A Randomized, Double-Blind, Multicenter, Phase 2 Study of Retifanlimab in Combination With INCAGN02385 (Anti-LAG-3) and INCAGN02390 (Anti-TIM-3) as First-Line Treatment in Participants With PD-L1-Positive (CPS >= 1) Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck

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To determine the efficacy of the combinations of retifanlimab + INCAGN02385 (TG2) and retifanlimab + INCAGN02385 + INCAGN02390 (TG3) compared with retifanlimab alone (TG1) in the overall study population.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON53614

Source
ToetsingOnline

Brief title
Incyte INCAGN 2385-203 Study

Condition

- Metastases

Synonym
Head and neck cancer; metastatic

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Biosciences International Sarl
Source(s) of monetary or material Support: Incyte Biosciences International Sarl

Intervention

Keyword: INCAGN02385 (Anti-LAG-3) en INCAGN02390 (Anti-TIM-3), PD-L1-Positive (CPS >= 1), Recurrent/Metastatic, Squamous Cell Carcinoma of the Head and Neck

Outcome measures

Primary outcome

PFS, defined as the interval between the date of randomization and the earliest

date of disease progression, based on investigator assessment per RECIST v1.1,

or death due to any cause.

Secondary outcome

• Objective response, defined as having a CR or PR, determined based on

investigator assessment per RECIST v1.1.

• DOR, defined as the time from earliest date of disease response (CR or PR)

until earliest date of disease progression, based on investigator assessment

per RECIST v1.1, or death from any cause if occurring sooner than progression.

•Disease control, defined as having CR, PR, or SD (>= 6 months) as best

response, based on investigator assessment per RECIST v1.1.

• OS, defined as the interval between the date of randomization until death due

to any cause.

• AEs, assessed in body systems with symptoms, through physical examinations, changes in vital signs and ECGs, and through clinical laboratory blood sample evaluations.

• Impact on study treatment, assessed by treatment interruptions, dose reductions, and withdrawal of study treatment due to AEs.

Study description

Background summary

According to GLOBOCAN epidemiological estimates of incidence and mortality of cancer worldwide, in 2018, there were approximately 835,000 new cases of cancer arising from the lips, oral cavity, oropharynx, hypopharynx, and larynx, the primary tumor sites that generally comprise SCCHN, with the number of deaths in the same year being approximately 431,000. A large percentage of patients with SCCHN primarily present with locally advanced, stage III/IV disease that is initially treated with multimodal therapy including systemic treatment, radiation, and/or surgery. Patients who progress after initial definitive therapy require subsequent treatment for R/M disease; patients who initially present with metastatic disease generally receive the same therapy as those with recurrent disease after definitive treatment.
For patients with recurrent unresectable or metastatic SCCHN, platinum-based chemotherapy has been the standard first-line treatment for the last decade, conferring a median OS of around 10 months. In 2016, the PD-1 inhibitors nivolumab and pembrolizumab were approved by the FDA as second-line treatment for patients who had progressed after platinum-based therapy following positive data demonstrating improved OS of nivolumab/pembrolizumab over investigator's choice systemic therapy in this population. In 2019, based on the results of the KEYNOTE-048 study, the approval of pembrolizumab as first-line therapy has changed the treatment paradigm for patients with R/M SCCHN. Pembrolizumab as monotherapy in patients with PD-L1-positive (CPS-1) tumors, or in combination with chemotherapy irrespective of PD-L1 status, demonstrated superior OS over the EXTREME regimen.
For patients with R/M SCCHN who have progressed on anti-PD-1 therapy, there are limited therapeutic options. Those who progressed on or after PD-1 plus chemotherapy may be treated with single-agent chemotherapy, cetixumab, or other experimental therapies. Those whose disease progresses on PD-1 monotherapy may be eligible for treatment with platinum-based chemotherapy regimens or

single-agent platinum chemotherapy, other single-agent chemotherapies, cetuximab, or other experimental treatments.
While antibodies directed towards the PD-(L)1 axis have revolutionized the treatment of cancer, the majority of patients either do not respond or lose response to these drugs. The mechanisms for failure of anti-PD-1 therapy are poorly understood, but in some cases are likely due to existence of additional checkpoint pathways that either abrogate a response when present or cause loss of response when induced. This study aims to evaluate the clinical and biological effects of blocking additional key checkpoint pathways, LAG-3 and TIM-3, which have been implicated in the lack of/loss of response to PD-1 inhibitors.
Retifanlimab is a humanized, hinge-stabilized, IgG4* monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1-expressing cells, including T cells, and sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.
INCAGN02385 is an Fc-modified IgG1* monoclonal antibody that binds to human LAG-3 with an estimated affinity (KD) of 1.7 nM and was chosen for clinical development based on its selectivity for human LAG-3 with no cross-reactivity to related IgSF proteins. INCAGN02385 functions as a potent LAG-3 antagonist antibody via its ability to inhibit LAG-3 binding to MHC class II, leading to enhanced TCR signaling.
INCAGN02390 is a recombinant, aglycosylated fully human IgG1* monoclonal antibody that binds to the ECD of the TIM-3 receptor. Antagonist TIM-3 antibodies have demonstrated enhanced antitumor activity in several mouse tumor models when combined with blockade of the PD-(L)1 pathway.
This is a randomized, Phase 2 study to evaluate the efficacy and safety of the combination of retifanlimab and INCAGN02385 and the triplet combination of retifanlimab, INCAGN02385, and INCAGN02390 compared with retifanlimab alone in participants with systemic therapy-naive, metastatic or with unresectable, recurrent SCCHN whose tumors express PD-L1.

Study objective

To determine the efficacy of the combinations of retifanlimab + INCAGN02385 (TG2) and retifanlimab + INCAGN02385 + INCAGN02390 (TG3) compared with retifanlimab alone (TG1) in the overall study population.

Study design

Randomized, double-blind, multicenter study evaluating the efficacy and safety of TG2 (retifanlimab + INCAGN02385) and TG3 (retifanlimab + INCAGN02385 + INCAGN02390) compared with TG1 (retifanlimab alone)

Intervention

This is a randomized, double-blind, Phase 2 study to evaluate the efficacy and safety of the combination of retifanlimab plus INCAGN02385(TG2) and retifanlimab plus INCAGN02385 and INCAGN02390 (TG3) compared with retifanlimab alone as first-line treatment in participants with PD-L1-positive and systemic therapy-naive R/M SCCHN.
Study treatment will begin on Day 1. Randomized participants will continue study treatment in 4-week cycles for up to 2 years or until discontinuation criteria are met. The duration for enrollment is expected to be approximately 12 months.
After 30 participants have been randomized and have received treatment for at least 4 weeks (at least 2 doses), an interim analysis of safety will be performed by an independent external DSMB.

- Treatment group 1 (TG1): retifanlimab and placebos for INCAGN02385 and INCAGN02390
o Retifanlimab will be administered by vein once every 4 weeks.
o Placebo (for INCAGN02385) will be administered by vein once every 2 weeks.
o Placebo (for INCAGN02390) will be administered by vein once every 2 weeks.

- Treatment group 2 (TG2): retifanlimab + INCAGN02385 + Placebo for INCAGN02390
o Retifanlimab will be administered by vein once every 4 weeks.
o INCAGN02385 will be administered by vein once every 2 weeks.
o Placebo (for INCAGN02390) will be administered by vein once every 2 weeks.

- Treatment group 3 (TG3): retifanlimab + INCAGN02385 + INCAGN02390
o Retifanlimab will be administered by vein once every 4 weeks.
o INCAGN02385 will be administered by vein once every 2 weeks.
o INCAGN02390 will be administered by vein at once every 2 weeks.

Study burden and risks

Subjects will undergo the procedures and procedures indicated in Table 3 - Table 5 of the study protocol. Subjects have additional blood tests, scans, biopsies and multiple visits to the hospital. These will be more compared to regular care.

Possible known side effects are described in the Investigators Brochure and patient information and can also occur during this study. There is also a risk that unknown side effects occur and there is a chance that the treatment will not be efficacious for the patient. Please refer to IB and patient information on details regarding possible side effects with the study treatments.
Additionally, the study procedures (blood draw, ECG, biopsy, CT/MRI Scan) may also give discomforts, which are described in patient information.

Patients may benefit from treatment with investigational drugs and their disease may improve.

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. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age 18 years or older (or as applicable per local country requirements), inclusive at the time of signing the ICF.
3. Histologically or cytologically confirmed R/M SCCHN that is not amenable to therapy with curative intent (surgery and/or radiation therapy with or without chemotherapy). Participants who refuse potentially curative salvage surgery for recurrent disease are ineligible.
a. Eligible primary tumor locations are oropharynx, oral cavity, hypopharynx,

and larynx.
b.Participants with primary tumors of the nasopharynx, sinonasal cavity, or salivary gland are excluded.
c.Participants must not have received prior systemic therapy for R/M SCCHN.
4. PD-L1 positive tumor status defined by CPS >= 1% per central laboratory determination.
5.For participants with primary oropharyngeal tumors, documentation of HPV p16 status (positive or negative) based on local institutional standard is required. HPV p16 status is not required for other eligible SCCHN primary tumor sites.
6.Participant must have at least 1 measurable tumor lesion per RECIST v1.1.
7.Availability of archival tissue for biomarker analysis from a core or excisional biopsy or willingness to undergo a fresh biopsy.
8.ECOG performance status of 0 or 1.
9.Willingness to avoid pregnancy or fathering children based on the criteria below:
a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 180 days after the last dose of study treatment and must refrain from donating sperm during this period.
b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 180 days after the last dose of study treatment and must refrain from donating oocytes during this period.
c. Female participants not considered to be of childbearing potential

Exclusion criteria

1. Progressive or recurrent disease within 6 months of the last dose of systemic treatment for locally advanced SCCHN.
2. Prior PD-(L)1, LAG-3, or TIM-3 directed therapy, or any other checkpoint inhibitor therapy, for SCCHN (in any disease setting) or any other malignancy.
3. Treatment with anticancer therapies or participation in another interventional clinical study within 21 days before the first administration of study treatment
4. Presence of tumors that invade major blood vessels, as shown unequivocally by imaging, and with active bleeding.
5. Less than 3-month life expectancy (based on investigator judgement).
6. Participant has not recovered to <= Grade 1 or baseline from residual toxicities of prior therapy (with exceptions for anemia not requiring transfusion support, fatigue, or any grade of alopecia).
7. Participant has not recovered adequately from toxicities and/or complications from surgical intervention before starting study treatment.
8. Palliative radiation therapy administered within 1 week before the first

dose of study treatment or radiation therapy in the thoracic region that is > 30 Gy within 6 months before the first dose of study treatment.
9. Known active CNS metastases and/or carcinomatous meningitis. Participants will be excluded if it has been < 4 weeks since radiation therapy was delivered to the CNS.
10. Participants with laboratory values at screening as defined
11. Has known active HBV or HCV, defined as follows (testing must be performed to determine eligibility):
a. Active HBV is defined as a known positive HBsAg result and positive total anti-HBc results. Note: When HBsAg is negative AND HBcAb and/or HBsAb is positive, HBV-DNA should be measured. When HBV-DNA is negative, this participant could be enrolled with close monitoring of HBV activities.
b. Active HCV is defined as a positive HCV antibody result and quantitative HCV-RNA results greater than the lower limits of detection of the assay. Note: Participants positive for HCV antibody will be eligible if they are negative for HCV-RNA. Participants who have had definitive treatment for HCV are permitted if HCV-RNA is undetectable.
12. Participants who are known to be HIV-positive, unless all of the following criteria are met:
a. CD4+ count >= 300/µL.
b. Undetectable viral load.
c. Receiving antiretroviral therapy that is not a potential risk for a drug-drug interaction with the assigned study drug.
13. Any known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of the first dose of study treatment with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year after treatment with curative intent.
14. Has active autoimmune disease requiring systemic immunosuppression with corticosteroids (> 10 mg/day of prednisone or equivalent) or immunosuppressive drugs within 2 years before the first dose of study treatment.
15. Is on chronic systemic steroids (> 10 mg/day of prednisone or equivalent).
16. Active infections requiring systemic antibiotics or antifungal or antiviral treatment (within 14 days before first dose of study treatment).
17. Evidence of interstitial lung disease or history of interstitial lung disease, or active, noninfectious pneumonitis.
18. History of organ transplant, including allogeneic stem cell transplantation.
19. Receiving probiotics as of the first dose of study treatment.
20. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 460 milliseconds is excluded
21. Has had a significant cardiac event within 6 months before the first dose of study treatment
22. Has received a live vaccine within 30 days of planned start of study treatment.
23. Known hypersensitivity to another monoclonal antibody that cannot be

controlled with standard measures
24. Known allergy or hypersensitivity to any component of either retifanlimab, INCAGN02385, or INCAGN02390 study drug formulation (including excipients and additives).
25. Women who are pregnant or breastfeeding.
26. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
27. The following participants are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection, or who are unable to express their consent per article L.1121-8 of the French Public Health Code

Study design

Design

Study phase:	2
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):	15-08-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INCAGN02385
Generic name:	INCAGN02385

Product type:	Medicine
Brand name:	INCAGN0290
Generic name:	INCAGN0290
Product type:	Medicine
Brand name:	Retifanlimab
Generic name:	Retifanlimab

Ethics review

Approved WMO Date:	06-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-03-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2023
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
EudraCT	EUCTR2021-005775-39-NL
CCMO	NL81256.056.22