Imaging tumor-infiltrating CD8+ T-cells in non-small cell lung cancer upon neo-adjuvant treatment with Durvalumab (MEDI4736).

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

Summary

ID

NL-OMON48406

Source
ToetsingOnline

Brief title
Donan trial

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Non-small cell lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,Bedrijf

Intervention

Keyword: Durvalumab, neo-adjuvant, NSCLC, T-cells

Outcome measures

Primary outcome

he primary endpoint of this study will be to demonstrate 1) feasibility and 2)

safety of two courses durvalumab (MEDI4736) 750 mg Q2W in neo-adjuvant setting

in resectable NSCLC.

Study parameter 1): no delayed surgical procedures, all surgery should be

performed within 42 days after the first therapeutic dose of durvalumab

(MEDI4736).

Study parameter 2): number of grade 3 or higher adverse events related to

durvalumab (MEDI4736).

Secondary outcome

1. Correlative studies across different imaging modalities.

2. Validation of in vivo imaging findings with other potential biomarkers

derived from quantitative immune histochemistry and peripheral blood immune

profiling.

3. Assessment of neo-adjuvant durvalumab (MEDI4736) on outcome measures related

to clinical care.

Study description

Background summary

The approved indications of immunotherapy for non-small cell lung cancer
(NSCLC) patients are expanding. High recurrence rates in early stage resectable

NSCLC patients require novel treatment strategies to reduce micrometastatic disease. Adjuvant therapy has recently demonstrated to improve time-to-recurrence which has elicited the application of immune therapy in neo-adjuvant setting.

Study objective

The overall aim of this study is to demonstrate increase of tumor-infiltrating CD8+ T cells in non-small cell lung cancer during neo-adjuvant treatment with durvalumab (MEDI4736).

Study design

This is an interventional study, to assess feasibility and safety of durvalumab (MEDI4736) in neo-adjuvant setting in patients with resectable NSCLC. Additional analyses of potential imaging biomarkers, e.g. Zr-89 labelled durvalumab (MEDI4736), ex vivo In-111-oxine labelled CD8+ T-cells and high-resolution immune cell imaging, in relation to immunotherapy induced immune responses on quantitative immune histochemical analysis of the resected tumor specimen, will be performed.

Intervention

Patients will receive two courses of durvalumab (MEDI4736)at a fixed dose of 750mg Q2W intravenously, prior to scheduled resection of NSCLC. Patients are amendable to adjuvant chemo and/or radiation treatment, per standard-of-care. Additionally, patients will undergo a Zr-89 labelled durvalumab (MEDI4736) PET/CT and dedicated perfusion-CT prior to treatment with durvalumab (MEDI4736) and ex vivo In-111-oxine labelled CD8+ T-cells after two courses of treatment, prior to surgery.

Study burden and risks

1. Related to neo-adjuvant durvalumab (MEDI4736):
In monotherapy clinical studies, AEs (all grades) were reported commonly (>= 10% of patients) mostly fatigue, nausea, decreased appetite, dyspnea, cough. Approximately 3.5% of patients experienced a SAE related to durvalumab (MEDI4736) (See IB version 12, Appendix 1)].
The majority of treatment-related AEs were manageable using established treatment guidelines for immune-mediated toxicity. The only published study to date demonstrated safety and feasibility PD-1/PD-L1 axis directed immune therapy in neo-adjuvant setting without compromising current standard-of-care: curative resection.

2. Related to Zr-89 durvalumab (MEDI4736) PET/CT scan:
Patients will undergo a PET/CT with acquisition time of 45 minutes, for which

no extra preparation is needed. PET/CT will be scheduled at the same visit as first injection with therapeutic dose durvalumab (MEDI4736). The committed effective dose for the study population related to 37 MBq Zr-89-labelled durvalumab (MEDI4736) and low-dose CT is 5,7 mSv [18].

3. Related to In-111-oxine labelled CD8+ T-cell scan:
Three days prior to surgery, an aphaeresis will be performed to isolate autologous CD8+ T-cells. At 4 hrs and 48 hrs after intravenous injection of In-111-oxine labelled CD8+ T-cells, during hospital admission, a planar scintigraphy and SPECT/CT, acquisition in total 60 min, will be performed. There will be no extra preparation necessary.
The committed effective dose of In-111-labelled autologous cells for the study population is, based on dosimetry data from the guideline EANM on In-111-oxine labelled leukocytes, maximum 4.8 mSv (excluding low-dose CT).

4. Related to contrast-enhanced CT perfusion scan:
Prior to start of immunotherapy and prior to surgery, patients will receive an CT perfusion scan. This dedicated acquisition protocol consists of several ultra-low dose CT scans following the standard bolus injection of iodine-based contrast. There is no need for additional administration of iodine-based contrast agent and the scans will be acquired during the standard venous phase contrast-enhanced CT of the chest during routine clinical care. The committed effective dose for this study population related to the perfusion CT protocol is 0.64 mSv.

5. Related to translational and biomarker investigations:
Extra peripheral blood will be drawn via a venous canula at three time points; prior to start of immunotherapy, after neo-adjuvant immunotherapy/prior to surgery and during follow-up at 3 months after surgery. Per procedure 41 ml peripheral blood is required (10ml EDTA, 27ml heparin and 4ml serum tubes). A complete overview of study related procedures is provided in Figure 1, Table 2 and Section 9.4.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All patients must meet all of the following criteria:;1. Male or female subjects aged >50 years at time of study entry
2. Histopathological proven primary non-small cell lung cancer, with fully evaluable histological biopsies available
3. ECOG performance status of 0 or 1
4. AJCC stage I, II or IIIa as determined by contrast-enhanced CT chest-abdomen and F-18-FDG PET/CT: cT1cN0-1M0, cT2aN0-1M0 en cT3N0-1M0 (T3 separate nodule)
5. Solid appearance of the tumor on contrast-enhanced CT
6. Scheduled for resection with curative intent
7. Patients should be medically operable defined by:
8. Sufficient cardiopulmonary function
9. Major contra-indications for surgery.
10. No underlying immune disease (neutro- or lymphopenia, coagulation disorders) that could interfere with T-cell isolation
11. Life expectancy at least 6 months
12. Written informed consent and comply with study protocol for the duration of the study and follow-up
13. Adequate laboratory values (refer to study protocol)

Exclusion criteria

A patient will be excluded from participation in the trial if one or more of the following criteria are met:;1. Inability to lie supine for more than 30 minutes

2. Documented previous severe allergic reaction to iodine-based contrast media, despite adequate pre-medication.
3. Indication for cervical mediastinoscopy
4. Participation in another clinical study with an investigational product during the past 6 months
5. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
6. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) <6 months prior to the first dose of study drug
7. Any unresolved toxicity NCI CTCAE Grade >=2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
8. Patients with Grade >=2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
9. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab (MEDI4736) may be included only after consultation with the Study Physician.
10. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
11. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 6 months of the first dose of study drug
12. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.
13. History of allogenic organ transplantation.
14. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]).
15. History of another primary malignancy except for: Malignancy treated with curative intent and with no known active disease >=5 years before the first dose of IP and of low potential risk for recurrence, Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, Adequately treated carcinoma in situ without evidence of disease
16. History of active primary immunodeficiency
17. Active infection including: tuberculosis, hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, human immunodeficiency virus (positive HIV 1/2 antibodies), Epstein Barr Virus (EBV, positive IgM antibodies), cytomegalo virus (CMV, positive IgM antibodies)
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab (MEDI4736); exceptions apply.
19. Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab (MEDI4736). Note: Patients, if enrolled, should not receive live vaccine whilst receiving durvalumab (MEDI4736) and up to 30 days after the last dose of durvalumab (MEDI4736).
20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab (MEDI4736) monotherapy.

21. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
22. Prior randomisation or treatment in a previous durvalumab (MEDI4736) and/or tremelimumab clinical study regardless of treatment arm assignment.
23. Patients who have received prior anti-PD-1, anti PD-L1 or anti CTLA-4.
24. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-09-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[111In]In-oxine-T-cellen (CD8+)
Generic name:	[111In]In-onxine-T-cellen (CD8+)
Product type:	Medicine
Brand name:	[89Zr]Zr-DFO-durvalumab
Generic name:	[89Zr]Zr-DFO-durvalumab
Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-03-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-05-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2019-000670-37-NL
ClinicalTrials.gov	NCT(nognietbekend)
CCMO	NL68987.091.19