Randomized Phase II, 2-arm study of Pembrolizumab after high dose radiation (SBRT) versus Pembrolizumab alone in patients with advanced non-small cell lung cancer.

Published: 27-03-2015
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Primary objective:To observe an increase in Overall Response Rate (ORR) from 20% in the pembrolizumab alone arm to 50% in the pembrolizumab after SBRT arm at 12 weeks.
Secondary Objective: - Disease Control Rate, defined as the percentage of...

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

Summary

ID

NL-OMON44895

Source
ToetsingOnline

Brief title
Pembrolizumab after SBRT versus Pembrolizumab in advanced NSCLC. PEMBRO-RT

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Merck Sharp & Dohme (MSD)

Intervention

Keyword: advanced NSCLC, High dose radiation (SBRT), Pembrolizumab, Randomized

Outcome measures

Primary outcome

Primary outcome: ORR (Overall Response Rate) at 12 weeks

Secondary outcome

Secondary outcome: DCR (Disease Control Rate), PFS (Progression Free Survival),

OS (Overall Survival) and toxicity

Exploratory outcome: biomarkers

Study description

Background summary

Despite the availability of accepted second line chemotherapy agents, patients with recurrent NSCLC will still progress quickly; have significant side effects and die of the disease. Therefore new treatment options should be considered.

Recently, immune checkpoint inhibitors have attracted attention and have shown to have both effectiveness and a very good toxicity profile. One of these classes of drugs is the anti-PD1 monoclonal antibodies and these are currently tested in different tumor types including NSCLC.

Radiation therapy (Stereotactic body radiation therapy (SBRT) or high fractionated standard radiation) can be given successfully to small tumors. SBRT has shown to be a successful treatment for tumors of the lung with sizes of < 5 cm. SBRT can be given in doses varying up to 3x18 Gy. Toxicity is very limited, but the treatment is until now restricted to early stages of lung cancer or oligometastatic disease. Other organ sites suitable for SBRT are

primary tumors and/or metastases e.g. brain, liver, adrenal gland and bone (spine) tumors.

The traditional, palliative role of radiotherapy in metastatic disease is now evolving into that of a powerful initiator for immunotherapy. From different preclinical studies the expression of tumor antigens has shown to be up-regulated directly after radiotherapy and might therefore lead to changes in the immune response of the body. At this stage little is known about the impact of different total dose and fractionation regimens on the anti-tumor immune response. Both SBRT and standard palliative treatment regimens such as 5x4 Gy have shown to be successful. Therefore it is of great interest to investigate the effect of a treatment with radiotherapy, directly followed by the administration of pembrolizumab and to compare these results to treatment with pembrolizumab alone.

Since PD-L1 expression is not yet validated to be the best marker for immune modulation it is imperative that this study will be accompanied by a translational research focusing on factors involved in the immune response.

Study objective

Primary objective:
To observe an increase in Overall Response Rate (ORR) from 20% in the pembrolizumab alone arm to 50% in the pembrolizumab after SBRT arm at 12 weeks.

Secondary Objective:
- Disease Control Rate, defined as the percentage of patients having a complete response, partial response or stable disease at 12 weeks
- PFS, defined as time from randomization to disease progression or death,
- OS, defined as time from randomization to death (of any cause).
- Toxicity

Exploratory Objective:
Paired tumor material and blood samples will be used to identify possible new biomarkers for selection of patients who might benefit from immunotherapy.
Tumor tissue will be examined for at least the expression of the following:
PD-L1 expression (DAKO kit); PD1 expression; Tregs; NK infiltration; CD3+, CD8+ CD45RO T cells, and M2 macrophages.
Fluid Phase Biopsies (peripheral blood) will be collected for further analysis and comparative studies.

Study design

This is an open label, three center randomized 2-arm phase 2 study comparing pembrolizumab treatment alone with pembrolizumab after SBRT.

Intervention

Patients will be randomized into two arms.
Arm 1: High dose radiation (SBRT) followed by pembrolizumab treatment within 7 days after completion.
Arm 2: pembrolizumab treatment
There is a stratification for never/hardly smokers vs ongoing/recent smokers planned in this study.
The treatment duration of pembrolizumab (after 1 year) may be extended to 2 years, when no severe toxicity has occurred and it is in the best interest of the patient.

Study burden and risks

- Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection.
- IV line: may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely, infection, nausea, and lightheadedness. Because Pembrolizumab is an antibody, there is the possibility that an acute infusion reaction takes place. These are side effects that occur during or immediately after administration of Pembrolizumab. Possible signs and symptoms may include: change in blood pressure; coughing; dizziness; fast heart rate; the cold; the feeling that the tongue becomes swollen or that the airways are closed and have trouble breathing; fever; headache; joint pain; muscle pain; nausea; skin rash, hives or itching; shortness of breath; sweating; fatigue; vomiting.
- ECG: the procedure may cause minimal discomfort during the attachment and removal of the ECG leads to and from the skin.
- CT-scan: A CT-scan uses radiation. CT-scans may be done with or without oral or intravenous contrast. The scan may take between 30-90 minutes to complete depending on the areas of the body being scanned and the type of scanner.
- Tumor biopsy: having biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsy. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site. If a tumor in the lung is punctured a pneumothorax can occur.
- The CBCT that is created during each radiation treatment adds a tiny bit of extra radiation that is negligible compared to the radiation treatment. The radiation treatment itself can cause fatigue, dysphagia and light skin irritations. If patient will be irradiated on and around the rib, pain can arise after radiation. This pain can respond well to treatment with painkillers and then also usually go away.

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be >= 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Must provide newly obtained tissue from a core or excisional biopsy of a tumor lesion and are willing to have a second biopsy performed form any non-irradiated lesion after the radiation and immune-modulating treatment.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. Stage IV NSCLC; treated with at least 1 regimen of chemotherapy.
7. Have at least 2 separate (metastatic) lesions of which one is amenable for irradiation with a size of < 5 cm.
8. Demonstrate adequate organ function:
Absolute neutrophil count (ANC) >=1,500 /mcL; Platelets >=100,000 / mcL; Hemoglobin >=9 g/dL or >=5.6 mmol/L; Serum creatinine <=1.5 X upper limit of normal (ULN) OR measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) >=50 mL/min for subject with creatinine levels > 1.5 X institutional ULN; Serum total bilirubin <= 1.5 X ULN OR Direct

bilirubin <= ULN for subjects with total bilirubin levels > 1.5 ULN; AST (SGOT) and ALT (SGPT) <= 2.5 X ULN OR <= 5 X ULN for subjects with liver metastases; International Normalized Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) <=1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
All screening labs should be performed within 10 days of treatment initiation.
9. 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.
10. Female subjects of childbearing potential should be willing to use 2 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 (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
11. 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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., <= Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had prior chemotherapy or targeted small molecule therapy within 4 weeks prior to study Day 1 or who has not recovered (i.e., <= Grade 1 or at baseline) from adverse events due to a previously administered agent.
- Note: Subjects with <= Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
5. Have had previous radical radiation to any tumor site within 6 months prior to study Day 1.
6. Have known but untreated driver mutations of the EGFR gene or ALK translocation.
7. 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.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least six weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to trial treatment.
9. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history 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 Sjögren*s syndrome will not be excluded from the study.
10. Has evidence of symptomatic interstitial lung disease or a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. 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.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. 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 120 days after the last dose of trial treatment.
15. 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).
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
18. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
19. Has had major surgery or major blood transfusions (>3 packed cells) in the past 3 months.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-07-2015
Enrollment:	74
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pembrolizumab
Generic name:	nog niet bekend

Ethics review

Approved WMO Date:	27-03-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-06-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	01-09-2015
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-10-2017
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	23-09-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-10-2024
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2014-005118-49-NL
CCMO	NL51468.031.14