALKS 4230 and descriptive PK parameters (Phase 1 and

Phase 2)

-Presence of anti-ALKS 4230 antibodies in serum (Phase 1 and Phase 2)

-Numbers of circulating cluster of differentiation (CD)8+ T cells, T regulatory

cells (Tregs), and natural killer cells in peripheral blood

(Phase 1 and Phase 2)

-Serum concentrations of interleukin-6 and other cytokines (Phase 1 and Phase 2)

-ORR, Disease Control Rate (DCR), Duration of Response (DOR), Time to Response

(TTR), and Progression Free Survival (PFS) per RECIST 1.1

(Phase 1)

-Immune ORR (iORR), immune DCR (iDCR), immune DOR (iDOR), immune TTR (iTTR),

and immune PFS (iPFS) per immune RECIST

(iRECIST) (Phase 1)

-DCR, DOR, TTR, and PFS, per RECIST 1.1 (Phase 2)

-iORR, iDCR, iDOR, iTTR, and iPFS, per iRECIST (Phase 2)

-Overall survival (OS) (Phase 2)

Exploratory endpoints may include the following:

• Density of tumor-infiltrating lymphocytes (TILs) in the tumor

microenvironment (TME)

• Ratio of cytotoxic TILs and immunosuppressive TILs in TME

• Density of signals of immune-cell-mediated killing in TME

• Gene expression signatures of TME

• Mutational status of tumors

• Mutational burden of tumors

• Select cytokine profiles in blood

Study description

Background summary

ALKS 4230 is an investigational drug, a new immunotherapeutic protein being developed by the Sponsor for the treatment of patients with metastatic solid malignancies. It is believed that this protein has the potential for antitumor effects against a wide range of cancer types alone and in combination with other anticancer agents.

Study objective

Primary Objectives:
• To characterize the safety and tolerability and to identify the recommended Phase 2 dose (RP2D) of ALKS 4230 administered subcutaneously (SC) as lead-in monotherapy and in combination with pembrolizumab in subjects with advanced solid tumors (Phase 1)
• To characterize the safety profile of SC ALKS 4230 at the RP2D in combination with pembrolizumab in subjects with advanced solid tumors (Phase 2)
• To estimate the clinical activity of combination treatment with ALKS 4230 and pembrolizumab in terms of overall response rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 (Eisenhauer et al, 2009) separately for:
* Non-small-cell lung cancer (NSCLC)
* Squamous cell carcinoma of the head and neck (SCCHN)
* GEJ cancer
* Ovarian cancer (Phase 2)

Secondary Objectives:
• To describe dose-limiting toxicity (DLT) of SC ALKS 4230 as lead-in monotherapy (Phase 1)
• To characterize the pharmacokinetics (PK), clinical pharmacodynamics (PD), and immunogenicity of SC ALKS 4230 as lead-in monotherapy (Phase 1) and in combination with pembrolizumab (Phase 1 and Phase 2)
• To describe antitumor activity observed with SC ALKS 4230 as lead-in monotherapy and in combination with pembrolizumab (Phase 1)
• To evaluate antitumor efficacy in subjects treated with SC ALKS 4230 in combination with pembrolizumab (Phase 2)

Exploratory Objectives:
• To identify properties of pretreatment subject blood and/or tumor tissue samples that may predict response or non-response to ALKS 4230 and pembrolizumab combination treatment
• To identify changes in post-treatment subject blood and/or tumor tissue

samples compared to the baseline/pretreatment samples that may predict response or non-response to the ALKS 4230 and pembrolizumab combination treatment
• To assess any correlation between the pretreatment gut microbiome and efficacy

Study design

This is a Phase 1/2 study. The study will be conducted in two phases: Phase 1 is a dose-escalation phase with multiple ascending doses of SC ALKS 4230 as lead-in monotherapy followed by combination with pembrolizumab. Phase 2 is a dose-expansion phase with SC ALKS 4230 administered at the RP2D (determined from Phase 1 based on interpretation of PK, PD, preliminary antitumor activity, and safety data) in combination with pembrolizumab. Phase 2 will enroll subjects into cohorts based on each subject*s specific tumor type and/or tumor histology.

Dose Expansion (Phase 2)
In Phase 2, following a 21-day screening window, subjects with the following tumor types and/or specific
histology will be enrolled into the following cohorts:
• NSCLC
• SCCHN
GEJ cancer
• Ovarian cancer
Subjects will receive treatment with the RP2D and recommended dosing schedule identified in Phase 1 of SC ALKS 4230 in combination with pembrolizumab 200 mg every 3 weeks. Subjects receiving combination treatment with SC ALKS 4230 and pembrolizumab will continue to receive treatment with the study regimen for up to 2 years following intiation of combination treatment, as long as the subject is deriving clinical benefit. Subjects who discontinue one drug (eg, due to unacceptable toxicity that cannot be managed by dose modification) must discontinue the entire study treatment.

Intervention

ALKS 4230 drug product is supplied in three concentrations: 1 mg/mL, 5 mg/mL, and 15 mg/mL. Each concentration is supplied as a single-dose vial. Reconstituted ALKS 4230 is administered by SC injection q7d or q21d. Injection-site locations will include the back of the arm, the thigh, or the abdomen. Anatomic injection sites should be rotated as feasible, based on individual subject consideration consistent with ALKS 4230 Directions for Use.

Following completion of the SC ALKS 4230 monotherapy lead-in period in Phase 1, if the subject has tolerated therapy, pembrolizumab will be added. Pembrolizumab is administered as an intravenous infusion over 30 minutes in a dose of 200 mg every 3 weeks. Pembrolizumab will also be administered with SC

ALKS 4230 in Phase 2. Pembrolizumab will be obtained from the Sponsor through central sourcing.

On Day 1 of the monotherapy lead-in period, an observation period of 8 hours following the SC ALKS 4230 injection will be required. Subjects may be observed for less time during subsequent injections.

During combination therapy in both Phase 1 and Phase 2, SC ALKS 4230 will be administered prior to pembrolizumab. Subjects will be observed for 60 to 90 minutes following administration of SC ALKS 4230 prior to pembrolizumab administration.

Study burden and risks

Participation in this study will last about one year. The study contains a screening phase, treatment phase, end of trial and follow-up phase. This study requires patient to visit the hospital about 35 times over a period of approximately 1 year. A visit with all assessments will take will take 8 to 2 hours for shorter visits. depending on when the visit is done.

To participate in this study, patients will have to undergo several examinations, tests and/or procedures before, during and after their treatment. During the study, patients may have discomforts and risks from taking the study medication and from the study procedures.
This may vary from person to person. Everyone taking part in the study will be watched carefully for side effects.
There may be other risks that are unknown and that we cannot predict. These may be mild or serious, and in some cases may be very serious, long-lasting, or may never go away. There is also a risk of death. The study doctor can give the patients medicines to help them reduce any negative affects they may experience.

The most commonly reported side effects of ALKS 4230 are: reduced lymphocytes, injection site reactions (including redness, itching, and pain),fever, chills, fatigue, nausea, tumor pain and disorders affecting blood vessels.

During the study blood will be drawn. Drawing blood may be painful or cause some bruising. No more than 90 ml will be taken during one cycle. This amount does not cause any problems in adults.

No studies of ALKS 4230 have been conducted in pregnant women. Pregnant or nursing female patients will be excluded from the clinical study. Patients enrolled in the study, and their spouses/partners, must use a highly effective method of contraception. In the event of a pregnancy, the patient will be discontinued from study drug.
Please refer to the IB and patient information regarding side effects that are expected and for other risks and discomforts.

The patient solid tumor may or may not improve while participating in this study. Patient participations in this study could provide important medical information about ALKS 4230 or ALKS 4230 given in combination with pembrolizumab. This information may help future subjects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is aged >=18 years.
2. Subject or the subject*s legal representative provides written informed consent.
3. For Phase 1, subject must have an advanced solid tumor and progressive disease following at least one line of therapy.
4. For Phase 2, subject must have one of the following tumor types or specific

histology:
• SCCHN cohort: subjects with regionally advanced and/or distantly metastatic head and neck squamous cell carcinoma of non-cutaneous origin that has relapsed or failed to achieve complete response after at least one line of systemic therapy given alone or in combination with surgery and /or radiation therapy, and that has failed to achieve complete response or relapsed after (or subject has become intolerant to) CPI (given alone or in combination with other agents), and that is presently considered inoperable and unamenable to (re-) irradiation.
• Gastric/GEJ cohort: subjects with unresectable metastatic or locally advanced gastric
or GEJ adenocarcinoma who have not been previously treated with immune CPIs (anti-PD-1, anti-PD-L1, anti-CTLA-4) and who have progressed on and/or after two prior regimens. Prior regimens had to have included a fluoropyrimidine and a platinum chemotherapy. Progression within 6 months of prior adjuvant or neoadjuvant chemotherapy will be deemed a rapid progressor and thus equivalent to
one advanced/metastatic disease treatment regimen. Changing from IV to oral fluoropyrimidine without noted progression is considered only one prior regimen. Her2 positive patients must have received prior anti-Her2 therapy and demonstrate
progressive disease. PD-L1 status must be known at the time of enrollment based on
an approved test. If PD-L1 status is unknown during Screening, tumor tissue (fresh
biopsy or archived samples) must be tested for PD-L1 expression prior to enrollment. Patients with known MSI-high/dMMR status are not eligible.
• Ovarian cancer cohort: subjects must have recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer. Subject must have experienced a response lasting at least 3 months to first-line platinum-based therapy but must be considered resistant to the last administered platinum containing therapeutic regimen. Subjects must have received prior monoclonal antibody that inhibits angiogenesis (e.g., bevacizumab) either as single agent or in combination or be deemed ineligible or intolerant. Subject with a known BRCA-1 or -2 mutation must have received prior poly ADP ribose polymerase (PARP) inhibitor. Subject must not have received prior checkpoint inhibitor therapy.
5. Subject must have at least one target lesion based on RECIST.
6. Subject has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 and an estimated life expectancy of at least 3 months.
7. Subject has adequate hematologic reserves, measured within 7 days prior to start of study treatment, as evidenced by:
• Absolute neutrophil count of >=1000/µL,
• Absolute lymphocyte count of >=500/µL,
• Platelet count of >=75,000/µL, and
• Hemoglobin of >=9 g/dL (subjects may be transfused to this level if necessary).
8. Subject has adequate hepatic function as evidenced by aspartate transaminase

and alanine aminotransferase values <=3 × the upper limit of normal (ULN) (<=5 × ULN if the liver is known to be involved by metastatic disease) and serum total bilirubin values of <=1.5 × ULN (<=2 × ULN for subjects with known Gilbert*s syndrome) for the reference laboratory measured within 7 days prior to start of study treatment.
9. Subject has adequate renal function as evidenced by a serum creatinine <=1.5 × ULN for the reference laboratory or a calculated creatinine clearance of >=45 mL/min by the Cockcroft-Gault equation measured within 7 days prior to start of study treatment.
10. Subject has recovered from the effects of any prior chemotherapy, immunotherapy, other prior systemic anticancer therapy, radiotherapy, or surgery (ie, toxicity no worse than Grade 1 [any grade alopecia and treatment associated peripheral neuropathy are acceptable]).
11. Subject who has received standard or investigational antineoplastic agents must wait at least 5 half lives or 4 weeks, whichever is shorter, before enrollment into the study or 4 weeks if the half life of the investigational agent is not known. Subjects may be enrolled within 3 weeks of previous treatment upon agreement between Medical Monitor and Principal Investigator.
12. Women of childbearing potential (WOCBP) must have a negative pregnancy test (serum or urine) within.3 days before the first dose of study drug (see the protocol for the definition of WOCBP).
13. Subject agrees to abide by the contraceptive requirements detailed in the protocol.
14. Subject has international normalized ratio (INR) AND/OR prothrombin time (PT) AND activated partial thromboplastin time (aPTT) <=1.5× ULN unless the subject is receiving anticoagulant therapy, in which case INR and/or PT and aPTT must be within desired therapeutic range of intended use for such anticoagulants.
15. Subjects enrolled in the dose expansion part of the study (Phase 2) must agree to provide archival tumor tissue biopsy sample(s) if available.
16. For subjects with underlying chronic lung disease, and/or lung primary or metastatic disease, and/or pleural effusions, room air oxygen saturation must be >=92%.

Exclusion criteria

1. Subject is currently pregnant or breastfeeding or is planning to become pregnant during the study period.
2. Subjects who are investigational site staff members directly involved in the conduct of the trial and their immediate family members, site staff members otherwise supervised by the Investigator, or subjects who are Alkermes or Syneos Health employees directly involved in the conduct of the study (immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted).
3. Subject has an active infection or a fever >=38.5°C (>=101°F) within 3 days of

the first scheduled day of dosing for the monotherapy lead-in of Phase 1 or Cycle 1 of Phase 2.
4. Subjects who have received therapeutic systemic antibiotics within 14 days prior to starting investigational therapy excluded unless specifically exempted on a case-by-case basis by the Medical Monitor. Antibiotics given for peri-procedural prophylaxis or given presumptively for a limited time (e.g., until infection was ruled out), as well as topical or intra-ocular antibiotics, shall not be exclusionary.
5. Subject has known hypersensitivity (Grade >=3) to any components of ALKS 4230, to pembrolizumab, or any of its excipients.
6. Subjects with mean QT interval corrected by the Fridericia Correction Formula values of >470 msec (in females) or >450 msec (in males) following a standard 12-lead electrocardiogram (ECG); subjects who are known to have congenital prolonged QT syndromes; or subjects who are on medications known to cause prolonged QT interval on ECG.
7. Subject has developed Grade >=3 autoimmune disorders while on prior immunotherapy, (e.g., pneumonitis, nephritis, and neuropathy). Subjects who have immune-mediated endocrinopathies and are stable on hormone replacement therapy are not excluded. Subjects who developed other autoimmune disorders of Grade <=2 may enroll if the disorder has resolved and the subject is off systemic steroids for >=28 days. Subjects who experienced autoimmune colitis as a toxicity of prior immunotherapy must undergo colonoscopy to rule out ongoing inflammation. Vitiligo is not exclusionary.
8. Subjects who have received radiotherapy within the last 4 weeks before start of study treatment, with the exception of limited field palliative radiotherapy that has been completed at least 2 weeks before starting study treatment.
9. Subject has active or symptomatic central nervous system metastases unless the metastases have been treated by surgery and/or radiation therapy, and/or gamma knife, the subject has been tapered to a dose of 10 mg of prednisone (or equivalent) or less of corticosteroids for at least 2 weeks before the first dose of study agent(s), and the subject is neurologically stable.Patients with history of brain metastases or a suspicion of brain metastases must have a brain magnetic resonance imaging (MRI) at baseline.
10. Subject has an active autoimmune disease that has required systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease that has required systemic steroids and/or immunosuppressive agents. Limited exceptions may be granted on a case-by-case basis by the Medical Monitor. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
11. Subjects known to be positive for human immunodeficiency virus are excluded. Subject with active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) are excluded, however, a subject with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) may be enrolled provided that HBV DNA is negative. Subjects with active hepatitis C (eg, hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] are detected) is excluded, however, a

subject with cured hepatitis C (negative HCV RNA status) may be enrolled.
12. Subjects with active tuberculosis or a known history of tuberculosis are excluded.
13. Subjects requiring pharmacologic doses of systemic corticosteroids (greater than 10 mg of prednisone daily, or equivalent) are excluded; however, replacement doses, topical, ophthalmologic, inhalational intra-articular, and epidural corticosteroids are permitted.
14. Subject has had a second malignancy within the previous 3 years. This criterion does not apply to subjects with an adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, prostate cancer of highest Gleason score <=6 with undetectable prostate-specific antigen (PSA) over the previous 12 months, breast carcinoma in situ with full surgical resection.
15. Subject has any other concurrent uncontrolled illness, including mental illness or substance abuse disorder, which may interfere with the ability of the subject to cooperate and participate in the study. Other examples of such conditions would include unstable, poorly controlled, or severe hypertension; clinically significant pericardial effusion; New York Heart Association Class III or IV (see Appendix 1: New York Heart Association Heart Disease Classifications) congestive heart failure; known cardiopulmonary disease, defined as unstable angina, myocardial infarction, or cerebrovascular accident within 6 months of first dose; chronic obstructive pulmonary disease or diabetes mellitus that has required two or more hospitalizations in the last year; severe peripheral vascular disease; or recent serious trauma.
16. Subject has received a live vaccine within 30 days of planned start of study therapy. Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines and are not allowed.Note: COVID-19 vaccine is allowed.
17. Subject has taken immunosuppressive medication within 14 days of planned start of study therapy.
18. Subject has active uncontrolled coagulopathy.
19. Subjects with dyspnea at rest or requiring oxygen therapy.
20. Prior solid organ and/or non-autologous hematopoietic stem cell or bone marrow transplant recipients.
21. Subjects who have received prior IL-2-based or IL-15-based cytokine therapy.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-12-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALKS 4230
Generic name:	ALKS 4230

Ethics review

Approved WMO Date:	11-12-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-10-2020
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-002013-20-NL
ClinicalTrials.gov	NCT03861793
CCMO	NL72160.056.19

Study results

Date completed: 12-09-2022

Results posted: 21-02-2024

First publication
14-02-2024

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File