Companion biomarker development for MEDI4736 treated non-small-cell lung cancer patients using 89Zirconium-labeled MEDI4736 * a feasibility study

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To assess the safety and biodistribution of 89Zr-MEDI4736 and its uptake in tumor and target irAE tissues.

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

Summary

ID

NL-OMON45283

Source
ToetsingOnline

Brief title
89Zr-MEDI4736 in MEDI4736 patients with NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lungcancer, Non-small cel 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: 89Zirconium-labeled, MEDI4736, NSCLC

Outcome measures

Primary outcome

* To assess the safety of 89Zr-MEDI4736.

* To assess uptake of 89Zr-MEDI4736 in tumor lesions.

Secondary outcome

* Assess uptake of 89Zr-MEDI4736 in normal tissues to evaluate the

biodistribution and dosimetry.

* Characterize tumor uptake heterogeneity between patients and within and

between tumor lesions of the same patient

* Correlate 89Zr-MEDI4736 tumor uptake with tumor and TIL PD-1 and PD-L1

expression as well as other blood and tissue parameters.

* Correlate 89Zr-MEDI4736 organ uptake with irAEs. The focus will be on the

lung, liver, thyroid, pancreas, kidneys and pituitary.

Study description

Background summary

Immune responses directed against tumors are one of the body*s natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung, renal , pancreatic, ovarian cancer, and hematologic malignancies, tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable

prognosis.

PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell . This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination.
MEDI4736 is being developed as a potential anticancer therapy for patients with advanced solid tumors. MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-*).

To identify patients that will benefit the most from treatment with mAbs like MEDI4736, better knowledge of the in vivo behavior of the drug is warranted. For this, positron emission tomography (PET) imaging with radiolabeled mAbs (immuno-PET) is an attractive option. In this study, MEDI4736 will be radiolabeled with 89Zirconium (89Zr-MEDI4736). 89Zr-MEDI4736 quantifies the PD-L1 receptor on tumor cells, the most important (ex-vivo) tissue biomarker for patient selection in current trials with anti-PD-(L)1 mAbs. With 89Zr-MEDI4736 PET it will be possible to perform in vivo PD-L1 immunohistochemistry and provide unique insight in the performance of tumor tissue PD-L1 IHC.

Study objective

To assess the safety and biodistribution of 89Zr-MEDI4736 and its uptake in tumor and target irAE tissues.

Study design

Single arm open label exploratory pilot (imaging) study. To visualize the PD-L1 pathway, positron emission tomography will be combined with the radiolabeled anti-PDL1 monoclonal antibody MEDI4736. Imaging with 89Zr-MEDI4736 allows for non-invasive quantification of its direct target, the PD-L1 receptor on the tumor cells, the most important biomarker for patient selection in current trials with anti-PD-(L)1 mAbs. Because the technique is non-invasive and whole body, it allows for serial measurements of tumor uptake as well as looking at heterogeneity within and between tumor lesions. After 89Zr-MEDI4736 injection (day 0), sequential PET imaging will be performed at 1 hour, 72 hours and 120

hours post injection. On day 12, 89Zr-MEDI4736 will be injected within two hours after a therapeutic non-radiolabeled dose of MEDI4736, followed by sequential PET imaging to minimize the possibility of negative imaging findings. At a tracer dose the labeled antibody may not sufficiently reach the target due to sink effects in e.g. liver, spleen, blood or other compartments/organs. After a therapeutic non-radiolabeled dose, 89Zr-MEDI4736 may not accumulate in the tumor due to saturation of the PD-L1 target by the therapeutic dose. After enrollment of the first three patients the data will be analyzed. When tumor targeting is not seen with both imaging strategies, the dose of non-radiolabeled MEDI4736 might be adjusted.
To correlate the imaging results to tumor and peripheral immune parameters like PD-1, PD-L and T cell subsets, tumor and blood samples will be obtained at baseline. Two additional biopsies are allowed in case the PET scans show heterogeneous uptake between tumor lesions of the same patient. In this way, imaging with 89Zr-MEDI4736 PET will aid further validation of PD-L1 IHC.
89Zr-MED4736 might also predict for immune related adverse events (irAE). Whole body imaging allows to quantify MEDI4736 binding in target irAE tissues and the level of tracer uptake might predict for irAEs. Imaging results will be correlated to irAE findings during MEDI4736 treatment. From day 12 on, patients will be treated with 750 mg MEDI4736 IV Q2W until disease progression or unacceptable toxicity and to a maximum of 12 months.

Intervention

Not applicable

Study burden and risks

No toxicity is expected from PET scans with tracer microdoses. The amount of 89Z-MEDI4736 (2 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 because of the limited life expectancy of patients with stage IV NSCLC the long term risk of developing a secondary malignancy due to radiation exposure is only theoretical. Patients do not derive benefit from the PET scan results. Since there is a lack of a well performing predictive biomarker of response, the results of this imaging biomarker study can be of high interest for NSCLC patients that are eligible for anti-PD-(L)1 treatment in the future.

Up to two on study biopsies are allowed in this study (after the first and before the second 89Zr-MEDI4736 PET scan) in case the first 89Zr-MEDI4736 PET scan shows heterogeneous uptake between tumor lesions in individual patients (defined in section 3.1.2). Although this is demanding for patients, tumor biopsies in lung cancer patients are considered safe with a low and manageable complication rate. These biopsies will be used to explain heterogeneous tracer

uptake and relate the imaging results to that of the tissue biomarkers PD-1 IHC (locally) PD-L1 IHC (Ventana assay using SP263).

The overall response rate for second line treatment with single agent chemotherapy is ~10%. In a phase I trial of MEDI4736, 14% of 149 patients with advanced NSCLC had a best overall response of complete response (CR)/partial response [Rizvi N, ASCO 2015, Abstract ID 8032]. MEDI4736 is therefore a very promising drug for the treatment of NSCLC in the second line setting and beyond. It is therefore not unlikely that patients derive benefit from this study. As can be found in the Investigator*s Brochure, the toxicity is manageable and the safety profile acceptable.

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

For inclusion in the study subjects must fulfill all of the following criteria:
* Have a histologically or cytologically confirmed diagnosis of stage IV, EGFR wt and EML4-ALK fusion negative NSCLC and have received at least one line of platinum based doublet chemotherapy.
* 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 more than 3 months.
* Have measurable disease based on RECIST 1.1.
* Must provide tissue from a histological biopsy of a tumor lesion that is not radiated prior to biopsy and obtained after the last line of systemic therapy to determine the PD-L1 status.
* Willing to undergo up to two additional biopsies when the first 89Zr-MEDI4736 PET scan shows heterogeneous uptake.
* Adequate normal organ and marrow function.
* Females of childbearing potential must use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment.
* 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

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:
* Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment in the present study.
* Participation in another clinical study with an investigational product during the last 4 weeks.
* Any previous treatment with a PD1 or PD-L1 inhibitor, including MEDI4736.
* History of another primary malignancy except for: * Malignancy treated with curative intent and with no known active disease *3 years before the first dose of study drug. * Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. * Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ.
* Receipt of the last dose of anti-cancer therapy * 14 days prior to the first dose of study drug.
* Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, 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
* Any unresolved toxicity (CTCAE grade <2) from previous anti-cancer therapy.
* 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 autoimmune disease within the past 2 years requiring systemic

steroid treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids. NOTE: Subjects with vitiligo, Grave*s disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
* Active or prior documented inflammatory bowel disease (e.g., Crohn*s disease, ulcerative colitis)
* History of primary immunodeficiency
* History of allogeneic organ transplant
* History of hypersensitivity to MEDI4736 or any excipient
* Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
* Known history of previous clinical diagnosis of tuberculosis
* History of leptomeningeal carcinomatosis
* Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving MEDI4736
* Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control
* Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
* Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids exceeding a daily dose equivalent of 10 mg prednisolone. Patients with asymptomatic brain metastases are allowed if these do not exceed a maximal diameters of 2 cm.
* Subjects with uncontrolled seizures.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-03-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89-Zirconium labeled MEDI4736
Generic name:	89-Zirconium labeled MEDI4736
Product type:	Medicine
Brand name:	MEDI4736
Generic name:	Durvalumab

Ethics review

Approved WMO Date:	18-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	First submission
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	EUCTR2015-005765-23-NL
CCMO	NL59976.029.16