A Phase 2 Randomized Study of Relatlimab plus Nivolumab in Combination with Chemotherapy vs. Nivolumab in Combination with Chemotherapy as First Line Treatment for Participants with Stage IV or Recurrent Non-small Cell Lung Cancer (NSCLC)

Published: 13-01-2021
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This study has been transitioned to CTIS with ID 2023-508372-10-00 check the CTIS register for the current data. Part 1: dose safety confirmationPrimary: To evaluate the proportion of participants with TRAEs leading to discontinuation within 12...

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

Summary

ID

NL-OMON56032

Source
ToetsingOnline

Brief title
CA224-104 study in participants with Stage IV or Recurrent NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: industry

Intervention

Keyword: Nivolumab, Non-small Cell Lung Cancer (NSCLC), Phase 2, Relatlimab

Outcome measures

Primary outcome

Part 1.

- TRAEs leading to discontinuation within 12 weeks after the first dose

Part 2:

- ORR per RECIST v1.1 by BICR

Secondary outcome

Part 1:

- Incidence of TRAEs leading to discontinuation, AEs, SAEs, and select AEs

Part 2:

- DoR per RECIST v1.1 by BICR, including DoR at 6, 12 and 18 months

- ORR and PFS per RECIST v1.1 by BICR

- Incidence of AEs, SAEs, TRAEs, IMAEs and select AEs

Study description

Background summary

NSCLC remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths.Until recently, the treatment of participants with advanced NSCLC whose tumors did not have a targetable genetic alteration was cytotoxic chemotherapy alone. In spite of treatment, participants with metastatic NSCLC treated with PDCT had a median survival of approximately 10 months and a 5-year survival rate of less than 5%.

Nivolumab, relatlimab, and platinum doublet chemotherapy (PDCT) each have non-overlapping
anti-cancer mechanisms and may have synergistic and/or additive activity as combination therapy, with few overlapping toxicities. Lymphocyte-activation gene 3 (LAG-3) is often expressed on chronically exhausted T-cells and is frequently co-expressed with programmed death-ligand 1
(PD-L1) on tolerized tumor-infiltrating lymphocytes (TILs) across tumor types. The rationale for combining a LAG-3 inhibitor and an anti-programmed cell death protein 1 (PD-1)/PD-L1 agent originates from evidence suggesting that LAG-3 has a potential role in T-regulatory cells
suppression and anti-PD-1 resistance. The current standard of care, anti-PD-(L)1 (± anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] antibody) in combination with PDCT has demonstrated significant improvement in overall survival (OS) as well as progression-free survival
(PFS) in participants with previously untreated metastatic non-small cell lung cancer (NSCLC).
There are several candidate biomarkers which may select participants who will benefit from the addition of relatlimab to nivolumab plus chemotherapy. Multiple clinical trials have established the correlation between PD-L1 expression and increased response to PD-1 and PD-L1 immune checkpoint inhibition. Data from CA224020 demonstrated preliminary evidence that participants with LAG-3 expression are more likely to respond to treatment with relatlimab in combination with nivolumab. Recently, fibrinogen-like protein 1 (FGL-1) was identified as a new ligand for
LAG-3 that is responsible for its T-cell inhibitory function and potentially a new mechanism for immuno-evasion. Therefore, FGL-1 may be a novel biomarker to predict outcomes of anti-PD-1 and anti-LAG-3 tumor therapies.
The benefit of the relatlimab plus nivolumab combination continues to be explored in several types of metastatic malignancies. The combination therapy of relatlimab plus nivolumab has had an acceptable safety profile at all dose levels tested up to 1440 mg of relatlimab plus 480 mg of
nivolumab given every 4 weeks with no maximum tolerated dose reached. The combination of nivolumab 360 mg every 3 weeks (Q3W) plus relatlimab 720 mg or 360 mg Q3W and 4 cycles of PDCT is expected to have a synergistic effect in the

first line (1L) NSCLC population based on
the clinical activity shown by the 2 individual combinations (nivolumab plus relatlimab and nivolumab plus PDCT) and their distinct but complementary mechanisms of action.

The aim of this randomized Phase 2 study is to confirm the safety profile of nivolumab plus relatlimab in combination with PDCT and to determine if nivolumab plus relatlimab in combination with PDCT improves ORR when compared to nivolumab plus PDCT in participants with previously untreated Stage IV or recurrent NSCLC.

Study objective

This study has been transitioned to CTIS with ID 2023-508372-10-00 check the CTIS register for the current data.

Part 1: dose safety confirmation

Primary:
To evaluate the proportion of participants with TRAEs leading to discontinuation within 12 weeks after the first dose of nivolumab plus 2 different dose levels of relatlimab (360 mg and 720 mg) in combination with PDCT in dose safety evaluable participants with histologically confirmed 1L Stage IV or recurrent NSCLC

Secondary:
To evaluate the safety and tolerability of nivolumab plus 2 different doses of relatlimab (360 mg and 720 mg) in combination with PDCT in all participants with histologically confirmed 1L Stage IV or recurrent NSCLC that were treated during the dose safety confirmation period

Part 2:

Primary:
To evaluate ORR nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC

Secondary:
- To evaluate the PFS of nivolumab plus relatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC.
- To evaluate the duration of response (DoR) of nivolumab plusrelatlimab in combination with PDCT relative to nivolumab in combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC
-To evaluate ORR and PFS of nivolumab plus relatlimab in combination with PDCT

relative to nivolumab in
combination with PDCT in participants with histologically confirmed 1L Stage IV or recurrent NSCLC, in subgroups defined by PD-L1 expression, LAG-3 expression, FG-L1 expression
- To evaluate the safety and tolerability of nivolumab plus relatlimab in combination with PDCT in histologically confirmed 1L Stage IV or recurrent NSCLC.

Study design

This multi-center, randomized trial will evaluate the efficacy and safety of the combination of nivolumab plus relatlimab and PDCT vs nivolumab and PDCT in adults with untreated Stage IV or recurrent NSCLC. The study will be carried out in 2 parts: Part 1, a site-and-subject blind dose
safety confirmation and Part 2, a open-label randomized, controlled trial.

Part 1 - Dose safety confirmation (n * up to 120): Site-and-subject blinded, randomized dose safety confirmation. Eligible participants will be randomized 1:1 to Arms A or B to evaluate the safety and tolerability of the combination of nivolumab plus relatlimab 720 mg and PDCT and confirm the safety profile. The relatlimab 360 mg Q3W dose in Arm B will be evaluated to generate additional safety data at this dose level. The randomization will be stratified by histology (SQ vs NSQ). After all treated participants have been followed-up for a minimum of 12 weeks, an analysis will take place to determine whether the established threshold for the dose-safety evaluable population has been met and to evaluate the totality of the Part 1 safety data. In addition, the proportion of treatment-related adverse events (TRAEs) leading to discontinuation within
12 weeks of the first dose will be monitored for each arm separately using Bayesian continuous monitoring plan.

Part 2 (n = 300): Randomized,open-label controlled trial that will further evaluate the efficacy and safety of the nivolumab, relatlimab plus chemotherapy combination vs nivolumab plus chemotherapy. Only after the safety of nivolumab plus relatlimab and PDCT has been evaluated
in Part 1 of the study can enrollment begin in Part 2 of the study, with the selected Phase 2 dose of relatlimab in combination with nivolumab + PDCT. At this time, participants that are in screening and found to be eligible will be randomized 1:1 into experimental Arm C or control Arm D of Part 2 of the trial. Enrollment will end when approximately 300 participants have been randomized. The primary analysis for ORR is planned to occur approximately 5 months after the last patient is randomized. The final analysis for PFS will occur when approximately 235 events have occurred.The stratification factors for randomization in Part 2 are histology (SQ vs NSQ), and ECOG performance status (0 vs 1) and PD-L1 level (>= 1% [including NQ] vs < 1%).

Intervention

The Part 1 dose safety confirmation period is 12 weeks after the first dose. Up to approximately 120 eligible participants to enroll in the study will be randomized 1:1 to experimental Arms A or B. Nivolumab plus relatlimab, the immune checkpoint inhibitors hereon referred to as immunotherapy, will be administered in a site-and-subject blinded manner, whereas chemotherapy will be administered as open label.

Arm A: Nivolumab 360 mg Q3W + relatlimab 720 mg Q3W + 4 cycles of histology-based PDCT
Arm B: Nivolumab 360 mg Q3W + relatlimab 360 mg Q3W + 4 cycles of histology-based PDCT

During the treatment phase of Part 2 of the study, participants will receive the following treatments. Immunotherapy will be administered in a double-blinded manner whereas chemotherapy will be administered as open label:

Arm C: Nivolumab 360 mg Q3W + relatlimab 720 mg (or 360 mg(a)) Q3W + 4 cycles of histology based PDCT(b) or

Arm D: Nivolumab 360 mg Q3W + placebo Q3W + 4 cycles of histology-based PDCT

(a) The relatlimab dose to be included in Arm C will be determined by the outcome of the dose safety confirmation that will take place in Part 1 of the study.
(b) Histology-based PDCT will be as follows:
- NSQ: Carboplatin area under the concentration-time curve (AUC) 5 or 6 or cisplatin 75 mg/m2 + pemetrexed 500 mg/m2 (maintenance permitted)
- SQ: Carboplatin AUC 6 + paclitaxel 200 mg/m2 or nab-paclitaxel 100 mg/m2

Dose reductions are not permitted for immunotherapy.
All participants will be treated until progression, presence of intolerable toxicities, withdrawal of consent, or study end, whichever comes first. Continuous safety evaluations and tumor assessments will guide the decision to treat a participant with additional cycles of study therapy if the participant has confirmed clinical benefit.

Participants will be allowed to continue study treatment until the first occurrence of any of the following situations:
* Progressive disease defined by RECIST v1.1 unless participants meet criteria for treatment beyond progression.
* Clinical deterioration suggesting that no further benefit from treatment is likely.

* Intolerability to therapy.
* Participant meets criteria for discontinuation of study treatment.

Study burden and risks

For full details, see the study schedules on pages 17-24 of the study protocol.

* Participation in this study will last approximately 33 months and include approximately 16 visits to the study site (based on 12 cycles of treatment)

The study visits will take approximately 2-6 hours on average each

* During the screening, the patient is presented with an informed consent form. This is reviewed and if the patient wishes to take part it is signed by the patient. Medical history of the patient is reviewed with the patient.
* In the study participants will get physical examinations including temperature, blood pressure, heart rate, respiratory rate and oxygen in blood and measurement of height and body weight.
* Blood and urine tests will be performed. Drawing blood may be painful or cause some bruising.
* Subjects will be tested for hepatitis and HIV
* ECGs will be done and CT/ MRI scans and echocardiogram
* Women of childbearing potential will have a pregnancy test done.
* A sample of a previously taken tumor biopsy will be obtained if possible at screening or an optional fresh biopsy may be taken.Also optinal tumor biopsies during treatment can be done. Risks of tumor biopsy include pain, small chance of bruising. The biopsy procedure is usually performed while under local anesthesia.
* The patient will be questioned during visits regarding (adverse events) side effects and the medication use.
* participants will be asked to complete questionnaires
* participants will receive an unregistered drugs and additional chemo that will have potential side effects

Possible side effects of the study drug that are already known are described in the Patient Information and Investigator's Brochure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Males and females; >= 18 years of age or local age of majority.
•Histologically confirmed metastatic NSCLC of squamous (SQ) or non squamous (NSQ) histology with Stage IV or recurrent disease following multi-modal therapy for locally advanced disease.
•Measurable disease by computed tomography or magnetic resonance imaging per Response
•Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria; radiographic tumor assessment performed within 28 days before randomization.
•No prior systemic anti-cancer treatment given as primary therapy for advanced or metastatic disease.
•ECOG PS of less than or equal to 1 at screening and confirmed prior to randomization.
•Participants must have a life expectancy of at least 3 months at the time of first dose.
•A formalin-fixed paraffin-embedded tissue block containing enough tissue to cut 20 sections (preferred; please see study Laboratory Manual for specific guidance) or a minimum of 20 unstained slides of tumor tissue from core biopsy, punch biopsy, excisional biopsy, or surgical specimen obtained during screening or prior to enrollment (within 3 months of enrollment if stored at 2-8°C or within 2 months of enrollment if stored at ambient

temperature and with no intervening systemic anti-cancer treatment between time of acquisition and enrollment) must be sent to the central laboratory.
•Participants must have PD-L1 immunohistochemistry (IHC) results from a central laboratory during the screening period prior to randomization.

Exclusion criteria

•Women who are pregnant or breastfeeding.
•Participants with EGFR, ALK, or ROS-1 mutations which are sensitive to available targeted inhibitor therapy. All participants with NSQ histology must have been tested for EGFR, ALK, or ROS-1 mutation status. Participants with NSQ histology and unknown EGFR, ALK, or ROS-1
status are excluded.
•Participants with known BRAFV600E mutations that are sensitive to available targeted inhibitor therapy. Participants with unknown or indeterminate BRAF mutation status are eligible.
•Participants with untreated central nervous system metastases.
•Participants with leptomeningeal metastases (carcinomatous meningitis).
•Concurrent malignancy requiring treatment.
•Participants with an active, known, or suspected autoimmune disease.
•Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-LAG-3, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
•Participants with history of myocarditis

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-06-2021
Enrollment:	13
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Anti-LAG-3-3.7 mL vial
Generic name:	relatlimab
Product type:	Medicine
Brand name:	CARBO-cell® 10 mg/ml, concentrate for solution for infusion
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carbomedac 10 mg/mL concentrate for solution for infusion
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin Bendalis 10 mg/ml, concentrate for solution for infusion
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo (100 mg / 10 ml)
Generic name:	Nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-01-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	29-03-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	20-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	22-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2023-508372-10-00
EudraCT	EUCTR2020-004026-31-NL
CCMO	NL75941.028.20
Other	U1111-1256-8115