A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor (INTERLINK-1)

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The study will compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of Overall Survival in HPV-unrelated participants. The formal statistical analysis will be performed to test the following...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56351

Source
ToetsingOnline

Brief title
INTERLINK-1

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer of head and neck, squamous cell carcinoma of the head and neck

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever/sponsor: AstraZeneca

Intervention

Keyword: Head and Neck carcinoma, Monalizumab and Cetuximab, Previous treatment by Immune Checkpoint Inhibitor, Recurrent or Metastatic

Outcome measures

Primary outcome

Primary:

- To compare the effect of monalizumab and cetuximab (Arm A) relative to

placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated

participants.

• Population: The primary population is the HPV-unrelated Analysis Set which

will include all randomized participants who are either OPC HPV negative or

non-OPC regardless of the HPV status.

• Endpoint: OS, which is defined as time from randomization until the date of

death due to any cause

• Intercurrent events: If a participant is lost to follow-up or withdraws

consent, OS will be censored based on the last recorded date on which the

participant was known to be alive

• Summary measure: p-value of treatment comparison using a stratified log rank

test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model

Secondary outcome

- To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS
- To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR, and DoR in participants who are HPV-unrelated and in all randomized participants.
- To assess disease-related symptoms, functioning, and HRQoL in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants.
- To assess the PK of monalizumab
- To investigate the immunogenicity of monalizumab
- To characterize the association between clinical outcome and protein expression in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants.

Secondary safety:

- To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN

previously treated with ICI

Study description

Background summary

Overall, outcomes in patients with R/M SCCHN remain poor and most patients will ultimately experience disease progression and eventually die of the disease.
For 1L treatment of R/M SCCHN, the combination therapy of cetuximab plus platinum and 5-FU followed by cetuximab until progression or intolerance (EXTREME regimen) has been the standard of care in the European Union and the USA. In clinical practice other single agents or doublet combinations, such as a taxane or cisplatin plus cetuximab, are also sometimes used as 1L treatment for R/M SCCHN when patients are not fit enough for the EXTREME regimen.

SCCHN, like many other malignancies, create a highly immunosuppressive environment and are amenable to therapeutic intervention with immune-modulating agents.
Recently, the PD-1 inhibitor pembrolizumab received US FDA approval as: (i) a single agent for the 1L treatment of patients with metastatic or with unresectable, recurrent SCCHN whose tumors express PD L1 or (ii) in combination with platinum and 5-FU for the 1L treatment of patients with metastatic or with unresectable, recurrent SCCHN.

Patients who progress or are intolerant to 1L therapy are typically treated with single-agent cetuximab, single-agent chemotherapy, or since recently with PD 1 inhibitors.

Cetuximab remained for a decade the only drug indicated for the treatment of patients with R/M SCCHN progressing after platinum-based therapy.
In 2016, the US FDA granted approval to pembrolizumab and another PD-1 inhibitor nivolumab in patients with R/M SCCHN with disease progression on or after platinum therapy.
Treatment for patients with R/M SCCHN who progress after receiving a PD-1 inhibitor in monotherapy or pembrolizumab in combination with platinum chemotherapy, in the 1L or second-line setting is not clearly defined. As no treatment strategies in the immunotherapy-refractory disease setting are currently approved or uniformly adopted by the medical community, a suggested approach is to enroll a patient with R/M SCCHN into a clinical study assessing combination immunotherapy.

Human leukocyte antigen E (HLA-E) is expressed on tumor cells in 78% to 86% of patients with SCCHN. HLA-E is the ligand of the CD94/NKG2A receptors that are found on NK cells and CD8+ T cells in a variety of tumor types, including

SCCHN.
The interaction of HLA-E with CD94/NKG2A receptor results in the inhibition of NK cell and cytotoxic T lymphocyte-dependent tumor lysis and may represent a significant immune escape mechanism by tumor cells. Monalizumab is a monoclonal antibody that specifically binds and blocks the function of CD94/NKG2A. Cetuximab is a monoclonal antibody that is specifically directed against the EGFR. The EGFR is an important regulator of cell growth and differentiation. Targeting EGFR is an important treatment modality for head and neck cancers. Several studies have suggested that ADCC activity is important for cetuximab clinical efficacy and is dependent on tumor cell surface EGFR expression.

It is expected that monalizumab will increase cetuximab-dependent NK cell-mediated ADCC activity, which could subsequently lead to increased clinical benefit.

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of monalizumab and cetuximab is provided in the Monalizumab IB and cetuximab (ERBITUX®) current US PI or local label.

Study objective

The study will compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of Overall Survival in HPV-unrelated participants.

The formal statistical analysis will be performed to test the following main hypotheses for monalizumab plus cetuximab (Arm A) or placebo plus cetuximab (Arm B):
• H0: No difference between Arm A and Arm B
• H1: Difference between Arm A and Arm B

The study is powered to demonstrate superiority in the OS benefit of Arm A vs Arm B in HPV-unrelated participants with R/M SCCHN previously treated with an ICI.

There will be two planned interim analyses and one Futility Analysis for the study.

Study design

Study D7310C00001 is a Phase 3, randomized, double-blind, multicenter, global study assessing the safety and efficacy of monalizumab or placebo in combination with cetuximab in patients with R/M SCCHN not amenable to curative treatment previously treated with platinum-based chemotherapy and an ICI, regardless of the sequence of these therapies.

Approximately 624 eligible participants will be randomized in a 2:1 ratio to one of the following treatment arms:
• Arm A (n = 416): monalizumab and cetuximab
• Arm B (n = 208): placebo and cetuximab

Intervention

Approximately 624 eligible participants will be randomized in a 2:1 ratio to one of the following treatment arms.
• Arm A (n = 416): monalizumab iv 750 mg Q2W and cetuximab 400 mg/m2 iv initial dose followed by 250 mg/m2 iv Q1W, as per label
• Arm B (n = 208): placebo iv Q2W and cetuximab 400 mg/m2 iv initial dose followed by 250 mg/m2 iv Q1W, as per label

Participants will be stratified by the following :
• Human papillomavirus status (OPC HPV positive or OPC HPV negative/non OPC),
• World Health Organization/ECOG PS (0 or 1), and
• Number of prior lines of therapy in the R/M setting (1 or 2)

Study burden and risks

Patients are subject to the following assessments throughout the study:
- Anamnesis (at screening, including medical history)
- Physical examination
- HPV status for OPC participants
- ECOG performance status
- Vital functions (blood pressure, heart rate, body temperature and respiratory rhythm)
- Body weight measurement
- CT scan with IV contrast or MRI
- ECG
- blood - and urine examination
- questionnaires (in hospital using a tablet) (EORTC QLQ-C30, EORTC QLQ-H&N35, EQ-5D-5L, PGIS, PRO-CTCAE, PGI-TT + optional SPFQ)
- pregnancy test when applicable
- AE/SAE assessment
- IP administration
- biopsy (new biopsy or <3 months old)

Bleeding events have been reported in up to 10% or more in patients with head and neck cancer. It is not yet known whether the risk of bleeding in the experimental treatment would be higher or lower than in standard therapy.

Monalizumab:
Uncommon side effects (affecting between 1 in 1000 and 1 in 100 people):
Infusion-related reaction: flu-like symptoms or allergic reactions shortly

after or within a few hours of receiving medicines with the following symptoms: flushing, rash, fever, chills, chills or shortness of breath.
Rarely, autoimmune reaction can happen. The reactions can be mild and temporary, but they can also be severe and permanent.

Combination of monalizumab and cetuximab: To date, there is no evidence that monalizumab or cetuximab increase each other's risks when given together.

Cetuximab: very common side effects: mild or moderate infusion reaction, acne and rash, inflammation of the mucous membrane, increased blood liver enzymes, low blood magnesium. Common side effects: severe infusion reaction, fatigue, dehydration, headache, diarrhea, nausea, vomiting, loss of appetite, decrease in blood calcium, conjunctivitis

The side effects can range from mild to severe or in some cases even life-threatening. Conditions have been built into the study to identify as early as possible the side effects that can be serious

Moreover, the study procedures might also cause the following ailments:
- pain or bruises through collection of blood
- rash through ECG stickers
- health risks through radiation of CT-scan/MRI

Contacts

Public
Astra Zeneca

Södertälje na
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SE
Scientific
Astra Zeneca

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SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Participant must be >= 18 years of age at the time of signing the informed consent.
2. Histologically or cytologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx who have progressed on or after previous systemic cancer therapy and are not amenable to curative therapy
3. Must have received prior treatment with a systemic PD-(L)1 inhibitor (in any setting)
4. Prior platinum failure as defined in the protocol.
5. Received 1 or 2 prior systemic regimens for R/M SCCHN
6. At least one measurable lesion by RECIST 1.1 at baseline. Tumor assessment by CT scan or MRI must be performed within 28 days prior to randomization.
7. Provide fresh or recently acquired tumor tissue (<= 3 months prior to screening) for the purpose of biomarker testing.
8. For participants with OPC only: known HPV status prior to randomization
9. WHO/ECOG PS of 0 or 1 at enrollment
10. Adequate organ function (see definition in the protocol)
11. Minimum life expectancy of 12 weeks
12. Body weight > 30 kg
13. Male and/or female
14. Negative pregnancy test for female participants of childbearing potential.
15. Female participants must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception
16. Male participants must be surgically sterile or using an acceptable method of contraception
17. Capable of giving signed informed consent
18. Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses
19. Provision of signed and dated written informed consent for genetic sample and analysis (optional)
20. Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research

that supports Genomic Initiative

Exclusion criteria

1. Histologically or cytologically confirmed head and neck cancer of any other primary
anatomic location in the head and neck not specified in the inclusion criteria including
participants with squamous cell carcinoma of unknown primary or non-squamous histologies (eg, nasopharynx or salivary gland)
2. Prior cetuximab therapy (unless in Locally Advanced setting with
radiotherapy and no disease progression for at least 6 months following the last cetuximab
dose)
3. Any unresolved toxicity NCI CTCAE >= Grade 2 from previous anticancer therapy with
the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
4. Has carcinomatous meningitis and/or untreated central nervous system metastases identified either on the baseline brain imaging obtained during the screening period or identified prior to signing the ICF.
5. Major surgical procedure (as defined by the investigator) within 28 days prior to the first
dose of study intervention
6. History of allogeneic organ transplantation
7. History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition to cetuximab and monalizumab or any of their excipients
8. History of active primary immunodeficiency
9. Active or prior documented autoimmune or inflammatory disorders
10. Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus
11. Uncontrolled intercurrent illness
12. History of another primary malignancy
13. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >= 500 ms
calculated from 3 ECGs
14. Any concurrent anticancer treatment
15. Receipt of the last dose of anticancer therapy or radiotherapy with curative intent <= 28 days prior to the first dose of study intervention.
16. Current or prior use of immunosuppressive medication within 14 days before the first dose of study intervention.
17. Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention.
18. Participation in another clinical study with an investigational product

administered in the
last 28 days prior to randomization or concurrent enrollment in another
clinical study
19. Prior treatment with monalizumab

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2021
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	niet beschikbaar
Generic name:	Monalizumab

Ethics review

Approved WMO Date:	29-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-10-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-06-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2019-004770-25-NL
ClinicalTrials.gov	NCT04590963
CCMO	NL73538.031.20