A Phase III, Open-label, Randomised, Multi-centre, International Study of MEDI4736, Given as Monotherapy or in Combination with Tremelimumab, Determined by PD-L1 Expression, Versus Standard of Care in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB IV) who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum based Chemotherapy Regimen and Do Not Have Known EGFR TK Activating Mutations or ALK Rearrangements (ARCTIC)

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This study is a Phase III, randomised, open label, multi-centre study assessing the efficacy and safety of MEDI4736 versus Standard of Care in NSCLC patients with PD-L1-positive tumours and the combination of MEDI4736 plus tremelimumab (MEDI4736+…

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

Summary

ID

NL-OMON45219

Source
ToetsingOnline

Brief title
D4191C00004 - ARCTIC

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 (NSCLC), Oncology, Phase III, Tremelimumab

Outcome measures

Primary outcome

Sub-study A (PD-L1-positive population)

To assess the efficacy of MEDI4736 monotherapy compared with Standard of Care

in terms of OS and PFS.

Sub-study B (PD-L1-negative population)

To assess the efficacy of MEDI4736+tremelimumab treatment compared with

Standard of Care in terms of OS and PFS.

Secondary outcome

To further assess the efficacy of MEDI4736 compared with Standard of Care in

terms of: OS12, ORR, DoR, APF6, APF12, and PFS2.

To assess the safety and tolerability profile.

To assess the PK of MEDI4736 and tremelimumab.

To investigate the immunogenicity of MEDI4736 and tremelimumab.

To assess symptoms and health-related QoL using EORTC QLQ-C30 v3 and LC13.

Sub-study B (PD-L1-negative population)

To evaluate the efficacy of MEDI4736+tremelimumab treatment compared with a)

MEDI4736 monotherapy and b) tremelimunab monotherapy in terms of PFS.

Study description

Background summary

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total) (GLOBOCAN 2008). Non-small cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and Le Chevalier 2005).

Despite advances in the diagnosis, imaging, staging and treatment of NSCLC, the estimated overall 5-year survival for patients in Europe continues to be low (11%) (D*Addario et al 2010). Once patients have treatment failure following initial therapy, the outlook for those with refractory advanced NSCLC is extremely poor, with response to further systemic treatment of <10% (GLOBOCAN 2008, Hanna et al 2004) and median survival of approximately 6 months.

Common third-line treatment for NSCLC in major global markets includes: vinorelbine (NAVELBINE®), tyrosine kinase inhibitors (TKIs such as erlotinib [TARCEVA®] and gefitinib [IRESSA®]), pemetrexed (ALIMTA®), and docetaxel (TAXOTERE®) for non-squamous NSCLC, and vinorelbine, TKIs, gemcitabine (GEMZAR) and docetaxel (TAXOTERE®) for squamous NSCLC (Decisions Resources 2013). For these patients, clinical trials, experimental treatment, or best supportive care are among the treatment options (Azzoli et al 2009, Syrigos et al 2011).

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, of Clinical Study Protocol D4191C00004 Version 2 29 August 2014.

Study objective

This study is a Phase III, randomised, open label, multi-centre study assessing the efficacy and safety of MEDI4736 versus Standard of Care in NSCLC patients with PD-L1-positive tumours and the combination of MEDI4736 plus tremelimumab (MEDI4736+tremelimumab). The study will enrol male and female patients with locally advanced or metastatic NSCLC (Stage IIIB-IV), who have received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen for NSCLC. Patients with known epidermal growth factor receptor (EGFR) tyrosine kinase (TK) activating mutations and anaplastic lymphoma kinase (ALK) rearrangements are not eligible for the study

(prospective testing is not planned within this study).

This study will consist of 2 sub-studies: Sub-study A will address the research hypotheses for MEDI4736 monotherapy in patients with programmed death ligand 1 (PD-L1)-positive tumours and Sub-study B will address the research hypotheses for MEDI4736 plus tremelimumab (MEDI4736+tremelimumab) in patients with PD-L1-negative tumours.

Study design

Patients will be randomised in a 1:1 ratio in Sub-study A and a 1:1:1:1 ratio in Sub-study B.

Sub-study A (patients with PD-L1-positive tumours)
* MEDI4736 (10 mg/kg Q2W iv for up to 12 months) (125 patients)
* Standard of care (restricted to the erlotinib, gemcitabine or vinorelbine) (125 patients). For each agent 4 weeks equates to 1 cycle of treatment.
* Erlotinib: 150 mg once daily as a tablet for oral administration taken at least 1 hour before or 2 hours after the ingestion of food
* Gemcitabine: 1000 mg/m2 iv over 30 minutes on Days 1, 8, and 15 of a 28-day cycle
* Vinorelbine: 30 mg/m2 iv on Days 1, 8, 15 and 22 of a 28-day cycle.

Sub-study B (patients with PD-L1-negative tumours)
* MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg once every 4 weeks [Q4W] iv for up to 12 weeks [4 doses]) then MEDI4736 alone (10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses]) (180 patients)
* Standard of care (see sub-study A) (120 patients)
* MEDI4736 (10 mg/kg Q2W iv for up to 12 months) (120 patients)
* tremelimumab (10 mg/kg Q4W iv for 24 weeks then Q12W for a further 24 weeks) (60 patients)

The sub-studies may not run concurrently with completion of recruitment potentially occurring at different time points. Assignment to the applicable sub-study will be preceded by the Pre-screening Period during which assessment of the patient*s PD-L1 status, based on a tumour sample, will take place. After confirmation of PD-L1 status, patients will enter the main Screening Period within their assigned sub-study if it remains open for recruitment.

The primary objective of this study is to assess the efficacy of MEDI4736 monotherapy and MEDI4736+tremelimumab compared with Standard of Care in terms of overall survival (OS) and progression free survival (PFS).

Please refer to the PROTOCOL SYNOPSIS for more details on study design.

Intervention

Sub-study A (patients with PD-L1-positive tumours)
* MEDI4736 (10 mg/kg Q2W iv for up to 12 months)
* Standard of care (restricted to the erlotinib, gemcitabine or vinorelbine).
For each agent 4 weeks equates to 1 cycle of treatment.
* Erlotinib: 150 mg once daily as a tablet for oral administration
taken at least 1 hour before or 2 hours after the ingestion of food
* Gemcitabine: 1000 mg/m2 iv over 30 minutes on Days 1, 8, and 15 of a
28-day cycle
* Vinorelbine: 30 mg/m2 iv on Days 1, 8, 15 and 22 of a 28-day cycle.

Sub-study B (patients with PD-L1-negative tumours)
* MEDI4736+tremelimumab (MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg once every 4 weeks [Q4W] iv for up to 12 weeks [4 doses]) then MEDI4736 alone (10 mg/kg Q2W iv, starting at Week 16, for 34 weeks [18 doses])
* Standard of care (see sub-study A)
* MEDI4736 (10 mg/kg Q2W iv for up to 12 months)
* tremelimumab (10 mg/kg Q4W iv for 24 weeks then Q12W for a further 24 weeks)

Study burden and risks

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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- At least 18 years of age
- Documented evidence of NSCLC (Stage IIIB/ IV disease)
- Disease progression or recurrence after both a platinum-baed chemotherapy regimen and at least 1 additional regimen for treatment of NSCLC
- World Health Organization (WHO) Performance Status of 0 or 1
- Estimated life expectancy more than 12 weeks

Exclusion criteria

- Prior exposure to any anti-PD-1 or anti-PD-L1 antibody
- Brain metastases or spinal cord compression unless asymptomatic, treated and stable (not requiring steroids)
- Active or prior documented autoimmune disease within the past 2 years
- Evidence of severe or uncontrolled systemic disease, including active bleeding diatheses or active infections including acute or chronic hepatitis B, C and HIV

- Any unresolved toxicity CTCAE >Grade 2 from previous anti-cancer therapy
- Known EGFR TK activating mutations or ALK rearrangements. Patients with EGFR TK inactivating mutations, e.g. exon 20, are eligible
- Any prior Grade *3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)

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):	26-11-2015
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	gemcitabine
Generic name:	gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	tremelimumab

Product type:	Medicine
Brand name:	Navelbine
Generic name:	vinorelbine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tarceva
Generic name:	erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-03-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2017
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-000338-46-NL
ClinicalTrials.gov	NCT02352948
CCMO	NL49408.056.15