A Randomized, Open-Label, Phase 3 Study to Evaluate Zimberelimab and Domvanalimab in Combination with Chemotherapy Versus Pembrolizumab With Chemotherapy for the First-Line Treatment of Patients With Metastatic Non-Small Cell Lung Cancer With No Epidermal Growth Factor Receptor or Anaplastic Lymphoma Kinase Genomic Tumor Aberrations

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This study has been transitioned to CTIS with ID 2023-509825-38-00 check the CTIS register for the current data. To compare the effect of ZIM and DOM in combination with chemotherapy relative to PEMBRO in combination with chemotherapy (Group A...

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53866

Source
ToetsingOnline

Brief title
STAR-121

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
Untreated metastatic NSCLC; Untreated Metastatic Non-Small Cell Lung Cancer With No Epidermal Growth Factor Receptor or Anaplastic Lymphoma Kinase Genomic Tumor Aberrations

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc.

Intervention

Keyword: Domvanalimab, Metastatic, NSCLC, Zimberelimab

Outcome measures

Primary outcome

• PFS is defined as the time from the date of randomization until disease

progression (PD) as assessed by BICR according to RECIST v1.1 or death from any

cause, whichever comes first.

• OS is defined as the time from the date of randomization to the date of death

from any cause.

Secondary outcome

• ORR is defined as the proportion of participants who have achieved a complete

response (CR) or partial response (PR) that is confirmed at least 4 weeks later

as assessed by BICR according to RECIST v1.1.

• DOR is defined as the time from the first response (CR or PR), to the first

documented PD as assessed by BICR according to RECIST v1.1 or death from any

cause, whichever comes first.

• Incidence, severity, seriousness, and relatedness of treatment-emergent adverse events (TEAEs) and incidence and severity of clinical laboratory abnormalities.

• Time to first symptom deterioration in NSCLC SAQ total score. NSCLC-SAQ Total Score is the sum all 5 domain scores (cough, pain, dyspnea, fatigue, and appetite).

Study description

Background summary

This is a Phase 3, global, multicenter, randomized, open-label, controlled study to compare the efficacy and safety of zimberelimab and domvanalimab in combination with chemotherapy relative to PEMBRO in combination with chemotherapy in participants with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations who have not received previous systemic therapy for metastatic disease.

Despite the success of targeting the immune system through the use of the anti-PD-(L)1 antibodies, further improvement can still be made to improve current therapeutic options for patients with NSCLC, since many will still progress and die of their cancer.

Given the ongoing need for novel agents and combinations in the treatment of NSCLC, the promising activity of dual PD-(L)1 and TIGIT inhibition in this disease and the manageable toxicity profile from the combination zimberelimab and domvanalimab looks a promising new treatment for patients with metastatic NSCLC.

Zimberelimab is a fully human IgG4 monoclonal antibody targeting human PD-1. PD-1 is a type I transmembrane protein that is part of the immunoglobulin gene superfamily and the CD28 family of cell surface receptors. PD-L1 is abundantly expressed on a variety of human tumors, and its expression correlates with reduced patient survival in esophageal, pancreatic, and other types of cancers. Therefore, the PD-(L)1 pathway is
an important target for tumor immunotherapy. Activation of the PD-(L)1 signaling pathway results in a decrease in tumor-infiltrating lymphocytes, a

decrease in T-cell proliferation, and an increase in immune evasion by cancerous cells. Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1, and the effect is additive when the interaction of PD-1 with PD-L2 is also blocked.

Domvanalimab (DOM) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets TIGIT, which functions as an immune checkpoint. As a result of blocking TIGIT, DOM reverses the inhibitory effects of CD155-expressing antigen-presenting cells on the activation of T-cells and potentiates immune responses

Study objective

This study has been transitioned to CTIS with ID 2023-509825-38-00 check the CTIS register for the current data.

To compare the effect of ZIM and DOM in combination with chemotherapy relative to PEMBRO in combination with chemotherapy (Group A versus Group B) on:
• Progression-free survival (PFS) according to RECIST v1.1 as assessed by blinded independent central review (BICR)
• Overall survival (OS)

Secondary Objectives:
• To compare the effect of ZIM and DOM in combination with chemotherapy relative to PEMBRO in combination with chemotherapy (Group A vs Group B) on objective response rate (ORR) as assessed by BICR according to RECIST v1.1
• To evaluate duration of response (DOR) as assessed by BICR according to the RECIST v1.1
• To evaluate the safety and tolerability of ZIM and DOM in combination with chemotherapy versus PEMBRO in combination with chemotherapy (Group A vs Group B)
• To compare the effect of ZIM and DOM in combination with chemotherapy relative to PEMBRO in combination with chemotherapy (Group A vs Group B) on health-related quality of life (QOL) using non-small cell lung cancer Symptom Assessment Questionnaire (NSCLC-SAQ).

Study design

Participant involvement will include screening, treatment, and follow-up. Screening will last no longer than 28 days. Approximately 720 participants will be randomized in a 4:4:1 ratio to Groups A, B, and C, respectively, as outlined below.

Randomization will be stratified by baseline PD-L1 status (tumor proportion score [TPS] < 50% vs >= 50%), predominant histology (squamous vs non-squamous), and geographic region of enrollment (East Asia vs non East Asia).

ZIM, DOM, or PEMBRO will be administered until disease progression (as determined by BICR per RECIST v1.1), intolerable toxicities, or for a maximum of 35 doses.

The dual primary endpoints of the study are PFS as assessed by BICR and OS. Key secondary endpoints are ORR as assessed by BICR and time to first symptom deterioration in NSCLC SAQ total score.

Adverse event monitoring will be ongoing throughout the study and AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v 5.0).

The follow-up period will begin at the time of completion of the end of treatment (EOT) visit. All participants will be followed for survival until death, lost to follow-up, withdrawal of consent, or study termination by Sponsor.

An external Data Monitoring Committee (eDMC) will evaluate the safety, tolerability, and efficacy of the study intervention on an ongoing basis as outlined in the DMC charter.

To detect potentially early safety signals, the first eDMC review is planned after a safety run-in period, defined as approximately 20 participants randomized in Group A completing at least 1 full study cycle.

Intervention

• Group A (ZIM+DOM + chemotherapy):
Approximately 320 participants will be randomized to Group A to receive ZIM 360 mg by IV infusion plus DOM 1200 mg by IV infusion with platinum doublet chemotherapy Q3W on Day 1 of each 21-day cycle.
• Group B (PEMBRO + chemotherapy).
Approximately 320 participants will be randomized to Group B to receive PEMBRO 200 mg by IV infusion with platinum doublet chemotherapy Q3W on Day 1 of each 21-day cycle.
• Group C (ZIM + chemotherapy).
Approximately 80 participants will be randomized to Group C to receive ZIM 360 mg by IV infusion with platinum doublet chemotherapy Q3W on Day 1 of each 21-day cycle.

The chemotherapy regimen will be selected by the investigator based on histology and administered during the first 4 cycles as follows.
For squamous histology:
• Carboplatin AUC 6 (maximum dose 900 mg) IV Q3W + paclitaxel 200 mg/m2 IV Q3W
or
• Carboplatin AUC 6 (maximum dose 900 mg) IV Q3W + nab-paclitaxel 100 mg/m2 D1, D8 and D15 of each 21 days cycle.

For nonsquamous histology:
• Carboplatin AUC 5 (maximum dose 750 mg) IV Q3W + pemetrexed 500 mg/m2 IV Q3W, or
• Cisplatin 75 mg/m2 IV Q3W + pemetrexed 500 mg/m2 IV Q3W.
After the completion of the first 4 cycles, participants with nonsquamous histology may continue with maintenance pemetrexed 500 mg/m2 IV Q3W until disease progression or intolerable toxicities.

Study burden and risks

Participation does not mean that patients will suffer less their metastatic NSCLC. But if they take part, they will help investigators to get more insight into the treatment of metastatic NSCLC.

Participants may experience side effects of study treatment. Some side effects from study treatment may prevent patients from being eligible to receive certain types of treatment after this study. There may also be risks associated with infusion reactions and allergic reactions.

Biopsy sampling may cause pain, bruising, bleeding, swelling, scarring or very rarely, infection. For CT scans and PET scans, X-rays are used. There may be some discomfort from study procedures like blood sampling and 12-lead ECG. Some questionnaires may make patients feel uncomfortable.

Study participation will take time and patients have to comply with the study agreements:
• They will receive the study drug and undergo the tests and examinations as explained by the site staff
• They will not take part in any other medical research during this study.
• They need to go to every appointment.
• They need to carry the participant card of the study with them.
• They are not allowed to take certain medications while in the treatment phase of this study.
• They need to prevent a pregnancy
• They should contact the study doctor if:
o They want to start taking other medication including homoeopathic remedies, natural remedies, vitamins or over-the-counter medicines.
o They are hospitalized or get treatment in a hospital.
o They suddenly experience any health problems.
o They no longer want to take part in the study.
o Their telephone number, address or email address changes.

Contacts

Public
Gilead Sciences

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Members of all genders, races, and ethnic groups are eligible for this study.
Participants must meet all the following eligibility criteria to be eligible for participation in this study (no waivers for participant eligibility will be permitted).
1) Participants assigned male at birth and participants assigned female at birth, 18 years of age or older, able to understand and give written informed consent.
2) Life expectancy >= 3 months.
3) Pathologically documented NSCLC that meets both criteria below:
a) Have documented evidence of Stage IV NSCLC disease at the time of enrollment (based on AJCC, Eighth Edition).
b) Have documented negative test results for EGFR and ALK mutations.
Note: Tumor testing for EGFR or ALK mutations is required for participants with nonsquamous NSLC tumor histology if status is unknown (Section 6.3.9).
4) Have no actionable genomic alterations such as ROS proto-oncogene 1,

neurotrophic tyrosine receptor kinase, proto-oncogene B-raf, RET mutations, or other driver oncogenes with approved frontline therapies. Testing of actionable genomic alterations required by local regulations will be performed locally.
5) Provide adequate tumor tissue from locations not radiated prior to biopsy to evaluate PD L1 expression prior to randomization. Bone biopsies, cytology, and fine needle aspirates are not suitable tissues. If no tissue is available, a new biopsy will need to be obtained prior to enrollment in the study.
6) Have not received prior systemic treatment for metastatic NSCLC. Participants who received chemotherapy for nonmetastatic disease are eligible if the therapy was completed at least 12 months prior to the start of study treatment.
7) Measurable disease as per RECIST v1.1 criteria by investigator assessment.
8) ECOG performance status score of 0 or 1.
9) Organ function requirement.
10) Participants assigned male at birth and participants assigned female at birth of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception from screening visit until 6 months after the last dose of chemotherapy and 120 days after the last dose of DOM, ZIM, or PEMBRO (or longer according to local regulatory requirements), as described in Appendix 4 of the study protocol.
11) Willing and able to comply with the requirements and restrictions in this protocol.

Exclusion criteria

Participants who meet any of the following exclusion criteria at screening/Day -1 are not eligible to be enrolled in this study (no waivers for patient eligibility will be offered or permitted):
1) Have mixed SCLC and NSCLC histology.
2) Positive serum pregnancy test or participants who are breastfeeding or have plans to breastfeed during the study period and for the required duration of contraception use after the last dose of study drug.
3) Received prior treatment with any anti-PD-1, anti-PD-L1, or any other antibody targeting an immune checkpoint. Participants who received PD-(L)1 inhibitors as a part of treatment for early or locally advanced stage NSCLC are not eligible.
4) Known hypersensitivity to the study drug, its metabolites, or formulation excipient.
5) Requirement for ongoing therapy with or prior use of any prohibited medications listed in Section 5.6.3.
6) Have an active second malignancy or have had an active second malignancy within 3 years prior to enrollment. Participants with a history of malignancy that has been completely treated, with no evidence of active cancer for at least 3 years prior to enrollment, or with surgically cured tumors with low risk of recurrence (eg, nonmelanoma skin cancer, histologically confirmed

complete excision of carcinoma in situ, or similar) are allowed to enroll.
7) Have an active autoimmune disease that required systemic treatment in past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
8) Are receiving chronic systemic steroids (> 10 mg/day prednisone equivalent). Use of topical, inhalational, intra nasal, and intra ocular steroids will be permitted.
9) Have significant third-space fluid retention (eg, ascites or pleural effusion) and is not amenable for required repeated drainage
10) Have untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 weeks prior to enrollment and all neurologic symptoms have returned to baseline, have no evidence of new or enlarging brain metastases and are not requiring use of steroids for at least 14 days prior to the start of study treatment. All participants with carcinomatous meningitis are excluded regardless of clinical stability.
11) Met any of the following criteria for cardiac disease:
a) Myocardial infarction or unstable angina pectoris within 6 months of enrollment.
b) History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication).
c) New York Heart Association Class III or greater congestive heart failure or known left ventricular ejection fraction less than 40%.
12) Active chronic inflammatory bowel disease (ulcerative colitis, Crohn*s disease) or gastrointestinal perforation within 6 months of enrollment.
13) Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
14) Has received radiotherapy within 2 weeks prior to first dose of study intervention or radiotherapy to the lung that is > 30 Gy within 6 months of the first study treatment. Participants must have recovered to Grade 1 or lower from all radiation-related toxicities, not requiring corticosteroids, and have not had radiation pneumonitis.
15) Has had an allogenic tissue/solid organ transplant.
16) Have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu and COVID-19 vaccines that do not contain live virus are permitted.
17) Have active infection requiring treatment (eg, antibiotics).
18) Have known history of HIV-1 or 2 with uncontrolled viral load (ie, >= 200 copies/mL or CD4+ T-cell count < 350 cells/µL), or taking medications that may interfere with metabolism of study drugs. No HIV testing is required unless mandated by local health authority.
19) Have known acute hepatitis B, known chronic hepatitis B infection with

active untreated disease, or known active hepatitis C infection. In participants with a history of hepatitis B virus of hepatitis C virus, participants with detectable viral loads will be excluded. No hepatitis testing is required unless mandated by local health authority.
20) Have other concurrent medical or psychiatric conditions that, in the investigator*s opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-02-2023
Enrollment:	20
Type:	Anticipated

Medical products/devices used

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

Product type:	Medicine
Brand name:	Zimberelimab
Generic name:	Zimberelimab

Ethics review

Approved WMO Date:	26-09-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	22-02-2024
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	CTIS2023-509825-38-00
EudraCT	EUCTR2022-000578-25-NL
ClinicalTrials.gov	NCT05502237
CCMO	NL81915.056.22