A Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

Published: 18-06-2015
Last updated: 14-04-2024

To demonstrate superiority with regard to overall survival (OS) of avelumab versus docetaxel in subjects with programmed death ligand 1 (PD-L1) positive (+; as determined by a companion diagnostic test under development), non-small cell lung cancer...

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

Summary

ID

NL-OMON42011

Source
ToetsingOnline

Brief title
EMR 100070-004

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non-small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: avelumab, docetaxel, MSB0010718C, non-small cell lung cancer

Outcome measures

Primary outcome

The primary endpoint for the trial is OS time, defined as the time (in months)

from randomization to the date of death.

Secondary outcome

Secondary endpoints include

- PFS time according to RECIST 1.1 and as adjudicated by the IERC,

- BOR according to RECIST 1.1 and as adjudicated by the IERC,

- changes in subject-reported outcomes / quality of life as assessed by the

EQ-5D and the EORTC QLQ-C30 and module QLQ LC13 questionnaire, and

- the safety profile of the trial drugs as measured by the incidence of AEs,

serious AEs (SAEs), clinical laboratory assessments, vital signs, physical

examination, ECG parameters, and ECOG PS.

Study description

Background summary

Lung cancer is the leading cause of cancer death in men and women in the USA and results in more cancer deaths than breast cancer, prostate cancer, and colorectal cancer combined. The American Cancer Society estimated that in 2014 there would be 224,210 new cases of lung cancer in the USA alone, and 159,260 people would die from their lung cancers (2). 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 (3). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer.

In NSCLC, results of standard therapy are poor except for the most localized cancers where surgery and / or combined modality therapy can provide cure in a small percentage of patients. In advanced-stage disease, chemotherapy offers modest benefit, though overall survival is poor. There are 5 agents indicated for the treatment of advanced NSCLC in the second line setting: docetaxel, pemetrexed, and the tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and crizotinib. These agents have an overall response rate of < 10% in an unselected patient population and there is a growing body of evidence suggesting chemotherapy is preferable to erlotinib and gefitinib, especially in patients whose tumors do not harbor epidermal growth factor receptor (EGFR) activating mutations.

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral roles in immune regulation. Expressed on activated T cells, PD-1 is activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T-cell death and localized immune suppression, potentially providing an immune-tolerant environment for tumor development and growth. Conversely, inhibition of this interaction can enhance local T-cell responses and mediate antitumor activity in nonclinical animal models.

In the clinical setting, treatment with antibodies that block the PD-1 * PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles. Notably, responses appeared prolonged, with durations of 1 year or more for the majority of patients.

There are relatively few studies looking at PD-L1 expression in NSCLC and estimates of the proportion of patients with PD-L1 positive (PD-L1+) tumors vary widely from 25% to close to 60%; however, treatment of unselected patient populations with NSCLC with antibodies directed against PD-1 or PD-L1 showed some clinical activity, with 30 responses recorded in 188 patients.

The Investigational Medicinal Product (IMP) for the present trial is avelumab (formerly designated MSB0010718C), a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype. This anti-PD-L1 therapeutic antibody concept is being developed in oncological settings by Merck KGaA, Darmstadt, Germany, and by its subsidiary, EMD Serono R&D, Billerica, MA, USA. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2 * PD-1 pathway intact to promote peripheral self-tolerance.

Study objective

To demonstrate superiority with regard to overall survival (OS) of avelumab versus docetaxel in subjects with programmed death ligand 1 (PD-L1) positive (+; as determined by a companion diagnostic test under development), non-small cell lung cancer (NSCLC) after failure of a platinum-based doublet.

Study design

This is a multicenter, international, randomized, open label, Phase III trial in subjects with locally advanced unresectable, metastatic, or recurrent NSCLC that has progressed after a platinum doublet.
Approximately 650 subjects, among them 522 PD-L1 assay positive subjects, will be randomized in a 1:1 ratio to receive either
- avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks, or
- docetaxel at a starting dose of 75 mg/m2 (per label) by IV infusion once every 3 weeks.
Subjects will be stratified according to PD-L1 assay status (positive versus negative expression in tumor cells) and NSCLC histology and epidermal growth factor receptor (EGFR) status (squamous cell versus non-squamous cell EGFR normal versus non squamous cell EGFR-activating mutations).

Tumor measurements by computed tomography (CT) scan or magnetic resonance imaging (MRI) will be performed every 6 weeks to determine response to treatment. A central imaging laboratory will be used to read and interpret all CT / MRI data; however, treatment decisions will be made by the treating Investigator. Response will be evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. For subjects receiving avelumab, treatment may continue past the initial determination of disease progression per RECIST 1.1 if the subject*s performance status has remained stable, and if in the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outlined in the protocol. Subjects receiving avelumab who have experienced a confirmed complete response (CR) should be treated for a minimum of 6 months and a maximum of 12 months after confirmation, at the discretion of the Investigator. If the Investigator believes that a subject may benefit from treatment beyond 12 months, it may be permissible after discussion with the Sponsor. In case a subject with a confirmed CR relapses after stopping treatment, but prior to the end of the trial, 1 re initiation of treatment is allowed at the discretion of the Investigator and agreement of the Medical Monitor. In order to be eligible for re-treatment, the subject must not have experienced any toxicity that led to

treatment discontinuation of the initial avelumab therapy. Subjects who re initiate treatment will stay on trial and will be treated and monitored according to the protocol and the *until progression* schedule in the Schedule of Assessments.

Patients assigned to docetaxel will not be allowed to crossover to avelumab as long as superiority of avelumab versus docetaxel in terms of the primary objective has not been demonstrated in the planned interim or final analysis.

Decisions regarding medical management of subjects will be made by the Investigator; however, the secondary endpoint determinations (response and disease progression) will be according to the central imaging assessment and review by a blinded Independent Endpoint Review Committee (IERC).

Adverse events (AEs) will be assessed throughout and evaluated using the National Cancer Institute (NCI) Common Technology Criteria version for Adverse Events version 4.03 (CTCAE v 4.03).

Periodic evaluations of the trial data will be conducted by an Independent Data Monitoring Committee (IDMC) to ensure subject safety, the validity and scientific merit of the trial, and to evaluate efficacy at the 75% interim analysis.

Intervention

- avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks, or
- docetaxel at a starting dose of 75 mg/m2 (per label) by IV infusion once every 3 weeks.

Study burden and risks

The risk-benefit relationship has been carefully considered in the planning of the trial. Based on the nonclinical and Phase I data available to date, the conduct of the trial is considered justifiable using the dose and dose regimen of the avelumab as specified in this clinical trial protocol. An IDMC will assess the risk-benefit ratio on an ongoing basis. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk benefit relationship that would render continuation of the trial unjustifiable.

The primary known risks of exposure to avelumab include:
- infusion-related reactions and
- irAEs.

As of 05 November 2014, two Grade 4 infusion reactions have been reported in

480 subjects (0.4%) treated with avelumab (see Section 3.3.1.1); therefore, already implemented risk mitigation measures for infusion-related reactions / hypersensitivity have been extended by a mandatory premedication with H1 receptor blockers and acetaminophen for all subjects prior to any infusion. A premedication regimen of 25 to 50 mg diphenhydramine and 500 to 650 mg acetaminophen (IV or oral equivalent) is recommended prior to each dose of trial drug. This regimen may be modified based on local treatment standards and guidelines as appropriate.

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome.

As noted above, trials with antibodies that block the PD-1 * PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with response durations of 1 year or more for the majority of patients.
Furthermore, recent snapshot in Trial EMR100070-001 of subjects with NSCLC who had progressed after platinum-containing therapy (n=184 treated subjects with a minimum follow-up time of at least 13 weeks by the cut off date of 15 October 2014) demonstrated an objective response rate (ORR) of 12.0% (22 of 184 subjects; 95% confidence interval [CI]: 7.6%, 17.5%), including 1 subject with complete response (CR) and 21 subjects with partial response (PR). There were also 70 subjects with stable disease (SD), 68 subjects with progressive disease (PD), and 24 subjects who were not evaluable. Eighteen out of the 22 responses were still on-going at the cut-off date for this analysis. The onset of response was rapid, with 11 of 22 (50.0%) subjects having their first documented response by Week 7.

Given the suboptimal treatment options for patients with recurrent locally advanced or metastatic NSCLC and the safety profile of avelumab as currently demonstrated by ongoing Phase I trials, the risk benefit ratio of treatment with avelumab in the targeted trial population is considered positive.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and the applicable national regulatory requirements.

Contacts

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Scientific
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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. Signed written informed consent before any trial related procedure is undertaken that is not part of the standard patient management
2. Male or female subjects aged * 18 years
3. Availability of a formalin-fixed, paraffin-embedded block containing tumor tissue or 7 unstained tumor slides suitable for PD-L1 expression assessment
4. Tumor determined to be evaluable for PD-L1 expression per the evaluation of a central laboratory
5. Subjects with histologically confirmed Stage IIIb/IV or recurrent NSCLC who have experienced disease progression
6. Subjects must have progressed after an acceptable therapy defined as follows:
a. Subjects must have progressed during or after a minimum of 2 cycles of 1 course of a platinum based combination therapy administered for the treatment of a metastatic disease. A history of continuation (use of a non platinum agent from initial combination) or switch (use of a different agent) maintenance therapy is permitted provided there was no progression after the initial combination. A switch of agents during treatment for the management of toxicities is also permitted provided there was no progression after the initial combination
OR
b. Subjects must have progressed within 6 months of completion of a platinum-based adjuvant, neoadjuvant, or definitive chemotherapy, or concomitant chemoradiation regimen for locally advanced disease
7. Subjects with non-squamous cell NSCLC of unknown EGFR mutation status will require

testing (local laboratory, or central laboratory if local testing is not available). For subjects with a tumor that harbors an activating EGFR mutation, acceptable prior therapy is also defined as a treatment with an EGFR-targeting tyrosine kinase inhibitor (TKI) given before or after treatment with a platinum-based combination chemotherapy as defined above. Subjects with a tumor that harbors an activating EGFR mutation must have failed both the platinum-based doublet and the EGFR-targeting TKI. Treatment with more than 1 EGFR targeting TKI is acceptable
8. ECOG PS of 0 to 1 at trial entry
9. Estimated life expectancy of more than 12 weeks
10. Adequate hematological function defined by WBC count * 2.5 × 109/L with absolute neutrophil count (ANC) * 1.5 × 109/L, lymphocyte count * 0.5 × 109/L, platelet count * 100 × 109/L, and hemoglobin * 9 g/dL (may have been transfused)
11. Adequate hepatic function defined by a total bilirubin level * 1.0 × the upper limit of normal (ULN) range and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels * 2.5 × ULN for all subjects
12. Adequate renal function defined by an estimated creatinine clearance > 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
13. Effective contraception for both male and female subjects if the risk of conception exists (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use effective contraception, defined as 2 barrier methods, or 1 barrier method with a spermicide, an intrauterine device, or use of oral female contraceptive. Effective contraception must be used 30 days prior to first trial drug administration, for the duration of trial participation, and at least for 60 days after stopping trial participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this trial, the treating physician should be informed immediately.)

Exclusion criteria

1. In the United States only, subjects with a squamous cell histology will be excluded
2. Systemic anticancer therapy administered after disease progression during or following a platinum based combination, with the following exception: Subjects whose disease harbors an activating EGFR mutation who received an EGFR inhibitor AFTER a minimum of 2 cycles of first-line platinum-based therapy. Subjects who tested undetermined or wild-type for EGFR but were previously treated with a TKI are not eligible unless retested and confirmed to be activating EGFR mutation positive
3. Subjects with non-squamous cell NSCLC whose disease harbors an anaplastic lymphoma kinase (ALK) rearrangement will not be eligible for this trial. Subjects of unknown ALK status will require testing for ALK rearrangement (local laboratory, or central laboratory if local testing is not available) and must be determined to be ALK wild-type to be eligible for this trial
4. Prior therapy with any antibody / drug targeting T cell coregulatory proteins (immune checkpoints) such as PD-1, PD L1, or cytotoxic T lymphocyte antigen-4 (CTLA-4). Prior therapy with a cancer vaccine is acceptable
5. Concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with

the exception of palliative bone-directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin)
6. Major surgery for any reason, except diagnostic biopsy, within 4 weeks of randomization and/or if the subject has not fully recovered from the surgery within 4 weeks of randomization
7. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before initiation of the trial treatment (with the exception of patients with adrenal insufficiency, who may continue corticosteroids at physiologic replacement dose, equivalent to < 10 mg prednisone daily). Note: Subjects receiving bisphosphonate or denosumab are eligible provided treatment was initiated at least 14 days before first dose of trial treatment
8. All subjects with brain metastases, except those meeting the following criteria:
a. Brain metastases have been treated locally, and
b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
9. Previous malignant disease (other than NSCLC) within the last 5 years with the exception of basal or squamous cell carcinoma of the skin or carcinoma in situ (bladder, cervical, colorectal, breast)
10. Prior organ transplantation, including allogeneic stem cell transplantation
11. Significant acute or chronic infections including, among others:
* Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
* Any positive test for HBV or HCV indicating acute or chronic infection (test to be conducted at Screening)
12. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
b. Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses * 10 mg or 10 mg equivalent prednisone per day
c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable
13. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the daily dose after 14 days will be * 10 mg per day of equivalent prednisone
14. Known severe hypersensitivity reactions to monoclonal antibodies (Grade * 3 NCI CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)
15. History of hypersensitivity reaction to taxanes
16. History of hypersensitivity to Polysorbate 80 that led to unacceptable toxicity requiring treatment cessation
17. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v 4.03 (except neuropathy, see exclusion criterion #18)
18. Neuropathy * Grade 3
19. Pregnancy or lactation

20. Known alcohol or drug abuse
21. Clinically significant (that is, active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class * II), or serious cardiac arrhythmia requiring medication
22. All other significant diseases (for example, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the subject*s tolerance of trial treatment
23. Any psychiatric condition that would prohibit the understanding or rendering of informed consent
24. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines)
25. Legal incapacity or limited legal capacity

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):	28-01-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	avelumab
Generic name:	avelumab

Product type:	Medicine
Brand name:	docetaxel
Generic name:	docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-005060-15-NL
ClinicalTrials.gov	NCT02395172
CCMO	NL52081.078.15