Rescue by radiotherapy and anti-CTLA4/PD-1 after failure of anti-PD-1 therapy in metastatic NSCLC patients, a proof-of-concept study.

Published: 24-07-2020
Last updated: 15-05-2024

Primary objectives:• to assess the safety of combining nivolumab, ipilimumab and up to 3 fractions of medium dose hypofractionated radiotherapy (mRT) to multiple tumor sites (1 to 4, with at least 1 site receiving 24Gy)• to explore the efficacy of...

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

Summary

ID

NL-OMON49121

Source
ToetsingOnline

Brief title
RECLAIM

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: BMS,Bristol-Myers Squibb

Intervention

Keyword: immunotherapy, lung cancer, NSCLC, radiotherapy

Outcome measures

Primary outcome

Safety will be defined as (i) the percentage of patients with adverse events

(NCI CTCAE), the grade and the relationship to IPI/NIVO/mRT will be assessed.

Tumor responses will be assessed by ORR and DCR, overall and per study group.

Clinical outcome parameters such as PFS, and OS at 1 and 2 years, will be

registered.

Secondary outcome

-

Study description

Background summary

Only a minority of non-small cell lung cancer (NSCLC) patients with low or negative tumor PD-L1 levels benefit from anti-PD-1 therapy. We hypothesized that the combination of ipilimumab, nivolumab and medium dose radiotherapy using 3x8Gy (IPI/NIVO/mRT) will act synergistically by enhancing immune activation, thereby leading to better tumor control. In this study, we aim to prove that in patients with low and negative PD-L1 tumors following progression on first line chemotherapy-pembrolizumab, treatment with IPI/NIVO/mRT is safe, and that it could elicit tumor responses, and eventually improve disease free and overall survival.

Study objective

Primary objectives:

• to assess the safety of combining nivolumab, ipilimumab and up to 3 fractions of medium dose hypofractionated radiotherapy (mRT) to multiple tumor sites (1 to 4, with at least 1 site receiving 24Gy)
• to explore the efficacy of combining IPI/NIVO/mRT in terms of objective response rates (ORR) and disease control rates (DCR) (short term)

Secondary objectives:
• To evaluate the ORR and DCR differences between tumors with a low PD-L1 and with negative PD-L1 expression after IPI/NIVO/mRT
• To evaluate the effects of IPI/NIVO/mRT on PFS and OS (long term)

Study design

a single center, single arm, phase 1 / 2 trial. This will be a 2-stage study; in stage-1, a total of 22 patients in each of the 2 defined groups will be enrolled, and if at least 1 patient has an objective response, the study will proceed to stage-2, in which additional patients will be recruited. A total of 30 evaluable patients are needed.

Intervention

In the first 6 weeks, all patients will undergo treatment with the combination of ipilimumab (IPI, 1mg/kg on day 1), nivolumab (NIVO; 240mg, q2w) and medium-dose multi-site hypofractionated radiotherapy (using 8Gy fractions on days 8, 10 and 12). After this 6 week treatment period, and if no disease progression is observed, patients will continue IPI (1mg/kg, q6w) and NIVO (360mg, q3w) until disease progression or unacceptable toxicity.

Study burden and risks

The current literature lacks data on the toxicity and efficacy of this IPI/NIVO/mRT approach. However, by extrapolating data from the first line treatment setting in NSCLC, we expect that the burden and risks associated with study participation will be acceptable. The combination of IPI/NIVO has comparable treatment-related toxicity as chemotherapy in the 1st line. However, the combination of IPI/NIVO performed much better than chemotherapy in the first line setting, especially for PD-L1 negative tumors The safety of combining concomitant IPI/NIVO and medium dose RT is unknown, however, preliminary safety data on IPI/NIVO consolidation after chemoradiotherapy in stage 3 NSCLC shows that toxicities are manageable. Clinical trials evaluating combined immunotherapy and radiotherapy have shown encouraging results on immunotherapy efficacy. In this trial, there is a potential immunological synergy of combining anti-PD-1, anti-CTLA4 and medium-dose radiotherapy for priming and activating the effector T-cells. Therefore, we expect that patients are likely to derive clinical benefit from study participation. Furthermore, the current routine second line therapy is docetaxel, which has a comparable

toxicity profile with a response rate of about 10%. Patients are still eligible to receive docetaxel if they fail to respond to the IPI/NIVO/mRT. Consequently, we do not expect enrolled patients to be *undertreated* because of study participation. The insights obtained in the translational part of this study can provide valuable insights for improving treatment options for future NSCLC patients.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed NSCLC, negative for EGFR, ALK or other treatable oncogenic drivers
2. WHO PS 0-2
3. Be willing and able to provide written informed consent for the trial.

4. Be above 18 years of age on day of signing informed consent.
5. Patients must have radiological disease progression on chemo-pembrolizumab
6. Have at least 1 lesion (up to 4) that is amenable to treatment with radiotherapy (3x8Gy as per judgement of the radiation oncologist), and at least 1 other unirradiated lesion which can serve as a measurable lesion for assessing tumor response based on RECIST 1.1.
7. Demonstrate adequate organ function, as deemed acceptable by the treating physician in the context of metastatic NSCLC

Exclusion criteria

1. Patients with fast progressive disease as per judgement of the treating physician.
2. Patients who had received any radiotherapy during previous treatment with chemo-pembrolizumab.
3. 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.
4. Active autoimmune disease requiring systemic steroid treatment within the past 3 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids.
5. Evidence of interstitial lung disease or active, non-infectious pneumonitis.
6. Active infection requiring systemic therapy.
7. A history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
8. Active Hepatitis B or C.
9. Psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
10. Has received prior therapy with an anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways (except pembrolizumab).
11. Has developed immune related adverse events on immunotherapy that necessitated stopping pembrolizumab indefinitely.
12. Patient is pregnant or breastfeeding, or expecting to conceive 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.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-09-2020
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2021
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

ID: 25166
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-001097-29-NL

Register	ID
CCMO	NL73485.029.20
OMON	NL-OMON25166