89Zirconium-labeled nivolumab and 18F-labeled anti-PD-L1 as predictive imaging biomarkers of response and toxicity in nivolumab treated patients with non-small-cell lung cancer * a feasibility study

Published: 01-06-2016
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To assess uptake of 18F-PD-L1 and 89Zr- nivolumab in tumor lesions.

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

Summary

ID

NL-OMON43982

Source
ToetsingOnline

Brief title
89Zr-nivolumab and 18F-anti-PD-L1 in nivolumab treated patients with NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: 18F-labeled anti-PD-L1, 89Zirconium-labeled nivolumab, NSCLC

Outcome measures

Primary outcome

To assess uptake of 18F-anti-PD-L1 and 89Zr-nivolumab in tumor lesions and in normal tissue.

Secondary outcome

To assess the safety of 18F-anti-PD-L1 and 89Zr-nivolumab.

Characterize tumor uptake heterogeneity between patients and within and between tumor lesions of the same patient.

Characterize the relationship between 18F-anti-PD-L1 and 89Zr- nivolumab tumor uptake and tumor cell and tumor infiltrating lymphocyte (TIL) PD-1 and PD-L1 expression as well as other blood and tissue parameters (see section 6.3.16).

Explore the relationship between 89Zr- nivolumab and 18F-anti-PD-L1 organ uptake with irAEs. The focus will be on the gut, lung, liver, thyroid and pituitary.

Assess uptake of 18F-anti-PD-L1 and 89Zr- nivolumab in normal tissues to evaluate the biodistribution and dosimetry.

Study description

Background summary

Tumor PD-L1+ immunohistochemistry (IHC) seems to be related to nivolumab response, but the signal is not straightforward. Temporal and spatial variation

of tumor PD-L1 expression (within and between tumor lesions) might be responsible for its suboptimal predictive value as biomarker of response. Therefore there is a need to further validate tumor PD-L1 IHC as predictive biomarker, as well as looking at alternatives. Biological imaging of PD-1 and PD-L1 allows to monitor the PD-1/PD-L1 pathway from both sides, non-invasively.

Study objective

To assess uptake of 18F-PD-L1 and 89Zr- nivolumab in tumor lesions.

Study design

Single arm open label exploratory pilot (imaging) biomarker study.
To visualize the PD-1/PD-L1 pathway, positron emission tomography (PET) will be combined with radiolabeled anti-PD-1 monoclonal antibody nivolumab (89Zr-nivolumab) and with a radiolabeled PD-L1 binding biologic (18F-anti-PD-L1), developed by BMS (18F-anti-PD-L1). Imaging with 89Zr-nivolumab allows for non-invasive quantification of its direct target, the PD-1 receptor on tumor infiltrating lymphocytes, while imaging with 18F-anti-PD-L1 allows for non-invasive quantification of PD-L1 on tumor cells, the most important (ex-vivo) tissue 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.
89Zr-nivolumab might also predict for immune related adverse events (irAE). Whole body imaging with 89Zr-nivolumab allows to quantify nivolumab binding in target irAE tissues and the level of tracer uptake might predict for irAEs.

Intervention

Not applicable.

Study burden and risks

Nivolumab is a highly active 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. Toxicity is manageable and the safety profile acceptable. No toxicity is expected from PET scans with tracer microdoses. The amount of 18F-anti-PD-L1 will be in the pico to nano molar quantity, far below the dosis for a pharmacological effect. The amount of 89Z-nivolumab (1-2 mg) is far below the nivolumab 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. Up to two biopsies are allowed in this study. Although this is

demanding for patients, tumor biopsies in lung cancer patients are considered safe with a low and manageable complication rate. No side effects are expected from blood withdrawal.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Have a histologically or cytologically confirmed diagnosis of stage IV, EGFR WT and EML4-ALK fusion negative NCSLC and have received at least one line of platinum based doublet chemotherapy. EGFR and EML4-ALK testing is not necessary in patients with squamous NSCLC.
- Be willing and able to provide written informed consent/assent for the trial.

- Be > 18 years of age on day of signing informed consent.
- 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 actual PD-L1 status.
- Willing to undergo a second biopsy when the 18F-anti-PD-L1 or 89Zr-nivolumab PET scans show heterogeneous uptake.
- Have a performance status of 0-1 on the ECOG Performance Scale (Appendix 2).
- Demonstrate adequate organ function. All screening labs should be performed within 10 days of treatment initiation.
- Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception during the study and for 23 weeks after the last dose of nivolumab. Women who are not of childbearing potential (i.e. who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception during the study and for 31 weeks after the last dose of nivolumab.

Exclusion criteria

A subject who meets any of the following criteria will be excluded from participation in this study:
- Is currently participating in or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment or has not recovered (i.e., * Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 0 or who has not recovered (i.e., * Grade 1 or at baseline) from adverse events due to a previously administered agent.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 0. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- Has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Note: Subjects with asymptomatic CNS metastases are allowed to enter the study.
- Has an active autoimmune disease 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.
- Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that

might confound the results of the trial, interfere with the subject*s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks after the last dose of trial treatment.
- Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
- Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- Has known active Hepatitis B or C.

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):	07-09-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	18F-anti-PD-L1
Generic name:	18F-anti-PD-L1
Product type:	Medicine
Brand name:	89-Zr-Nivolumab
Generic name:	89-Zr-Nivolumab

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2016
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	EUCTR2015-004760-11-NL
CCMO	NL55422.029.16

Study results

Date completed:	29-05-2019
Actual enrolment:	13