A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high-risk for relapse and are ineligible for high-dose cisplatin

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON56150

Source
ToetsingOnline

Brief title
Phase III xevinapant and radiotherapy in resected LA SCCHN

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Locally Advanced Tumor / Locally Advanced Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Healthcare KGaA
Source(s) of monetary or material Support: The pharmaceutical industry.

Intervention

Keyword: - Adjuvant RT (Radiotherapy), - LA SCCHN (locally advanced squamous cell carcinoma of the head and neck).

Outcome measures

Primary outcome

Disease-Free Survival (DFS).

Secondary outcome

1. Overall Survival (OS)

2. Time to Subsequent Cancer Treatments

3. Occurrence of Adverse Events (AEs) and Treatment-related AEs

4. Change from Baseline in European Organization for Research and Treatment of

Cancer Quality of Life Head and Neck Module (EORTC QLQ-HN35) Score

5. Change from Baseline in European Organization for research and Treatment of

Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) Score

6. Change from Baseline in EuroQOL 5 Dimension 5 Level Health-Related Quality

of Life Measure Visual Analog Scale Score (EQ-5D-5L VAS)

Study description

Background summary

Xevinapant is an antagonist of IAPs that has been shown in nonclinical in vitro and in
vivo models to have both chemo- and radiosensitizing potential, as well as immunomodulatory
potential. In unresectable LA SCCHN patients, the addition of xevinapant to standard of care chemoradiotherapy recently showed a statistically significant and clinically meaningful improvement in locoregional control at 18 months compared to placebo and standard of care alone.

The purpose of this study is to demonstrate the superior efficacy of xevinapant vs placebo when added to radiotherapy in the treatment of high-risk participants with resected LA SCCHN who are ineligible to receive cisplatin-based chemoradiation concurrently.

Study objective

This study has been transitioned to CTIS with ID 2023-508528-36-00 check the CTIS register for the current data.

The purpose of this study is to demonstrate improvement in Disease-Free Survival (DFS) with xevinapant compared to placebo when added to RT irrespective of subsequent anticancer therapy.

Study design

This is a multicenter, randomized double-blind, placebo-controlled, 2-arm, parallel-group Phase III study.

Intervention

Participants who meet the eligibility criteria will be enrolled and randomized in a 1:1 ratio, using permuted block allocation to Arm A or Arm B and will receive the following treatments:
• Arm A: 3 cycles of xevinapant (oral solution 200 mg/day from Day 1 to 14, per 3-week cycle)
+ IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of
monotherapy of xevinapant (oral solution 200 mg/day from Day 1 to 14, per 3-week cycle)
OR
• Arm B: 3 cycles of placebo (matching oral solution from Day 1 to 14, per

3-week cycle) +
IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy
of placebo (matching oral solution from Day 1 to 14, per 3-week cycle).

• Study duration: Participants will be followed until the last on-study participant reaches his/her
60-month post-randomization visit, a decision to end the study has been triggered, or until
premature discontinuation from study, whichever occurs first.
• Treatment duration: 18 weeks, consisting of six 3-week cycles.
• Visit frequency: Weekly visit during combination therapy period, once every 3 weeks during
monotherapy period, and every 3, 4, or 6 months during the Disease-Free Survival Follow-up
period in Year 1, 2 and 3, or 4 and 5 (with telephone contact in between), respectively, and
every 3 months (telephone visits allowed) during the Overall Survival Follow-up period.

Study burden and risks

Subject*s participation in this study will last 5 years and consists of a screening period, treatment period and a follow-up period.
During the treatment period, subjects will need to visit the study site for 5 days every week for the first 6.5 weeks (which may be extended to 9 weeks only if radiotherapy is put on hold within the initial 6.5 weeks). There after subjects will need to visit the study site once every 3 weeks. During the follow-up period, subjects will need to visit the study site at Month 7, 9, and 12 for the first year, every 4 months for the 2nd to 3rd years, and every 6 months for 4th to 5th years, or earlier if there is disease progression.
If there is disease progression or subject has completed 4.5 years of disease-free health status follow-up, then subject may need to visit the study center or receive telephone calls every 3 months until approximately 5 years after the last participant receives the study medication or subject is no longer able to continue in the study.

Aside from the intervention described above, participation in this study involves blood draws at multiple visits, biopsy at at time of relapse, radiation exposure through CT & PET scan, and might involve radiation exposure through MRI scans. It also may involve an audiometry test and a dental exam.
Participants will be subjected to: questions regarding medical history, use of concomitant medications/procedures and adverse events; urine sampling; measurement of vital signs; physical examination; ECOG performance status; ECGs and patient reported outcomes questionnaires.
Subjects will be expected to come to their visits, to not take part in other medical studies, keep their appointments for visits, follow instructions

from the study team, keep a patient card with them at all times, not donate blood/sperm/ova and to use appropriate forms of contraception. Subjects will also be asked to complete a diary daily with questions about their Xevinapant/ Placebo intake.

The side effects listed below are those reported in other clinical medical scientific studies when xevinapant was given as a single drug or in combinations with various other drugs; however, a causal link to xevinapant has not been proved. In addition, there might be side effects not yet known that may occur. It is possible that giving xevinapant with radiotherapy will result in more severe or new side effects or that side effects will worsen more rapidly than expected. Some side effects of xevinapant may occur anytime during treatment or even after the treatment has ended.
Common (in more than 5 up to 100 in 100 people) side effects of xevinapant include: nausea, vomiting, stomatitis, dry mouth, decreased appetite, diarrhea, constipation, asthenia, fatigue, anemia, Alanine aminotransferase (ALT) increase (abnormal liver tests), Aspartate aminotransferase (AST) increase (abnormal liver tests), Hyperlipasemia/Lipase increase, rash, pruritus.

Based on current available efficacy and safety data available for xevinapant treatment, including the combination with chemoradiotherapy (CRT) and/or immunotherapy, and for Radiotherapy (RT) alone, the benefit/risk assessment for a study combining xevinapant with Radiotherapy (RT) is expected to be positive.

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

• Participants with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2 and able to tolerate standard of care IMRT treatment according to Investigator assessment.
• Participants with histologically confirmed squamous cell carcinoma with one of the following primary sites: oral cavity, oropharynx, hypopharynx or larynx. Participants have received surgery with curative intent on these sites in the past 4 to 8 weeks before start of treatment (Cycle 1 Day 1)
• Oropharynx (OPC) participants must have known human papillomavirus (HPV) status as determined by p16 expression using immunohistochemistry ICH)
• Participants with no residual disease by computed tomography (CT) or magnetic resonance imaging (MRI) and have a high risk of relapse with 1 or 2 of the following criteria, confirmed by local histopathology:
• nodal extra-capsular extension (ECE) and positive resection margins (R1 or close margin less than or equal to (<=) 1 millimeter (mm)
• Are unfit to receive high-dose cisplatin by meeting one or more of the following criteria: estimated glomerular filtration rate (eGFR) < 60 milliliter per minute per 1.73 meter square (mL/min /1.73 m^2); History of hearing impairment, defined as Grade >= 2 audiometric hearing loss or tinnitus Grade >=2. An audiogram is not required if one of the other criteria meets unfitness to receive high-dose cisplatin; Peripheral neuropathy > = Grade 2 and if >= 70 years, unfit according to G8 questionnaire (Score <= 14) or ineligible for cisplatin treatment due to age limit to national guidelines
• Participants with adequate hematologic, renal and hepatic function as defined in the protocol
• Other protocol-defined inclusion criteria could apply

Exclusion criteria

• Any condition, including any uncontrolled disease state other than SCCHN that in the Investigator*s opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with

the study objectives, conduct, or evaluation
• Participant with incomplete surgery
• Primary tumor of nasopharyngeal, paranasal sinuses, nasal cavity, salivary, thyroid or parathyroid gland, skin or unknown primary site
• Prior definitive, neoadjuvant, concurrent or adjuvant (C)RT to the head and neck region which may jeopardize the primary tumor irradiation plan,or any other prior SCCHN systemic treatment, including investigational agents
• Participation in any interventional clinical study within 28 days prior to screening or during participation in this study
• Known contraindication to undergoing positron emission tomography with 18F-FDG-PET-CT scans, or both contrast-enhanced MRI and contrast enhanced CT scans
• Known allergy to Xevinapant (Debio 1143) or any excipient known to be present in Xevinapant (Debio 1143) or in the placebo formulation
• Participants with recurrent or metastatic disease
• Other protocol-defined exclusion criteria could apply

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:	Recruiting
Start date (anticipated):	07-03-2024
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	N/A
Generic name:	Xevinapant

Ethics review

Approved WMO Date:	01-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2023
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
EU-CTR	CTIS2023-508528-36-00
EudraCT	EUCTR2022-001144-18-NL
ClinicalTrials.gov	NCT05386550
CCMO	NL82563.056.22