

A PHASE 2 STUDY OF ALX148 IN COMBINATION WITH PEMBROLIZUMAB AND CHEMOTHERAPY IN PATIENTS WITH ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA (ASPEN-04)

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This study has been transitioned to CTIS with ID 2023-508342-17-00 check the CTIS register for the current data. Primary Objective• To assess the effect of ALX148 + pembrolizumab + 5FU + platinum on 12-month overall survival (OS) rate and objective...

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

Summary

ID

NL-OMON54403

Source

ToetsingOnline

Brief title

ASPEN-04, AT148004

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 + pembrolizumab + 5FU + platinum.
- Objective response rate of ALX148 + pembrolizumab + 5FU + platinum (ORR; CR or PR using the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1).

Secondary outcome

Secondary Endpoints

- 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
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graded by NCI CTCAE v. 5.0) and timing.

- Pharmacokinetic parameters of ALX148 such as C_{max}, T_{max}, AUC, CL, and t_{1/2} 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 - SIRP α 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). SIRP α 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 SIRP α 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 - SIRP α 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 SIRP α 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 (Avicé 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

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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 (Burtneess 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. Preliminary

Study objective

This study has been transitioned to CTIS with ID 2023-508342-17-00 check the CTIS register for the current data.

Primary Objective

- To assess the effect of ALX148 + pembrolizumab + 5FU + platinum on 12-month overall survival (OS) rate and objective response rate (ORR) in patients with metastatic or unresectable, recurrent HNSCC 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 + 5FU + platinum and for pembrolizumab + 5FU + platinum.
 - To assess the safety and tolerability of ALX148 administered in combination
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with pembrolizumab + 5FU + platinum and for pembrolizumab + 5FU + platinum (including for patients in the safety lead-in cohort).

Study design

This is a non-comparative phase 2 open-label, multi-center study of the anti-tumor efficacy of ALX148 + pembrolizumab + chemo versus pembrolizumab + chemo in patients with metastatic or unresectable, recurrent HNSCC who have not yet been treated for their advanced disease HNSCC.

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 minimax study design will be used to evaluate the anti-cancer activity of ALX148 + pembrolizumab + chemotherapy versus pembrolizumab + chemotherapy for the treatment of patients with metastatic or with unresectable, recurrent HNSCC who have not yet been treated for their advanced disease. The control arm of pembrolizumab + chemo will serve as a validation of historical controls rather than a direct comparator. The study will randomize approximately 106 patients after the safety lead-in cohort. A total of 71 patients will be randomized in the experimental arm and 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), carboplatin dosed at AUC 5 mg/ml/min as a 60 min infusion Day 1 Q3W x6, OR cisplatin dosed at 100 mg/m² as a 60 min infusion Day 1 Q3W x 6 (Investigator's choice), and 5-FU dosed at 1000 mg/m²/day continuous infusion Days 1, 2, 3, 4 Q3W x 6. Patients who do not have disease progression and who continue to meet retreatment criteria may continue to receive ALX148. Pembrolizumab may continue up to a maximum of 35 cycles (approximately 24 months) in patients without disease progression. Carboplatin, cisplatin, and 5FU are administered per label for 6 cycles.

The patients in the safety lead-in will receive ALX148 + pembrolizumab + chemotherapy and will undergo additional PK sampling during cycles 1 and 3 with the goal of obtaining a dense PK sample set. The patients on ALX148 + pembrolizumab + chemo in the randomized portion of the study 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

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Scientific

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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) who have not received prior systemic therapy for their advanced disease. PD-L1 status as defined by combined positive score (CPS) and as assessed by an FDA-approved test using the 22C3 antibody must be available.

- 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

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31-05-2025

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. 3. Adequate bone marrow function. 4. Adequate renal function (estimated creatinine clearance by Cockcroft-Gault equation of ≥ 60 mL/min.). 5. Adequate liver function. 6. Age ≥ 18 years, except in regions in which the minimum age for subject participation is >18 years. 7. INR or PT and PTT <1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants. 8. ECOG performance status 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 \leq Grade 1 per NCI CTCAE v. 5.0 except for AEs not constituting a safety risk by Investigator judgment. Participants with \leq 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 and at least 6 months (or longer if required by local regulation) after the last dose of chemotherapy, whichever is later. 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.
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.
7. Prior treatment with any anti-CD47 or anti-SIRP α 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 or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
10. Has a diagnosis of complete dihydropyrimidine dehydrogenase (DPD) deficiency. Testing for DPD status is required for sites/regions in which such testing is standard of care (such as in the United Kingdom).
11. Has an active autoimmune disease that has required systemic treatment in past 2 years.
12. History of autoimmune hemolytic anemia, autoimmune thrombocytopenia, or hemolytic transfusion reaction.
13. 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.
14. Patients with significant hearing impairment.
15. Any experimental antibodies or live vaccines in the last 30 days prior to the first dose of study drug.
16. Patients with active, uncontrolled, clinically significant bacterial, fungal, or viral infection.
17. Has an active infection requiring systemic therapy.
18. Has had an allogeneic tissue/solid organ transplant.
19. 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.
20. 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.
21. 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 that have undergone potentially curative therapy.
22. Other severe acute or chronic medical or psychiatric condition.
23. Patients who are pregnant or breastfeeding.

Study design

Design

Study phase: 2

Study type: Interventional

Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	21-06-2023
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evorpacept
Generic name:	ALX148
Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paraplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Platinol
Generic name:	Cisplatin
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: 05-01-2022

Application type: First submission

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date: 17-01-2022

Application type: Amendment

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date: 15-03-2022

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: 13-07-2022

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:	07-09-2023
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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508342-17-00
EudraCT	EUCTR2020-004662-19-NL
ClinicalTrials.gov	NCT04675294,IND139180
CCMO	NL76478.042.21