An Adaptive Phase III, Multicenter, Randomized, Open-Label, Controlled Study of M7824 (bintrafusp alfa) versus Pembrolizumab as a First-line Treatment in Patients with PD-L1 Expressing Advanced Non-small Cell Lung Cancer (MS200647-0037)

Published: 05-09-2018
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To demontrate improvement of progression-free survival (PFS) and/or overall survival (OS) with M7824 compared with pembrolizumab in first-line participants with advanced NSCLC with high PD-L1 tumor expression.

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

Summary

ID

NL-OMON49475

Source
ToetsingOnline

Brief title
INTR@PID Lung 037 (MS200647-0037)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Industry (Merck KGaA)

Intervention

Keyword: M7824, Non-small Cell Lung Cancer, PD-L1, pembrolizumab

Outcome measures

Primary outcome

1) Progression-free survival (PFS) according to RECIST 1.1 assessed by the independent review committee (IRC)

2) Overall Survival (OS)

Secondary outcome

1) Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AE)s

2) OR according to RECIST 1.1 assessed by Independent Review Committee (IRC)

3) Duration of Response (DOR) assessed from complete response (CR) or partial response (PR) according to RECIST 1.1 assessed by IRC until progressive disease (PD), death, or last tumor assessment

4) Pharmacokinetic (PK) profile of M7824 in terms of Ceoi (concentration at end of infusion)

5) PK profile of M7824 in terms of Ctrough (concentration at end of the dosing interval)

6) Immunogenicity as measured by anti-drug antibodies (ADA) assays at Baseline

and Ontreatment

Study description

Background summary

Lung cancer is the leading cause of cancer death in the USA and results in more cancer deaths than breast cancer, prostate cancer, and colorectal cancer combined. Non-small cell lung cancer accounts for approximately 80% of all cases of lung cancer. It is estimated in 2018 there would be 234,030 new cases of lung and bronchus cancer and 154,050 people would die from their lung cancers in the USA alone. In the EU, 275,700 deaths due to lung cancer were predicted in 2017. Worldwide, an estimated 1.8 million new cases of lung cancer were diagnosed in 2012, approximately 13% of the total of all new cancers diagnosed.
M7824 is a first-in-class bifunctional fusion protein that combines a programmed death-ligand 1 (PD-L1) antibody and transforming growth factor * (TGF*) receptor II as a TGF* neutralizing *trap* into a single molecule. It thereby targets 2 major mechanisms of immunosuppression in the tumor microenvironment (blocking both the cell intrinsic PD-L1/PD-1 interaction and the immunosuppressive TGF*). Immune checkpoint inhibitors have shown improved treatment outcomes in patients with NSCLC; however, there is room to further improve benefits. A novel agent such as M7824 is hypothesized to be more effective than agents that target only a single pathway.

Study objective

To demontrate improvement of progression-free survival (PFS) and/or overall survival (OS) with M7824 compared with pembrolizumab in first-line participants with advanced NSCLC with high PD-L1 tumor expression.

Study design

This is an adaptive phase 3, multicenter, international, randomized, open-label, controlled study to examine the efficacy and safety of intravenous (iv) M7824 monotherapy versus pembrolizumab as first-line treatment for participants with advanced NSCLC with high PD-L1 tumor expression.

Intervention

Participants who meet the study criteria will be randomly assigned in a 1:1 ratio to receive either:
- M7824 at a dose of 1200 mg per i.v. infusion once every 2 weeks (q2w), or

- Pembrolizumab at a dose of 200 mg per i.v. infusion once every 3 weeks (q3w).

Study burden and risks

Preclinical data suggest that M7824 strongly enhances antitumor activity and prolongs survival in mouse tumor models above the effect of either the anti-PD-L1 antibody avelumab or the TGF* Trap control alone. M7824 is currently being investigated in Phase I trials (EMR200647-001, MS200647-0008) in patients with advanced solid tumors including NSCLC in which it has demonstrated an acceptable safety profile to date. In study EMR200647-001, the response rates for M7824 in second-line NSCLC participants are substantially better than historical controls, and are further improved with higher PD-L1 tumor expression. The benefit/risk ratio of the proposed trial is therefore considered 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

1. * 18 years of age inclusive, at the time of signing the informed consent
2. histologically confirmed diagnosis of advanced NSCLC and:
a. Have not received prior systemic therapy treatment for their advanced/Stage IV
NSCLC. Completion of treatment with cytotoxic chemotherapy, biological therapy, and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy
was completed at least 6 months prior to the diagnosis of metastatic disease. Confirmation of resolution of toxic effects of previous neoadjuvant/adjuvant chemotherapy therapy to Grade * 1. For radiation toxicity or prior major surgeries, participants should have recovered from side effects and/or complications.
b. Have measurable disease based on RECIST 1.1
c. Have a life expectancy of at least 3 months
d. Availability of tumor tissue (< 6 months old, excluding bone biopsies) before the first dose is mandatory to determine PD-L1 expression level prior to enrollment
e. PD-L1 high status by central testing is required
(other protocol defined criteria could apply)

Exclusion criteria

1. Participants with nonsquamous NSCLC histologies whose tumor harbors any of the following molecular alterations and targeted therapy is locally approved:
a. EGFR sensitizing (activating) mutation
b. ALK translocation(s) associated with responsiveness to ALK tyrosine kinase inhibitors
c. ROS1 rearrangement(s) associated with responsiveness to ROS1 tyrosine kinase inhibitors
d. BRAF V600E mutation
2. Has received major surgery within 4 weeks prior to the first dose of study intervention;
received thoracic RT of > 30 Gy within 6 months prior to the first dose of study
7. Known severe hypersensitivity reactions (Grade * 3 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) to investigational product (M7824 or pembrolizumab) or any components in their formulations, or uncontrolled asthma (ie, 3 or more features of partially controlled asthma)
8. Receipt of any organ transplantation
9. Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV steroids

10. Significant acute or chronic infections
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with participation for the full duration of the study, or is not in the best interest of the participant, in the opinion of the treating Investigator.
Participants with history of bleeding diathesis or recent major bleeding events considered by the Investigator as high risk for investigational drug treatment, such as patients with clinically relevant bleeding events of hemoptysis * Grade 2 within the last month, are also excluded
12. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways) intervention.
13. Previous malignant disease
14. Has active CNS metastases causing clinical symptoms or metastases that require therapeutic intervention and/or carcinomatosis meningitis
15. Active autoimmune disease that has required systemic treatment in past 1 year OR is
receiving systemic steroid therapy < 3 days prior to the first dose of study intervention or
receiving any other form of immunosuppressive medication.
16. Is expected to require any other form of systemic or localized antineoplastic therapy
while on study (including maintenance therapy with another agent for NSCLC, RT, and/or surgical resection) , (other protocol defined criteria could apply)

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:	Recruitment stopped
Start date (anticipated):	09-05-2019
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	PEMBROLIZUMAB
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	M7824
Generic name:	bintrafusp alfa

Ethics review

Approved WMO Date:	05-09-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-03-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-09-2020
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2018-001517-32-NL
ClinicalTrials.gov	NCT03631706
CCMO	NL66163.031.18