Combining SBRT and pembrolizumab in early stage non-small cell lungcancer patients planned for surgery: exploring safety and immunological proof of principle.

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To identify the immunological response to combined SABR and pembrolizumab treatment in early stage NSCLC. Expression rates andactivation states of immune effector subsets will be assessed in tumor core biopsy specimens, peripheral blood and tumor…

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

Summary

ID

NL-OMON49358

Source
ToetsingOnline

Brief title
Combining radiotherapy and immunotherapy in early stage NSCLC patients

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lungcancer, Non-small cell lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Merck Sharp & Dohme ,Merck Sharp & Dohme (MSD)

Intervention

Keyword: Non-small cell lungcancer (NSCLC), Pembrolizumab, SABR

Outcome measures

Primary outcome

Examination of tumor core biopsies and resection material. FACS analysis on

EBUS-FNA of tumor draining lymphnodes (TDLNs) and peripheral blood to detect

immunomodulation.

Secondary outcome

The correlations of in-vivo PD-1 expression, quantified by immune-PET, with

tissue and blood based immune-parameters.

Assessment of clinical signs of radiation pneumonitis

Study description

Background summary

The current standard treatment for early stage NSCLC is an anatomical surgical resection, with SABR being reserved for patients not fit to undergo resection. Despite the early stage of disease, a substantial number of patients with early stage non-small-cell lung cancer (NSCLC) relapse within five years of treatment. A pooled analysis of the ROSEL and STARS trials showed that stereotactic ablative radiotherapy (SABR) may provide an alternative to surgical treatment for patients with early stage disease. One of the reasons for the favorable effects of SABR may be due to an immunological response against tumor cells, elicited by radiotherapy. In this protocol we will explore the addition of immunotherapy to SABR to augment the antitumor T cell response, associated with radiotherapy. Because surgical resection is still the current standard of care for patients who are fit to undergo surgery, the subjects will

undergo a lobectomy with hilar and mediastinal lymph node dissection after pembrolizumab or SABR +/- pembrolizumab treatment. This is a key feature of this study and an unique opportunity to perform histological examination of the entire lung tumor, its associated lymph nodes and normal lung tissue after immunotherapy, allowing the study of immune response heterogeneity and correlating this with non-invasive imaging and blood results. In the surrounding normal lung tissue, radiation and immunotherapy induced toxicity can be evaluated.

Study objective

To identify the immunological response to combined SABR and pembrolizumab treatment in early stage NSCLC. Expression rates and activation states of immune effector subsets will be assessed in tumor core biopsy specimens, peripheral blood and tumor draining lymph nodes (TDLNs) by means of EBUS derived fine needle aspirates. Samples will be taken before and after treatment with SABR, pembrolizumab or SABR + pembrolizumab combined, and at surgery.

Study design

An open label randomized exploratory study of the mechanisms of action of combined treatment with SABR and immunotherapy (pembrolizumab, anti-PD1) for early stage NSCLC.

Intervention

Patients will be randomized between pembrolizumab or SABR with or without 2 cycles of pembrolizumab treatment (starting on the first day of radiotherapy). The patients will undergo a lobectomy with hilar and mediastinal lymph node dissection after pembrolizumab or SABR +/- pembrolizumab treatment. Translational research to explore the immune mechanism of action will include biological imaging with immuno-PET. This immuno-PET can be stressfull for patients and therefore, this immuno-PET is not obligated for participating in this study. Expression rates and activation states of immune effector subsets will be assessed in tumor core biopsy specimens, peripheral blood and tumor draining lymph nodes (TDLNs) by means of fine needle aspirates of TDLNs. Samples will be taken before and after pembrolizumab or SABR +/- pembrolizumab treatment and at surgery.

Study burden and risks

Combining SABR with surgery appears safe, according to previously performed studies. The addition of pembrolizumab to SABR might lead to a higher rate of pneumonitis. However, the incidence of pneumonitis depends on the target volume and is rarely seen with treatment of early stage lung cancer. Because only

patients with peripheral tumors are eligible for this trial and patients receive a lobectomy according to national guidelines on the treatment for NSCLC, the irradiated lung lobe will be resected and resection margins (i.e. central bronchial and vascular structures) are not involved in the radiation target volume.

Radiotherapy is a widely used therapy for lungcancer. Given the precise targeting of SABR, we expect no to little toxicity. Symptoms of fatigue, dysphagia and irritated skin could occur. With radiotherapy targeted at or in the area of a rib, it is possible that pain symptoms may occur months after therapy. This will be treated with pain medication and is self-limiting. Pain symptoms may also be prevented by the use of radiotherapy. Other toxicity is dependent of the target location.

The patient will be asked to undergo investigative procedures, in addition to the procedures that will take place for the (combination)therapy. The investigative procedures include:
- Physical examination
- Blood sampling
- Urine sampling
- Echocardiography (ECG)
- CT-scans
- MRI scans of the brain
- Endobronchial Ultrasound (EBUS)
- Biopsy of lungtumor

The patient will be exposed to addition ionizing radiation through the use of positron emitting radionuclides and CT-scanners. The totale radiation exposure will be around 20 mSv. It is possible that patients experience discomfort during scanning. To reduce the amount discomfort as much as possible, patients will be informed about the procedure and staff will be present during scanning.

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

Histologically or cytologically confirmed diagnosis of early stage (T1cN0, T2aN0 and T2bN0) peripherally located NSCLC, eligible for surgical resection.
Highly suspected NSCLC is defined as an a priori change of >85% that the lesion is malignant, according to the publication of Herder et al. (59)
Be willing and able to provide written informed consent/assent for the trial.
Be 18 years of age or older on day of signing imformed consent.
Have measurable disease based on RECIST 1.1.
Must provide tissue from a core or excisional biopsy of the primary tumor lesion.
Have a performance status of 0-1 on the ECOG Performance Scale.
Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.
Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Female subjects of childbearing potential should be willing to use two methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not ben free form menses for >1 year.
Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Exclusion criteria

Is currently participating in or has participated in a study of an investigational agent or using investigational device within 4 weeks of the first dose of treatment.
Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days proor to the first dose of trial treatment.
Has had a prior monoclonal antibody within 4 weeks prior to study day 1 or who has not recovered (i.e. grade 1 or lower, or at baseling) 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 1 or who has not recovered (i.e. grade 1 or lower at baseline) from adverse events due to a previously administered agent.
Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cel carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented histroy of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.
Has a history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
Has an active infection requiring systemic therapy.
Has a histroy 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 bst interest of the subject to participate, in the opinion of the treating investigator.
Has known psychiatric or substance abude disorders that would interfere with cooperation with the requirements of the trial.
Is pregnant or breastfeedig, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
Has known active Hepatitis B (e.g. HBsAg reactive) or Hepatitis C (e.g. HCV RNA

[qualitative] is detected).
Has received a live vaccine within 30 days prior to the first dose of trial treatment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-05-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-pembrolizumab
Generic name:	89Zr-pembrolizumab
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	25-04-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2019
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	EUCTR2016-003819-36-NL
CCMO	NL59360.029.17