A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD L1 ANTIBODY) IN COMBINATION WITH CARBOPLATIN OR CISPLATIN + PEMETREXED COMPARED WITH CARBOPLATIN OR CISPLATIN + PEMETREXED IN PATIENTS WHO ARE CHEMOTHERAPY-NAIVE AND HAVE STAGE IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Published: 29-03-2016
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The co-primary objectives of this study are: * To evaluate the efficacy of as measured by investigator-assessed PFS according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). * To evaluate the efficacy of atezolizumab as...

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

Summary

ID

NL-OMON50326

Source
ToetsingOnline

Brief title
GO29438

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Phase 3 Non-squamous non-small cell - Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Atezolizumab, Non-squamous non-small cell lung cancer, Open-Label, Randomized

Outcome measures

Primary outcome

The co-primary efficacy outcome measures for this study are:

* PFS, defined as the time from randomization to the first occurrence of

disease progression as determined by the investigator using RECIST v1.1 or

death from any cause, whichever occurs first. Patients who have not experienced

disease progression or death at the time of analysis will be censored at the

time of last tumor assessment. Patients with no post-baseline tumor assessment

will be censored at the randomization date plus 1 day.

* OS, defined as the time from randomization to death from any cause

Secondary outcome

The secondary efficacy outcome measures for this study are:

* Objective response, defined as PR or CR as determined by the investigator

according to RECIST v1.1

* DOR, defined as the time interval from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first

* OS at 1 and 2 year landmark timepoints

* TTD in patient reported lung cancer symptoms, defined as time from randomization to deterioration (10 point change) on each of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom subscales

* Change from baseline in patient reported lung cancer symptoms (cough, dyspnea, or chest pain) with use of the SILC scale symptom score

Study description

Background summary

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008. Non-small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases.

Research therapies have shown that focused on enhancing T cell responses against cancer, can result in a significant survival benefit in patients with Stage IV cancer.

This study is designed to evaluate whether the anti tumor effect seen in atezolizumab-treated patients would translate into statistically significant and clinically relevant improvement in PFS and OS when used in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed . This study will allow for the evaluation of the efficacy of atezolizumab in both the ITT population, as well as in patients with PD L1-selected tumors

Study objective

The co-primary objectives of this study are:
* To evaluate the efficacy of as measured by investigator-assessed PFS according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST

v1.1).
* To evaluate the efficacy of atezolizumab as measured by overall survival (OS).

The secondary efficacy objectives for this study are:
* To evaluate the efficacy of atezolizumab as measured by investigator-assessed objective response rate (ORR) according to RECIST v1.1
* To evaluate the efficacy of atezolizumab as measured by investigator-assessed duration of response (DOR) according to RECIST v1.1
* To evaluate the OS rate at 1 and 2 years
* To determine the impact of atezolizumab as measured by the change from baseline in patient reported lung cancer symptoms of cough, dyspnea (single item and multi item subscales), chest pain, or arm/shoulder pain, using the European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ LC13)
* To determine the impact of atezolizumab in each of the treatment regimens as measured by the change from baseline in patient reported lung cancer symptoms (chest pain, dyspnea, and cough) scores using the Symptoms in Lung Cancer (SILC) scale symptom severity scores

Safety Objectives The safety objectives for this study are:
* To evaluate the safety and tolerability of atezolizumab when giving in combination with carboplatin or cisplatin + pemetrexed or as maintenance therapy with pemetrexed alone
* To evaluate the incidence and titers of anti-therapeutic antibody (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objectives The PK objectives for this study are:
* To characterize the pharmacokinetics of atezolizumab when given in combination with carboplatin or cisplatin + pemetrexed or pemetrexed alone
* To characterize the pharmacokinetics of carboplatin when given in combination with atezolizumab and pemetrexed
* To characterize the pharmacokinetics of cisplatin when given in combination with atezolizumab + pemetrexed
* To characterize the pharmacokinetics of pemetrexed when given in combination with atezolizumab + carboplatin or cisplatin

Exploratory Objectives The exploratory objectives for this study are:
* To evaluate the PFS rate at 6 month and 1-year langmark timepoints
* To evaluate the OS rate at 3 years in each treatment arm
* To evaluate the efficacy of atezolizumab as measured by OS and investigator-assessed PFS according to RECIST v1.1 in subgroups based on demographic and baseline characteristics
* To evaluate the efficacy of atezolizumab as measured by milestone survival
* To evaluate the relationship between biomarkers in tumors and blood

(including, but not limited to PD L1, programmed death-1 (PD-1), somatic mutations and others), as defined by immunohistochemistry (IHC), quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR), next-generation sequencing (NGS), and/or other methods and measures of efficacy
* To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment
* To evaluate and compare patient*s health status as assessed by the EuroQoL 5 Dimensions 5-Level questionnaire to generate utility scores for use in economic models for reimbursement
* To determine the impact of atezolizumab in each of the treatment comparisons as measured by change from baseline in patient-reported outcomes (PROs) of health-related quality of life, lung cancer related symptoms, and health status as assessed by the EORTC QLQ-C30 and QLQ-LC13

Study design

This is a randomized, Phase III, multicenter, open-label (IMpower 132) study designed to evaluate the safety and efficacy of atezolizumab in combination with cisplatin or carboplatin + pemetrexed compared with treatment with cisplatin or carboplatin + pemetrexed in patients who are chemotherapy naive and have Stage IV non squamous NSCLC. Eligible patients will be stratified by sex (male vs. female), smoking status (never vs. current and/or former), Eastern Cooperative Oncology Group (ECOG) performance status 0 vs.1 chemotherapy regimen (carboplatin vs. cisplatin)randomized by a 1:1 ratio to receive one of the following treatment regimens:
* Induction phase (four or six 21-day cycles):
Arm A: Atezolizumab + carboplatin or cisplatin + pemetrexed
Arm B: Carboplatin or cisplatin + pemetrexed

* Maintenance phase (21-day cycles):
Arm A: Atezolizumab + pemetrexed
Arm B: pemetrexed

Treatment with chemotherapy (both in Arm A and B) should be discontinued in all patients who exhibit evidence of progressive disease by RECIST 1.1. During induction or maintenance treatment, patients randomized to Arm A may continue treatment with atezolizumab beyond progressive disease by RECIST v1.1, provided they are experiencing clinical benefit as assessed by the investigator.
Patients will undergo tumor assessments at baseline and every 6 weeks for the first 48 weeks following Cycle 1, Day 1, regardless of dose delays. After the completion of the Week 48 tumor assessment,, tumor assessment will be required every 9 weeks. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated only patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who

discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy. All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. The independent reviews of stored scans will be performed when requested.

Intervention

During this study, the patient will be randomly assigned (by chance) to one of the two treatment possibilities (called *treatment arms*). The patient will have a 1 in 2 (50%) chance of being assigned to Arm A or Arm B.

Patients randomized to atezolizumab will receive 1200 mg of atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Institutions should follow their standard administration regimens for pemetrexed. The premedication doses administered should be in compliance with the Summary of Product Characteristics.

Cisplatin will be administered by IV infusion approximately 30 minutes after completion of the pemetrexed infusion at a dose of 75 mg/m² over 1*2 hours or per standard of care at the institution. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin.
Carboplatin should be administered 30 minutes after completion of pemetrexed administration by IV infusion over 30-60 minutes to achieve an initial target area under the concentration time curve (AUC) of 6 mg/mL/min (Calvert formula dosing) with standard anti emetics per local practice guidelines

Study burden and risks

The required study drug can cause side effects.
- Risks (adverse events) related to MPDL3280A described in the study protocol under chapter 5.1.1 Risks Associated with MPDL3280A.
- Risks (adverse events) associated with carboplatine described in the study protocol under chapter 5.1.3 Risks Associated with carboplatine.
- Risks (adverse events) associated with ciplatine are described in the study protocol under Section 5.1.4 Risks Associated with ciplatine
- Risks (adverse events) related to pemetrexed are described in the study

protocol under chapter 5.1.2 Risks Associated with pemetrexed

Possible Risks and Discomfort Associated with drawing blood
During this study, small amounts of blood will be taken from a vein and used for tests that allow the patients study doctors to see how you are doing. Taking blood may cause pain where the needle is inserted, and there is a small risk of bruising or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is taken.

Possible Risks and Discomfort Associated with Biopsies
As with any procedure, there are risks and discomforts. The patient may feel some amount of pain or discomfort during the biopsy sample collection, including slight stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness at the biopsy sample site. If a general anesthetic is used, the patient will not feel pain during the procedure because the patient will be asleep. The doctor will explain the risks of the biopsy procedure to the patient to decide if you want to participate.

Benefit
Atezolizumab is an antibody (a protein used by the patients body's immune system to identify and neutralize foreign objects such as bacteria, viruses, and tumor cells) that affects the patients immune system by blocking a pathway that is involved in decreasing the patients body*s natural immune response to fight cancer. By blocking this pathway, atezolizumab may help the patients immune system stop or reverse the growth of tumors.

Contacts

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Scientific
Hoffmann-La Roche

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Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female, 18 years of age or older
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Histologically or cytologically confirmed, Stage IV non-squamous NSCLC
- No prior treatment for Stage IV non-squamous NSCLC
- Patients who have received prior neo-adjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last dose of chemotherapy and/or radiotherapy
-Measurable disease, as defined by RECIST v1.1
- Adequate hematologic and end organ function
- For patients enrolled in the extended China enrollment phase: current residence of mainland China, Hong Kong, or Taiwan and of Chinese ancestry.
- For women of childbearing potential: agreement to remain abstinent or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of ATZ and 6 months after the last dose of cisplatin, cisplatin, carboplatin, or pemetrexed. Women must refrain from donating eggs during this same period.

- For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm

Exclusion criteria

Cancer-Specific Exclusions
- Patients with a sensitizing mutation in the EGFR gene or an ALK fusiononcogene
- Active or untreated CNS metastases as determined by computed tomography (CT)

or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >= 2 weeks prior to randomization
- Leptomeningeal disease
- Uncontrolled tumor-related pain
- Uncontrolled or symptomatic hypercalcemia (> 1.5 millimole/Liter ionized calcium or calcium > 12 milligram/deciliter or corrected serum calcium > upper limit of normal)
- Malignancies other than NSCLC within 5 years prior to randomization
- Known tumor PD-L1 expression status from other clinical studies , General Medical Exclusions:
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- History of certain autoimmune disease
- History of idiopathic pulmonary fibrosis, organizing pneumonia, druginduced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis
- Severe infections within 4 weeks prior to randomization
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina , Exclusion Criteria Related to Medications and Chemotherapy:
- Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti*PD-1, and anti*PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents within 4 weeks or 5 half-lives of the drug prior to randomization
- Treatment with systemic immunosuppressive medications , Exclusion Criteria Related to Chemotherapy:
- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- Grade >= 2 peripheral neuropathy as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 criteria (cisplatin)
- Creatinine clearance (CRCL) =< 60 milliliter (mL)/minute (min) for cisplatin or < 45 mL/min for carboplatin

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):	13-12-2016
Enrollment:	59
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	n.v.t.
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	n.v.t.
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MPDL3280A
Generic name:	Atezolizumab

Ethics review

Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	08-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015-003605-42-NL
CCMO	NL55742.100.16