A PHASE 2 STUDY OF ALX148 IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA (ASPEN-03)

Published: 12-04-2021
Last updated: 19-03-2025

This study has been transitioned to CTIS with ID 2023-508340-22-00 check the CTIS register for the current data. Primary ObjectiveTo assess the effect of ALX148 plus pembrolizumab on 12-month overall survival (OS) rate and objective response rate (...

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

Summary

ID

NL-OMON56262

Source
ToetsingOnline

Brief title
ASPEN-03, AT148003

Condition

- Other condition

Synonym
Head and Neck cancer, Head and Neck squamous cell carcinoma

Health condition

Head and Neck squamous cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: ALX Oncology Inc.
Source(s) of monetary or material Support: ALX Oncology

Intervention

Keyword: ALX148, Squamous Cell Carcinoma

Outcome measures

Primary outcome

Primary Endpoint

• 12-month overall survival (OS) rate of ALX148 plus pembrolizumab.

• Objective response rate of ALX148 plus pembrolizumab (ORR; CR or PR using the

Response Evaluation Criteria in Solid Tumors [RECIST]

version 1.1).

Secondary outcome

• Disease control rate (DCR), duration of response (DOR), time to tumor

progression (TTP).

• Progression-free survival (PFS), and overall survival (OS).

• Adverse Events as characterized by type, frequency, severity (as graded by

National Cancer Institute Common Terminology Criteria for

Adverse Events (NCI CTCAE v. 5.0), timing, seriousness, and relationship to

study therapy.

• Laboratory abnormalities as characterized by type, frequency, severity (as

graded by NCI CTCAE v. 5.0) and timing.

• Pharmacokinetic parameters of ALX148 such as Cmax, Tmax, AUC, CL, and t1/2 as

data permit.

• Immunogenicity; Human serum ADA (i.e., anti-ALX148 antibody) samples will be

analyzed for the presence or absence of anti-ALX148

antibodies.

Study description

Background summary

The CD47 - SIRPα pathway is implicated in the regulation of myeloid cell functions and pathologic immune evasion by cancer cells. CD47 is a widely expressed cell surface protein that functions as a marker of self. CD47 provides a *don*t eat me* signal that distinguishes viable/healthy cells from apoptotic/abnormal cells (Oldenborg, 2013). SIRPα is the CD47 receptor on macrophages. CD47 binding to this receptor inhibits phagocytosis of healthy cells, while cells displaying low levels of CD47 are susceptible to macrophage-mediated destruction (Khandelwal et al, 2007; Oldenborg et al, 2000). Tumor cells overexpress CD47 to evade the macrophage component of immune surveillance. Abundant CD47 expression has been observed in a wide variety of hematologic and solid tumors. In some reports, elevated CD47 mRNA expression may correlate with poor survival in individuals with cancer (Willingham et al, 2012; Chao et al, 2010; Yoshida et al, 2015). Similar to the adaptive anti-tumor activity of T cells, the innate anti-tumor activity of macrophages is regulated via a balance between activating signals (*eat me*) and the inhibitory signals (*don*t eat me*). Phagocytosis requires both the activation of "eat me" signals and the disruption of "don't eat me" signals. Neither component alone is sufficient to trigger maximal phagocytic reaction against tumor cells. CD47 provides a fundamental *don*t eat me* signal through its interaction with SIRPα on macrophages. The pro-phagocytic "eat me" signal can be provided to the same macrophages by binding to their activating Fc gamma receptors. In this way, the CD47 - SIRPα interaction is considered to be a checkpoint for innate immunity similar to PD-L1 / PD-1 for adaptive immunity. CD47 blockers with an active Fc domain, such as CD47 blocking antibodies or CD47 blocking fusion proteins linked to an active Fc domain, are able to provide both components required for tumor cell phagocytosis. The pro-phagocytic *eat me* signal is provided through the interaction of their Fc domain with the Fc gamma receptors. Although such CD47 blockers have been shown to increase phagocytosis of cancer cells in nonclinical studies, they have also been associated with on-target toxicities such as anemia, neutropenia, and/or thrombocytopenia in clinical studies (Branimir et al, 2016; Ansell et al, 2016). Anemia has also been seen in animal studies with CD47 blocking

antibodies (Liu et al, 2015a). ALX148 is a high affinity engineered fusion protein containing the N-terminal D1 domain of SIRPα genetically linked to a modified Fc domain from human IgG1. ALX148 is a CD47 blocker specifically designed to avoid such potential on-target toxicity of CD47-expressing blood cells by containing an inactive Fc domain. It is intended to be used in combination with targeted immunotherapeutic agents for the treatment of adult patients with advanced malignancy. ALX148 is designed specifically to bind to CD47 and block the *don*t eat me* signal, however, it lacks an active Fc domain. Thus, it does not interact with Fc gamma receptors and is not expected to activate phagocytosis by itself. The second required "eat me" signal can be independently and selectively provided by anti-cancer therapeutics that contain an active Fc, such as Herceptin® (trastuzumab), Erbitux® (cetuximab) or Rituxan® (rituximab). By separating the two signals, it is possible to selectively direct macrophages to cancer cells and spare normal cells. Blocking the CD47 pathway may also enhance the adaptive immune response, leading to increased anti-tumor activity by multiple mechanisms. As suggested by preclinical studies, CD47 blockade may prime or boost tumor-specific CD8+ effector T cells by bridging innate immune dendritic cell (DC) activation and/or enhancing the phagocytosis and enabling processing and presentation of tumor antigens (Tseng et al, 2013; Soto-Pantoja et al. 2014; Liu et al. 2015b; Sockolosky et al. 2016). Additionally, by modulating the phagocytic activity of tumor associated macrophages (TAMs), CD47 blockade may result in the reprogramming of TAMs to lessen the inhibition of cytotoxic T cell lymphocytes. CD47 blockade may even directly augment activation of CTLs and inhibit T regulatory cells (Avice et al., 2000; Van et al 2008). Thus, ALX148, through its blockade of CD47, may augment anti-tumor adaptive immunity in combination with other cancer immunotherapies, including anti-PD-1 and anti-PD-L1 inhibitors such as Keytruda® (pembrolizumab), Opdivo® (nivolumab), & Tecentriq® (atezolizumab). Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in metastatic or unresectable recurrent HNSCC and an attractive combination partner for an anti-CD47 agent such as ALX148. Patients with solid tumor malignancies for which targeted immunotherapy treatment is indicated, such as recurrent, unresectable or metastatic HNSCC, may benefit from a combination approach with ALX148. HNSCC of the oropharynx is the 11th most common cancer worldwide and represents 3% of all new cancer cases in the United States, with an estimated 10,860 cancer related deaths to occur in 2019 (National Cancer Institute SEER 2019; World Health Organization 2019). For patients whose cancer has metastasized, the 5-year survival rate is 39.1%

(National Cancer Institute SEER 2019). In the paradigm-shifting KEYNOTE 48 study, pembrolizumab in combination with 5FU and platinum therapy was shown to improve patients* overall survival compared with cetuximab plus 5FU and platinum therapy with a HR 0.65 (95% CI 0.53-0.80, P< .0001) and median OS of 13.6 vs 10.4 months in patients with CPS (Combined Positive Score) >=1 thus establishing a new standard of care for patients with newly recurring/metastatic HNSCC (Burtness et al. 2019). In addition, pembrolizumab as a single agent improved overall survival vs the standard of care regimen of cetuximab, platinum and 5FU, with a median overall survival of 11.5 vs 10.7 months, respectively (HR = 0.83, 95% CI = 0.70-0.99, P = .0199). Lastly, although the overall response rate for single-agent pembrolizumab was noticeably lower than that for cetuximab/chemotherapy (16.9% vs 36.0%), the median duration of response for pembrolizumab alone was substantially longer (22.6 vs 4.5 months), suggesting that single-agent pembrolizumab is also an efficacious option for a subset of patients with R/M HNSCC, leading to FDA approval of pembrolizumab alone for patients with a CPS of at least 1. Despite these advances, patients who have not yet been treated for recurrent/metastatic HNSCC still have a median overall survival of only approximately 1 year and are in need of novel combination treatment options that do not significantly increase the toxicity of the currently available regimens. As reported in preliminary clinical results (Chow et al. 2020) in checkpoint nai*ve patients, and non-clinical studies (Kauder et al. 2018), coupling ALX148 with a checkpoint inhibitor demonstrates clinical benefit, and also provides a strong rationale for combining this doublet with standard of care chemotherapy regimens in patients with first-line metastatic or unresectable, recurrent HNSCC. Preli

Study objective

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Primary Objective
To assess the effect of ALX148 plus pembrolizumab on 12-month overall survival (OS) rate and objective response rate (ORR) in patients with metastatic or with unresectable, recurrent HNSCC that is PD-L1 positive (CPS >=1) and who have not yet been treated for their advanced disease.

Secondary Objectives
• To assess secondary measures of efficacy for ALX148 administered in combination with pembrolizumab and for pembrolizumab alone.
• To assess the safety and tolerability of ALX148 administered in combination with pembrolizumab and for pembrolizumab alone (including for patients in the safety lead-in cohort).

Study design

This is a non-comparative open-label, randomized phase 2 multi-center study of patients with metastatic or unresectable, recurrent HNSCC who have not yet been treated for their advanced disease administered ALX148 in combination with pembrolizumab versus pembrolizumab monotherapy (CPS >=1).

The study comprises of an initial safety lead-in followed by a randomized portion. At least six patients will be enrolled into the safety lead-in. These lead-in patients will be observed for toxicity for the first 21 days (Cycle 1). Once review of the safety lead-in is complete a non-comparative randomized phase 2 Simon admissible study design will be used to evaluate the anti-cancer activity of ALX148 + pembrolizumab and that of pembrolizumab alone. The control arm of single-agent pembrolizumab will serve as a validation of historical controls rather than a direct comparator. The study will randomize approximately 105 patients after the safety lead-in cohort. Approximately 70 patients will be randomized in the experimental arm and approximately 35 patients will be randomized to the control arm, using a 2:1 allocation ratio.

Intervention

Patients will be administered ALX148 45 mg/kg Q3W in a 21-day cycle with pembrolizumab dosed at 200 mg IV infusion over 30 minutes every 3 weeks for up to a maximum of 35 cycles (approximately 24 months). Patients who do not have disease progression and who continue to meet retreatment criteria may continue to receive ALX148. Pembrolizumab treatment may continue up to a maximum of 35 cycles (approximately 24 months) in patients without disease progression.

The patients in the safety lead-in will receive ALX148 + pembrolizumab and will undergo additional PK sampling during cycles 1 and 3 with the goal of obtaining a complete dense PK sample set (AT148003 Schedule of Assessments - Safety Lead-In Cohort). The remaining patients on the ALX148 + pembrolizumab arm will undergo sparse PK sampling pre- and post-infusion during the first 6 cycles of treatment.

Study burden and risks

The burden and risk mainly consist out of extra time spent in comparison to standard treatment and side effects, and the risks of medical evaluation, including venapuncture, biopsy and MRI/CT scans.

Contacts

Public
ALX Oncology Inc.

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Scientific
ALX Oncology Inc.

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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. Patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) that is PD-L1 positive (defined as CPS > 1 by an FDA-approved test utilizing the 22C3 antibody and by any required locally approved test) and who have not received prior systemic therapy for their advanced disease. - Patients cannot have received prior systemic therapy for the treatment of metastatic or recurrent disease. - Patients can have received prior systemic therapy for the treatment of locoregionally advanced disease if it was completed more than 6 months prior to signing informed consent.
2. Patients must have at least one measurable lesion as defined by RECIST version 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
3. Adequate bone marrow function (obtained within 10 days of first planned dose), including: a. Absolute Neutrophil Count (ANC) >=1,500/mm3 (>=1.5 x 109/L); b. Platelets >=100,000/mm3 (>=100 x 109/L); c. Hemoglobin >=9 g/dL (>=90 g/L) - must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable doses of erythropoietin (>= approximately 3 months)
4. Adequate renal function (obtained within 10 days of first planned dose),

including: a. Estimated creatinine clearance (using Cockroft-Gault equation) >= 30 mL/min.
5. Adequate liver function (obtained within 10 days of first planned dose), including:
a. Total bilirubin <=1.5 x ULN (<=3.0 x ULN if the patient has documented Gilbert syndrome);
b. Aspartate and Alanine transaminase (AST and ALT) <=2.5 x ULN; <=5.0 x ULN if there is liver involvement secondary to tumor.
6. Age >=18 years, except in regions in which the minimum age for subject participation is >18 years.
7. INR or PT and PTT <1.5X ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) must be 0 or 1.
9. Participants with oropharyngeal carcinoma must have available results from testing of human papillomavirus (HPV) (p16) status.
10. Participants must have recovered from all AEs due to previous therapies, procedures, and surgeries to baseline or <=Grade 1 per NCI CTCAE v. 5.0 except for AEs not constituting a safety risk by Investigator judgment (e.g. alopecia). Participants with <=Grade 2 neuropathy may be eligible.
11. Available core or incisional biopsy sample prior to study entry, preferably taken after the most recent therapy for HNSCC, for central confirmation of PD-L1 CPS and evaluation of other biomarkers. Fine needle aspirates are not acceptable.
12. Serum pregnancy test (for females of childbearing potential) negative at screening.
13. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 120 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active.
14. Evidence of a personally signed and dated informed consent document, from a patient with the capacity to consent for themselves or from a legal representative, indicating that the patient or legal representative has been informed of all pertinent aspects of the study before any study specific activity is performed. 15. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other procedures.

Exclusion criteria

1. Patients with disease suitable for local therapy with curative intent.
2. Patients with progressive disease within 6 months of completion of curatively intended systemic therapy for the treatment of locoregionally advanced HNSCC.

3. Patients with nasopharyngeal carcinoma (NPC).
4. Patients with known symptomatic CNS metastases requiring steroids or with leptomeningeal disease. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases and are clinically stable off anticonvulsants for at least 4 weeks and are neurologically stable before enrollment.
5. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
6. Prior radiotherapy within 2 weeks of start of study treatment. Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (defined as <=2 weeks of radiotherapy) to non-CNS disease.
7. Prior treatment with any anti-CD47 or anti-SIRPα agent.
8. Prior treatment with a PD-1 or PD-L1, or anti PD-L2 agent or with an agent directed to another
stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX-40, CD137).
9. Has a diagnosis of immunodeficiency (with the exception of hypogammaglobulinemia) or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
10. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
11. History of autoimmune hemolytic anemia, autoimmune thrombocytopenia, or hemolytic transfusion reaction.
12. Patients with intolerance to or who have had a severe allergic or anaphylactic reaction to antibodies or infused therapeutic proteins or patients who have had a severe allergic or anaphylactic reaction to any of the substances included in the study drugs (including but not limited to excipients, which are listed in the ALX148 IB in Section 4.4 *Formulation of the Dosage Form to be Used*).
13. Any experimental antibodies or live vaccines in the last 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
14. Patients with active, uncontrolled, clinically significant bacterial, fungal, or viral infection, including hepatitis B (HBV), hepatitis C (HCV), known infection with SARS-CoV-2, known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

15. Has an active infection requiring systemic therapy.
16. Has had an allogeneic tissue/solid organ transplant.
17. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident, or transient ischemic attack, deep venous thrombosis, arterial thrombosis, symptomatic pulmonary embolism, or any other significant thromboembolism. Any major surgery within 28 days prior to enrollment.
18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been at least 4 weeks after the last dose of the previous investigational agent.
19. Diagnosis of any other malignancy within the last 3 years prior to enrollment except for adequately treated non-melanomatous skin cancer, or carcinoma in situ (e.g., breast carcinoma in situ, cervical cancer in situ, prostate carcinoma in situ) that have undergone potentially curative therapy.
20. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.
21. Patients who are pregnant or breastfeeding.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-12-2022

Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evorpacept
Generic name:	Evorpacept
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-12-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	12-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	31-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-12-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 22954
Source: NTR
Title:

In other registers

Register	ID
EU-CTR	CTIS2023-508340-22-00
EudraCT	EUCTR2020-004093-21-NL
ClinicalTrials.gov	NCT04675294,IND139180
CCMO	NL76477.042.21
OMON	NL-OMON22954