A Phase III, Randomised, Double-blind, Placebo-controlled, Multi-centre, International Study of MEDI4736 as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III)Who Have Not Progressed Following Definitive, Platinum-based,Concurrent Chemoradiation Therapy (PACIFIC)

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The primary objective of this study is to assess the efficacy of MEDI4736 treatment compared with placebo in terms of overall survival (OS) and progression free survival (PFS; (per RECIST 1.1 as assessed by the investigator).

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

Summary

ID

NL-OMON50355

Source
ToetsingOnline

Brief title
D4191C00001 - PACIFIC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non-small cell lung cancer - lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: MEDI4736, Non-small cell lung cancer, Oncology, Phase III

Outcome measures

Primary outcome

To assess the efficacy of MEDI4736 treatment compared with placebo in terms of

OS and PFS.

PFS using investigator site assessments according to RECIST 1.1.

Secondary outcome

To further assess the efficacy of MEDI4736 compared with placebo in terms of:

OS24, ORR, DoR, APF12, APF18, PFS2 and TTDM.

To assess the safety and tolerability profile of MEDI4736 compared with placebo.

To assess the PK of MEDI4736.

To investigate the immunogenicity of MEDI4736.

To assess symptoms and health-related quality of life in patients treated with

MEDI4736 compared with placebo using EORTC QLQ-C30 v3 and LC13.

Study description

Background summary

Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers and 30% of patients present with Stage III disease. Standard treatment for patients with a good performance status and unresectable Stage III NSCLC is platinum-based doublet chemotherapy and radiotherapy administered with curative intent. A meta-analysis of concurrent versus sequential chemoradiotherapy showed better outcomes with concurrent therapy, but even with concurrent chemoradiotherapy 5-year overall survival (OS) is only approximately 15% (Butts et al 2014). Therefore, sequential/maintenance (consolidation) therapy has been and continues to be explored in an attempt to prolong a favourable clinical state after delivery of definitive chemoradiotherapy.

The immune system can identify tumour-associated antigens and eliminate the cancerous cells expressing them and thus plays an important role in preventing and combating the growth of tumours. Blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has shown promising clinical activity. PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer.

In vitro, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of anti-tumour T-cells (Blank et al 2006). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumour immune responses in patients with cancer. Results of several preclinical studies using mouse tumour models support this hypothesis, where antibodies directed against PD-L1, or its receptor PD-1, showed anti-tumour activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

For more details please also refer to chapter 1. INTRODUCTION, page 21-34 of Clinical Study Protocol D4191C00001 Version 1 19 February 2014.

Study objective

The primary objective of this study is to assess the efficacy of MEDI4736 treatment compared with placebo in terms of overall survival (OS) and

progression free survival (PFS; (per RECIST 1.1 as assessed by the investigator).

Study design

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study assessing the efficacy and safety of MEDI4736 compared with placebo, as sequential therapy in male and female patients with locally advanced, unresectable NSCLC (Stage III), who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy.

Approximately 880 patients will be enrolled and 702 patients randomised (patients will be in CR, PR or have SD following definitive, platinum-based, concurrent chemoradiation therapy) at 310 to 370 sites worldwide, in a 2:1 ratio (MEDI4736 to placebo) to 1 of 2 arms:
• MEDI4736 (10 mg/kg every 2 weeks [Q2W] intravenous [iv] for up to 12 months)
• Placebo (matching placebo for infusion Q2W iv for up to 12 months).

Randomisation will be stratified by: age at randomisation (<65 versus >=65 years of age), sex (male versus female), and smoking history (smoker versus non-smoker). Patients must complete their last dose of radiation therapy within 5 to 10 days prior to randomisation in the study (the last dose of radiation therapy is defined as the day of the last radiation treatment session). For patients who are recovering from toxicities associated with prior treatment, randomisation may be delayed by up to 14 days from the end of the chemoradiation therapy. For those patients randomised to the placebo arm no cross-in to the MEDI4736 arm is permitted and similarly those patients randomised to the MEDI4736 arm no cross-in to the placebo arm is permitted.

Tumour assessments will be performed using computed tomography/magnetic resonance imaging. The baseline assessment should be performed within 28 days of randomisation and within 5 to 10 days post the end of chemoradiation therapy, and ideally as close as possible before the start of study drug. Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks (relative to the date of randomisation) for the first 12 months, then every 12 weeks thereafter, until confirmed objective disease progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 (irrespective of the reason for stopping study drug/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. Blinded Independent Central Review (BICR) of a random sample of scans, from approximately 250 evaluable patients (with both progressive and non-progressive disease by investigator assessment) will be conducted and sensitivity analyses performed.

Following completion or discontinuation of study drug, patients will enter a follow-up period.

Once a patient has had objective progression recorded and has discontinued study drug, the patient will be followed up for survival status every 2 months until death, withdrawal of consent or the end of the study.

There will be 2 analyses of the study. The first analysis data cut off will occur at 35.5 months when it is expected that 491 PFS events have occurred (70% maturity). The second analysis data cut-off will occur at 62 months when it is expected that 491 OS events have occurred (70% maturity).

If the study achieves statistical significance for the co-primary endpoints of PFS and/or OS at one of the planned interim analyses, then that will be considered the final analysis for that endpoint. Further analyses for that particular endpoint may occur based on the needs for long term follow-up with more mature data. At the time of Amendment 07 finalisation, the study endpoints had been met and the planned analysis portion of the study had been concluded. The study will continue until all analyses for long term PFS / OS benefit are complete and those patients who have been in OS and PFS follow-up for approximately 5 years will be considered to have completed the study. Additional details on long-term follow up, including data collection for patients in follow-up or in re-treatment, are provided in the Long-term follow up section (9.5) of the protocol.

Intervention

Patients enrolled to the MEDI4736 arm will receive MEDI4736 10 mg/kg via a 60-minute iv infusion Q2W ± 3 days for up to 12 months.

Patients enrolled to the placebo arm will receive matching placebo via a 60-minute iv infusion Q2W ± 3 days for up to 12 months.

Study burden and risks

Chemoradiotherapy often induces initial tumour shrinkage followed by eventual PD as the tumours find mechanisms to bypass the chemoradiotherapy-induced growth inhibition. Triggering or augmenting an antigenic antitumour response with chemoradiotherapy and combining or following this treatment with anti-PD-L1 therapy, which acts to preserve ongoing immune responses by blocking an immunosuppressive signal theoretically may result in enhanced antitumour activity by improving local control and decreasing systemic spread.

Agents that act via antagonism of an inhibitory pathway modulate an existing antigen-specific T-cell receptor signal and have a limited potential to drive systemic, nonspecific activation of T cells. MEDI4736 antagonizes an inhibitory

receptor (PD-L1) and as such, in the absence of an antigen-specific T-cell receptor signal, inhibition of function of PD-L1 is not anticipated to elicit any response. MEDI4736 did not induce release of any cytokine from any donor at any concentration tested. Experience with MEDI4736 is limited, but for the 20 patients treated to date with available safety data (in the dose-escalation phase of the study on a Q2W schedule), there have been no DLTs. The majority of AEs (in 15 of the 20 patients) have been CTCAE Grade 1 or Grade 2. There have been no Grade 3 or higher treatment-related AEs. Six patients have had a total of 11 treatment-emergent SAEs. Four patients have died due to AEs but none of these events were considered by the reporting investigator to be related to treatment with MEDI4736.

The potential for clinical benefit associated with inhibition of the PD-1/PD-L1 pathway, supported by objective responses observed in earlier studies in patients with NSCLC, outweighs the known and potential risks based on the AEs reported in patients treated with MEDI4736 and other PD-1/PD-L1 inhibitors. Thus, the benefit/risk assessment, favours the conduct of this proposed study.

Contacts

Public
Astra Zeneca

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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. Provision of signed, written and dated informed consent prior to any study specific procedures
2. Male or female aged 18 years or older
3. Patients must have histologically- or cytologically-documented NSCLC who present with locally advanced, unresectable (Stage III) disease
4. Patients must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy.
5. Patients must have not progressed following definitive, platinumbased, concurrent chemoradiation therapy.
6. Provision of an archived tumour tissue block where such samples exist in a quantity sufficient to allow for analysis.
7. Life expectancy >=12 weeks
8. World Health Organization (WHO) Performance Status of 0 or 1
9. Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients.
10. Adequate organ and marrow function.

Exclusion criteria

1. Either Previous drug assignment in the present study or Prior randomisation or treatment in a previous durvalumab (MEDI4736) and/or tremelimumab clinical study regardless of treatment arm assignment.
2. Participation in another clinical study with an investigational product during the last 4 weeks
3. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
4. Mixed small cell and non-small cell lung cancer histology
5. Receipt of sequential chemoradiation therapy for locally advanced NSCLC
6. Patients with locally advanced NSCLC who have progressed whilst receiving definitive platinum based, concurrent chemoradiation therapy
7. Receipt of any immunotherapy, or investigational drug within 4 weeks prior to the first dose of study drug
8. Current or prior use of immunosuppressive medication within 28 days before the first dose of study drug, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are

not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Systemic steroid administration required as prophylaxis against or to manage toxicities arising from chemotherapy and/or radiation therapy delivered as part of the chemoradiation therapy for locally advanced NSCLC is allowed.
9. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody
10. Any unresolved toxicity CTCAE >Grade 2 from the prior chemoradiation therapy.
11. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study drug may be included (eg, hearing loss) after consultation with the AstraZeneca/MedImmune medical monitor.
12. Patients with >= grade 2 pneumonitis from prior chemoradiation therapy
13. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment.
14. Recent major surgery within 4 weeks
15. Active or prior documented autoimmune disease within the past 2 years, except for: Vitiligo, Grave's disease, or psoriasis not requiring systemic treatment
16. Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)
17. History of primary immunodeficiency
18. History of organ transplant that requires therapeutic immunosuppression
19. History of hypersensitivity to MEDI4736 or any excipient
20. Uncontrolled intercurrent illness
21. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study drug.
22. History of another primary malignancy within 5 years prior to starting study drug, except for adequately treated in situ malignancies such as basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study
23. Female patients who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control
24. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study results.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-06-2015
Enrollment:	59
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	durvalumab
Generic name:	N/A
Product type:	Medicine
Brand name:	N/A
Generic name:	placebo

Ethics review

Approved WMO Date:	06-08-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-12-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2015

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2018
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	06-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
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Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-02-2021
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	EUCTR2014-000336-42-NL
ClinicalTrials.gov	NCT02125461
CCMO	NL49365.060.14