An exploratory study of durvalumab (MEDI4736) uptake during concurrent chemoradiotherapy in stage III NSCLC patients using 89Zr-labeled durvalumab PET

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Primary Objectives:* To study early (1 week after start of cCRT) and late changes (after finishing cCRT) in durvalumab (MEDI4736) uptake in tumor and metastatic lymph nodes during cCRT * To study early and late changes in durvalumab (MEDI4736)...

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

Summary

ID

NL-OMON55251

Source
ToetsingOnline

Brief title
CONDOR

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,AstraZeneca

Intervention

Keyword: 89Zr, durvalumab, MEDI4736, NSCLC

Outcome measures

Primary outcome

Safety Assessments:

89Zr-MEDI4736 will be administered using microdosing, i.e. patients will be injected with 22.5 mg of MEDI4736 on 3 time points. Any toxicity suspected to be associated with MEDI4736 will be reported in the presentation of safety data. All toxicities associated with chemotherapy and radiotherapy will not be listed.

Efficacy Assessments:

This is an exploratory imaging study of 89Zr-labeled MEDI4736 and therefore the primary endpoint of this study is to assess 89Zr-MEDI4736 uptake in tumor lesions at 3 different time points. The effect cCRT on 89Zr-MEDI4736 uptake in tumor lesions, in malignant and non-malignant lymph nodes, and in the spleen will be quantified. The efficacy of MEDI4736 will not be assessed.

Pharmacodynamic Assessments

The imaging data will be correlated to tumor PD-L1 expression.

Secondary outcome

Venous blood samples will be used for PK analysis. (Ir)reversible uptake of 89Zr-durvalumab (89Zr-MEDI4736) in normal organs and tumorous lesions will be

modelled according Patlak analysis.

Study description

Background summary

We hypothesize that concurrent chemoradiotherapy (cCRT) sensitizes tumors to durvalumab therapy (MEDI4736), an anti-PD-L1 monoclonal antibody, through increase of PD-L1 expression on tumor cells and immune cells in tumor lesions, in metastatic and non-metastatic lymph nodes and in the spleen. Therefore, uptake of durvalumab in these organs will increase during cCRT.
To visualize the PD-L1 pathway, positron emission tomography (PET) will be performed with the radiolabeled MEDI4736. Imaging with 89Zr-MEDI4736 allows for non-invasive quantification of its direct target, the PD-L1 receptor on the tumor cells and in immune cells, which is now the most important biomarker for patient selection in current trials of anti-PD-(L)1 mAbs. As the technique is non-invasive and images the whole body, it allows for serial measurements of tumor uptake, as well as heterogeneity within and between tumor lesions. Repeated 89Zr-durva-PET (89Zr-MEDI4736-PET) scans can be used to monitor these changes, an approach which helps to understand the dynamics of durvalumab (MEDI4736) uptake induced by cCRT.

Study objective

Primary Objectives:
* To study early (1 week after start of cCRT) and late changes (after finishing cCRT) in durvalumab (MEDI4736) uptake in tumor and metastatic lymph nodes during cCRT
* To study early and late changes in durvalumab (MEDI4736) uptake in immune related organs (i.e. non-malignant lymph nodes and spleen) during cCRT

Secondary Objective(s):
* To study any correlations between baseline tumor PD-L1 expression (based on immunohistochemistry) and the baseline uptake and changes in 89Zr-durvalumab (89Zr-MEDI4736) uptake in tumor sites.
* To study (ir)reversible uptake of 89Zr-durvalumab (89Zr-MEDI4736) in normal organs and tumorous lesions using Patlak analysis.

Study design

Single arm open label proof-of-concept (imaging) study.

Treatment procedure: All patients will undergo concurrent chemotherapy and radiotherapy in accordance with Dutch national guidelines. Patients with a

non-squamous tumor will be treated using platinum/pemetrexed, and squamous tumors using platinum/etoposide. Thoracic radiotherapy will be delivered concurrent with the 1st of 2 cycles of chemotherapy in accordance with the guidelines of the EORTC (De Ruysscher et al 2017), and dose-fractionation schemes used will be as described in the guidelines of the ESMO (Eberhardt et al 2015).
For patients with oligometastatic disease, local consolidation radiotherapy will be allowed after the second 89Zr-durva-PET procedure.

Intervention

89Zr-durva-PET procedure: The PET tracer used will be 89Zr-durvalumab (89Zr-MEDI4736). 89Zr-durva-PET procedures will be performed at baseline (tracer injection 1-2 weeks prior to start of cCRT), 1 week after start of cCRT (tracer injection on day 0 of cCRT) and after finishing cCRT (tracer injection on the last fraction day of the cCRT regimen). PET imaging will be performed at 168hrs post-injection of 37 MBq 89Zr-durvalumab (89Zr-MEDI4736).

Optional: 3 patients can undergo 2x2 additional PET scans after administration of the tracer, namely on days 2 and 5 post injection.

blood sampling: 4x7cc blood will be drawn per PET procedure (around the tracer injection and the PET images); for the pts participating undergoing the optional scans this is a total of 7x7cc per PET procedure (at week 0 and at week 1) and 4x7cc during the last PET procedure

biopsy: optionally, a lymph node biopsy can be performed in patients with an easily accessible lymph node in whom increased uptake of tracer can be seen on the PET images

Study burden and risks

No pharmacological effect or toxicity is expected from PET scans with non-therapeutic tracer doses. The amount of 89Z-MEDI4736 (22.5 mg) is far below the MEDI4736 dose that is used in clinical studies and a pharmacological effect is therefore not anticipated. The total amount of radiation exposure is substantial, but immediate effects are not anticipated and risks associated with delayed effects are relatively small. Patients do not derive benefit from the PET scan results.

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

* Have a histologically or cytologically confirmed diagnosis of thoracic disease stage III NSCLC and planned to receive concurrent chemotherapy and radiotherapy on the thorax.
* Patients with oligometastatic stage IV comprising a thoracic stage III and up to 2 distant metastases amenable for radical local consolidative therapy are also eligible.
* Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
* Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
* Age > 18 years at time of study entry.
* Have a World Health Organisation (WHO) performance status of 0 or 1.
* Life expectancy of > 3 months.
* Have measurable disease based on RECIST 1.1.
* Must consent to allow use of PD-L1 measurements obtained from tumor biopsies.
* Adequate organ and bone marrow function, as deemed acceptable by the treating

physician in the context of cCRT.
* Females of childbearing potential must use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment. Acceptable methods of contraception include total sexual abstinence, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions, copper-banded intra-uterine devices and vasectomised partner. All methods of contraception must be used in combination with the use of a condom by their male sexual partners for intercourse.
* Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

Exclusion criteria

* 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.
* Participation in another clinical study with an investigational product during the last 4 weeks.
* Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) * 30 days prior to the first dose of study drug If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator.
* 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.
* Patients with Grade *2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
* Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
* Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Limited surgical excision of isolated lesions for palliative or diagnostic reasons is acceptable.
* History of allogenic organ transplantation.
* 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]). The following are exceptions to this criterion:
a. Patients with vitiligo or alopecia
b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on

hormone replacement
c. Any chronic skin condition that does not require systemic therapy
d. Patients without active disease in the last year may be included but only after consultation with the study physician
e. Patients with celiac disease controlled by diet alone.
* Active infection as judged to be unacceptable by the treating physician in the context of cCRT.
* History of active primary immunodeficiency.
* Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
* Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
* History of another primary malignancy except for
a. Malignancy treated with curative intent and with no known active disease *2 years before the first dose of IP and of low potential risk for recurrence
b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
c. Adequately treated carcinoma in situ without evidence of disease.
* History of leptomeningeal carcinomatosis.
* Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each with IV contrast of the brain prior to study entry. Patients with more than 2 brain metastases will be excluded. Patients with 1 or 2 brain metastases that are not amenable for stereotactic radiotherapy will be excluded.
* Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
* 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 monotherapy.
* Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
* Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.
* Any prior anti PD-1, PD-L1 and CTLA-4 therapy.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-06-2020
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-durvalumab
Generic name:	89Zr-durvalumab

Ethics review

Approved WMO Date:	06-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2019-004284-51-NL
CCMO	NL72282.029.19