A Randomized, Open-Label Phase 2/3 Study Comparing Cobolimab + Dostarlimab + Docetaxel to Dostarlimab + Docetaxel to Docetaxel Alone In Participants with Advanced Nonsmall Cell Lung Cancer Who Have Progressed on Prior Anti-PD-(L)1 Therapy and Chemotherapy (COSTAR Lung)

Published: 12-10-2021
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This study has been transitioned to CTIS with ID 2023-507475-21-00 check the CTIS register for the current data. Primary objective:To evaluate the efficacy of cobolimab + dostarlimab + docetaxel relative to docetaxel alone in participants with…

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

Summary

ID

NL-OMON56356

Source
ToetsingOnline

Brief title
213410 - COSTAR Lung

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Advanced Nonsmall Cell Lung Cancer; NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline BV

Intervention

Keyword: Cobolimab, Dostarlimab, Lung Cancer, Non-small cell lung cancer (NSCLC)

Outcome measures

Primary outcome

Overall Survival (OS) defined as survival from the date of randomization to

the date of death by any cause

Secondary outcome

Secondary:

OS defined as survival from the date of randomization to the date of death by

any cause

Confirmed ORR defined as the proportion of participants who have achieved

confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator

assessment

• PFS defined as the length of time until disease progression, from the time of

randomization to the earliest date of assessment of disease progression based

on RECIST v1.1 by Investigator assessment or death by any cause

• DOR defined as the time from first documented response (CR/PR) until the time

of first documentation of disease progression based on RECIST v 1.1 by

Investigator assessment

or death, whichever occurs first

• TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13

• Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains

The incidence of TEAEs, SAEs, irAEs, TEAEs leading to death, and AEs leading to discontinuation occurring while participants are on treatment or up to 90 days after the last dose of study treatment. Clinical laboratory parameters (hematology, chemistry, thyroid function, and urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications will be collected.

Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using iRECIST based on Investigator assessment

• PFS defined as the length of time until confirmed disease progression from the time of randomization to the earliest date of iRECIST iCPD by Investigator assessment or death by any cause. Additional PK parameters of cobolimab and dostarlimab will be determined, if appropriate.

Cobolimab and dostarlimab ADAs (including NAbs to dostarlimab/cobolimab), with associated drug concentrations. Number and percentage of participants who develop detectable ADAs and NAbs.

Exploratory:

Blood-based biomarkers may include, but are not limited to, serum cytokines, circulating immune cells, and ctDNA.

Tumor-based biomarkers will assess baseline expression of TIM-3 and PD-L1 and correlate with ORR and changes in immune cells, such as CD8 T cells, following treatment, in paired biopsies. Tumor-based biomarkers, where tissue is available, may also include gene expression profiling for immune-related and tumor-related proteins and assessment of tumor genome for mutations and/or genomic alterations.

Change from baseline in the NSCLC-SAQ

• Frequency and severity of patient-reported AEs based on the PRO-CTCAE and the FACT-GP5

• Change from baseline in overall symptom severity on the PGIS/PGIC

• Change from baseline as assessed by the EQ-5D-3L

Number and duration of non protocol healthcare encounters such as provider visits, emergency room visits, hospitalizations, medications, tests, and procedures

Study description

Background summary

In this study, cobolimab in combination with dostarlimab and docetaxel (taxane chemotherapy) is being investigated to treat advanced NSCLC, as this patient population represents a high unmet medical need. This study and select cohorts of the ongoing Phase 1 Study 4020-01-001 (AMBER; GSK Study 213348) and the ongoing Phase 1 Study 204691 (INDUCE-1) represent the only ongoing studies of cobolimab in NSCLC by the Sponsor at this time. In the AMBER expansion cohorts

B2 (dostarlimab 500 mg + cobolimab 100 mg), B3 (dostarlimab 500 mg + cobolimab 300 mg) and B4 (dostarlimab 500 mg + cobolimab 900 mg), eligibility requirements include histologically proven advanced or metastatic NSCLC that progressed following treatment with an anti-PD-(L)1 antibody and no limit on prior lines of anticancer therapy for advanced or metastatic disease.
Eighty-four participants were enrolled in Cohorts B2, B3, and B4 as of 01 December 2019.
There was a total of 10 participants with a partial response (PR) across all 3 cohorts, 6 of which
were confirmed by RECIST v1.1. Signs of combination activity were greater in Cohort B3
(300 mg cobolimab) compared to Cohort B2 (100 mg cobolimab) or Cohort B4 (900 mg cobolimab); there were 4 confirmed partial responses (cPRs) by RECIST v1.1 in Cohort B3
compared to 1 cPR each in Cohorts B2 and B4. Across all cohorts, durable responses and stable
disease (SD) were observed following treatment with cobolimab + dostarlimab, with
5 participants beyond a year of treatment. As of the data cut, 3 participants remained on
treatment.

Lung cancer is the most common cause of cancer mortality globally and the second most
common cancer in both men and women. Most recent lung and bronchus cancer incidence rates in the US from the Surveillance, Epidemiology, and End Results program estimate an incidence rate of 54.9 per 100,000 from 2016 data. The 2 major forms of lung cancer are NSCLC and small cell lung cancer. NSCLC is a heterogeneous disease that consists of adenocarcinoma, large cell carcinoma, and squamous cell carcinoma, and comprises approximately 84% of all lung cancers. The average age of diagnosis is approximately 70 years old. Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage, has poor prognosis, and is the leading cause of cancer deaths worldwide. In the US, the 5 year OS rate of all stages of NSCLC is approximately 19%, with advanced patients (Stage IIIB/IV) having a 5 year OS rate of <5%.

PD-(L)1 represents an immune inhibitory mechanism employed by tumors to subvert the
immune response and disruption of this axis enhanced the lysis of tumor cells by T cells.
Multiple clinical studies in tumors such as melanoma, renal cell carcinoma, and NSCLC have
yielded positive data using anti-PD-(L)1-targeted therapies.

The introduction of anti-PD-(L)1 therapy in the first-line setting has improved outcomes for

patients with NSCLC without an aberration in a driver oncogene. However, many patients with NSCLC do not respond to first-line anti-PD-(L)1 therapy (45% ORR in pembrolizumab monotherapy patients with tumor proportion score [TPS] >=50%; 48% ORR in pembrolizumab + chemotherapy patients with nonsquamous NSCLC), and most of those who do respond will typically progress within a year. For patients who progress on an anti-PD-(L)1 antibody and platinum-based chemotherapy, there are no drugs approved, nor is there an established standard of care in this setting. Drugs approved for second-line treatment of NSCLC following a platinum-based regimen (docetaxel, ramucirumab in combination with docetaxel, or pemetrexed [nonsquamous NSCLC only]) provide limited benefits with response rates ranging from 5.5% to 23%, progression-free survival (PFS) of 3 to 4.5 months

Study objective

This study has been transitioned to CTIS with ID 2023-507475-21-00 check the CTIS register for the current data.

Primary objective:
To evaluate the efficacy of cobolimab + dostarlimab + docetaxel relative to docetaxel alone in participants with advanced NSCLC who have progressed on prior anti-PD-(L)1 therapy and
Chemotherapy.
To evaluate the efficacy of dostarlimab + docetaxel relative to docetaxel alone in participants with advanced NSCLC who have progressed on prior anti-PD-(L)1 therapy and chemotherapy

Secondary Objectives:
To evaluate the efficacy of cobolimab + dostarlimab + docetaxel relative to dostarlimab + docetaxel
To evaluate additional measures of clinical benefit for cobolimab + dostarlimab +docetaxel relative to docetaxel alone
To evaluate additional measures of clinical benefit for dostarlimab + docetaxel relative to docetaxel alone
To evaluate additional measures of clinical benefit for cobolimab + dostarlimab + docetaxel relative to dostarlimab + docetaxel
To evaluate the safety and tolerability of cobolimab + dostarlimab + docetaxel and dostarlimab + docetaxel vs docetaxel alone

Exploratory:
To evaluate confirmed ORR and PFS by iRECIST
To characterize the PK of cobolimab, dostarlimab, and docetaxel
To assess the immunogenicity of cobolimab and dostarlimab at defined time points
To assess biomarkers related to studytreatment in all treatment arms
To assess PROs for treatment efficacy and tolerability in all treatment arms using
targeted PRO instruments

To evaluate the healthcare resource utilization in all treatment arms

Study design

A multicenter, parallel-group treatment, Phase 2/3 open-label, 3-arm study comparing
cobolimab + dostarlimab + docetaxel to dostarlimab + docetaxel to docetaxel alone for efficacy in male and female participants aged 18 years and older with advanced NSCLC who have progressed on prior anti-PD-(L)1 therapy and chemotherapy. Crossover between treatment arms will not be allowed in this study.
The 3 treatment arms will be as follows:
1. Arm A: Cobolimab + dostarlimab + docetaxel
2. Arm B: Dostarlimab + docetaxel
3. Arm C: Docetaxel

Intervention

Participants will be randomized 2:2:1 into the 3 study treatment arms (groups) and dosed with
the previously listed treatments as follows, following any visit-mandated assessments:

•Arm A: Cobolimab + dostarlimab + docetaxel
* 300 mg cobolimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered first)
* 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered second)
* 75 mg/m2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered third/last)

Arm B: Dostarlimab + docetaxel
* 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered first)
* 75 mg/m2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered second/last)

Arm C: Docetaxel
* 75 mg/m2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles

Study burden and risks

Cobolimab:
Very common side effects:
• Skin problems may include rash and itching (Immune-mediated Skin Reactions)

• Lung problems may include symptoms like shortness of breath, chest pain, new or worse cough (Immune-mediated Pneumonitis)
• Hormone gland problems especially the thyroid, pituitary and adrenal glands (Immune-mediated Endocrinopathy)
There are rare but serious immune-related adverse events which have been seen when cobolimab was used in combination with other medicines:
• Tingling, numbness, loss of sensation, or a burning sensation in the extremities (peripheral motor neuropathy)

Dostarlimab:
These side effects are considered (very) common in patients who took dostarlimab:
• Anaemia
• Hypothyroidism
• Nausea
• Vomiting
• Diarrhoea
• Pruritus
• Rash
• Pyrexia
• Increased levels of substances in the blood produced by the liver which may be a sign of liver injury (AST increased; ALT increased)
• Adrenal insufficiency
• Hyperthyroidism
• Pneumonitis
• Pancreatitis
• Colitis
• Myalgia
• Chills
• Inflammation of the liver (hepatitis)

These side effects are considered uncommon in patients who took dostarlimab:
Autoimmune haemolytic anaemia
• Thyroiditis
• Hypophysitis
• Diabetic Ketoacidosis
• Type 1 Diabetes Mellitus
• encephalitis
• Uveitis
• myocarditis
• Polymyalgia rheumatica
• Nephritis
• Myasthenia gravis
. Immune Mediated Arthritis (joint pain).
• Gastritis
• Esophagitis

• Enteritis
• Vasculitis gastrointestinal
• Myositis
• Systemic Inflammatory Response Syndrome

These are rare but serious immune-related adverse events which have been seen when dostarlimab was used alone or in combination with other medicines:

• Hemophagocytic Lymphohistiocytosis
• Guillain-Barré syndroom
• peripheral motor neuropathy
• eosinophilic fasciitis

Other risks called class effects that have been seen in patients receiving other drugs that work like dostarlimab. These effects could also occur with dostarlimab or cobolimab. The most significant class related side effects are *immune-related*, side effects caused by increased activity of the immune system, which can affect multiple organs of the body including gastrointestinal tract, endocrine system, cardiovascular system, lungs, liver, skin, musculoskeletal system and nervous system. These other immune related side effects may be life threatening or fatal.

Infusion-related reactions which can occur within 24 hours after receiving an intravenous infusion, or which can be delayed for up to about 2 weeks. Infusion-related reactions may include dizziness or fainting, flushing, rash, fever, chills, shortness of breath, increased or decreased blood pressure, increased heart rate, swelling of the lips, tongue or face, feeling sick to your stomach, back pain or pain at the site of infusion. Although infusion-related reactions are usually reversible, they can be severe or life threatening (Infusion related reactions).

Risks associated with study procedures/tests are listed below:
• Blood draws: When giving blood, the patient may feel faint or experience mild pain, bruising, irritation or redness from the needle.
• CT scans: The cumulative radiation exposure from these tests is considered small and is not likely to adverse ly affect the patient or the patient*s disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to the patients risk of injury or disease.
• MRI: Some people cannot have an MRI because they have some type of metal in their body. Some patients are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while scanning, ear plugs or specially designed headphones will be used to reduce the noise.

Considering the measures taken to minimize risk to study participants, the potential risks identified in association with cobolimab in combination with dostarlimab and docetaxel are justified by the anticipated benefits that may be

afforded to participants with NSCLC who progressed post-treatment with an anti-PD-(L)1 antibody and platinum-based chemotherapy.

The lack of benefit of current treatment options to patients with NSCLC may be due to additional immunosuppressive mechanisms, such as those mediated by TIM-3. Early combination treatment enables the assessment of TIM-3 and PD-1 blockade to address de novo resistance to anti-PD-1 blockade while preventing one of the mechanisms that may result in resistance to anti-PD-1 monotherapy.

To summarize, the possibility of improving the clinical benefit of immunotherapies for patients with advanced/metastatic NSCLC who have limited treatment options presents an opportunity to improve clinical outcomes. Given the clinical activity of antibodies targeting the PD-1 axis in a broad range of solid tumors, patients with NSCLC are expected to derive clinical benefit with the addition of TIM-3 blockade and taxane chemotherapy.

Contacts

Public
GlaxoSmithKline

Van Asch van Wijckstraat 55H
Amersfoort 3811 LP
NL
Scientific
GlaxoSmithKline

Van Asch van Wijckstraat 55H
Amersfoort 3811 LP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Participant is >=18 years old
2. Participant has histologically or cytologically proven advanced or metastatic NSCLC,
and only squamous or nonsquamous cell carcinoma.
3. Participant has received no more than 2 prior lines of therapy for advanced or metastatic disease, which must only include a platinum-based doublet chemotherapy regimen and an anti-PD-(L)1 antibody. Participants previously treated with targeted therapies, including angiogenesis inhibitors are not eligible.
a. Two components of treatment must have been received in the same line or as separate
lines of therapy as follows:
• A maximum of 1 line of therapy containing a platinum-based chemotherapy in the metastatic setting
and
• A maximum of 1 line of therapy containing an anti-PD-(L)1 antibody
4. Participant has measurable disease, that is, presenting with at least 1 measurable lesion
per RECIST v1.1
5. Participant has documented radiological disease progression on prior platinum-based
chemotherapy and on prior anti-PD-(L)1 therapy according to RECIST v1.1.
6. Participant agrees to submit an archival FFPE tumor tissue specimen that was collected
on or after diagnosis of metastatic disease from location(s) not irradiated prior to biopsy.
7. Participant has documented PD-L1 status by the 22C3 pharmDx assay (Agilent/Dako), the SP263 assay (Roche) or a LDT with published evidence of concordance with the 22C3 pharmDx assay. If a prior PD-L1 result by this testing methods is not available at the time of Screening, the participant must submit archival or fresh tumor tissue to be tested locally using 1 of these testing methods, or, if not available, centrally, using the 22C3 pharmDx assay.
8. Participant has an ECOG performance status score of 0 or 1.
9. Participant has a life expectancy of at least 3 months and is anticipated to be able to complete 4 cycles of docetaxel treatment.
10. Participant has adequate organ function as defined in the protocol.
11. Participant has recovered to Grade <=1 from any prior treatment-related toxicities at the time of randomization. A participant with Grade 2 alopecia is an exception to this criterion and may qualify for this study.
12. Contraceptive use by male and female participants should be consistent with local regulations regarding the methods of contraception for those

participating in clinical
studies.

Exclusion criteria

1. Participant has been previously treated with an anti-PD-(L)1 or anti-PD-L2 agent that resulted in permanent discontinuation due to an AE.
2. Participant has been previously treated with an anti-TIM-3 or anti-CTLA-4 agent or docetaxel.
3. Participant has a documented sensitizing EGFR, ALK, or ROS-1 mutation. Participants
whose tumors have not been tested for these driver mutations and therefore who have unknown driver mutation status are not eligible. Participants with squamous histology do not need to be tested for these driver mutations.
4. Participant had radiological or clinical disease progression <=8 weeks after initiation of prior
anti-PD-1 or anti-PD-L1 antibody. The clinical disease progression should have been confirmed by a subsequent radiological scan.
5. Participant has received radiation to the lung that is >30 Gy within 6 months prior to the
first dose of study treatment.
6. Participant has completed palliative radiotherapy within 7 days prior to the first dose of
study treatment.
7. Participant is ineligible if any of the following hepatic characteristics are present:
a. Alanine aminotransferase (ALT >2.5×ULN
b. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN) concomitant with alkaline phosphatase (ALP) >2.5×ULN
c. Bilirubin >1×ULN
d. Current active liver or biliary disease
8. Participant has a corrected QT interval (QTc) >450 msec
9. Participant has had major surgery within 3 weeks prior to the first dose of study treatment or has not adequately recovered from any AEs (Grade <=1) and/or complications from any major surgery.
10. Participant has an additional malignancy or a history of prior malignancy, with the exception of adequately treated basal or squamous skin cancer, cervical carcinoma in situ, or bladder carcinoma in situ without evidence of disease, or had a malignancy treated with curative intent and with no evidence of disease recurrence for 5 years since the initiation of that therapy.
11. Participant has known new or progressive brain metastases and/or leptomeningeal
metastases.
12. Participant has tested positive for the following at screening or within 3

months before the first dose of the study treatment:
a. presence of hepatitis B surface antigen
b. presence hepatitis C antibody in the absence of an RNA test voor hepatitis C virus.
13. Participant has an active infection requiring systemic therapy within 1 week prior to the anticipated first dose of study treatment.
14. Participant has known HIV (positive for HIV-1 or HIV-2 antibodies).
15. Participant has active autoimmune disease that required systemic treatment in the past 2 years, is immunocompromised in the opinion of the Investigator, or is receiving systemic immunosuppressive treatment.
17. Participant has symptomatic ascites or pleural effusion.
18. Participant has current interstitial lung disease, current pneumonitis, or a history of pneumonitis that required the use of oral or IV glucocorticoids to assist with management.
19. Participant has a history or current evidence of any medical condition, therapy, or laboratory abnormality that might confound the study results, interfere with participation for the full duration of the study treatment, or indicate it is not in the best interest of the participant to participate.
20. Participant has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal
obstruction, or peritoneal carcinomatosis.
21. Participant has pre-existing peripheral neuropathy that is Grade >=2 (NCI-CTCAE) v5.0 criteria.
22. Participant has received a live vaccine within 30 days of the first dose of study treatment.
23. Participant has a sensitivity to any of the study treatments, or components thereof, or a
history of drug or other allergy.
24. Participant is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs
(NSAIDs).
25. Participant has received prior anticancer therapy within 21 days, or less than 5 times the half-life of the most recent therapy prior to study Day 1, whichever is shorter.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-02-2022
Enrollment:	23
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	cobolimab
Generic name:	cobolimab
Product type:	Medicine
Brand name:	dostarlimab
Generic name:	Jemperli
Product type:	Medicine
Brand name:	Taxotare
Generic name:	docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2021
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	01-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2023
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
Other	213410/COSTAR
EU-CTR	CTIS2023-507475-21-00
EudraCT	EUCTR2020-003433-37-NL
CCMO	NL78624.056.21