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

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25166

Source NTR

Brief title RECLAIM

Health condition

NSCLC, stage IV, progression on chemo-immunotherapy

Sponsors and support

Primary sponsor: AmsterdamUMC, dept Pulmonology **Source(s) of monetary or material Support:** BMS

Intervention

Outcome measures

Primary outcome

• to assess the safety of combining nivolumab, ipilimumab and up to 3 fractions of medium

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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 outcome

• 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 description

Background summary

Rationale: 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.

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.

Study population: Patients with metastatic NSCLC who have progressive disease during or after first line chemo-pembrolizumab. We will include 2 groups of patients: group 1 will be patients with PD-L1 negative (<1%) tumors, and group 2 are tumors with a PD-L1 expression between 1-49%. All histologic subgroups of NSCLC are eligible, and patients with treatable

oncogenic drivers will be excluded.

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 multisite 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.

Main study parameters/endpoints: 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.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: 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

Study objective

We hypothesized that the combination of IPI/NIVO/mRT is highly synergistic in triggering an effective anti-tumor immune response, especially in patients with a low or negative PD-L1. Moreover, we hypothesized that the IPI/NIVO/mRT combination can reclaim an anti-tumor response in patients who fail after first line combination of chemotherapy and anti-PD-1 therapy.

Study design

Primary endpoints: Safety will be assessed throughout the entire study period. For efficacy, there will be a 2-stage design: if no responses are seen in the first 22 patients, the study will be halted, else, the study will continue to accrue till 30 evaluable patients (33 accounting for drop-offs), expected AUG 2023.

Secondary endpoints: PFS and OS will be reported separately when follow-up will be more

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mature, expected DEC 2024.

Publication main results DEC 2023.

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.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following 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:

a. Leukocytes \geq 3,000/mm3

b. Absolute neutrophil count (ANC) \geq 1500/mm3

c. Platelet count \geq 100,000/mm3

d. Hemoglobin \geq 6 mmol/L

e. Creatinine \leq 1.5 x ULN or creatinine clearance (CrCl) \geq 40 mL/min (if using the Cockcroft-Gault formula below):

i. Female CrCl = [(140 - age) x weight x 0.85]/(0.85 x creat in mmol/L)

ii. Male $CrCl = [(140 - age) \times weight \times 1.00]/(0.81 \times creat in mmol/L)$

f. Total Bilirubin \leq 1.5 x ULN (except subjects with Gilbert Syndrome)

g. AST and ALT \leq 3 times the upper limit of normal

Exclusion criteria

A subject who meets any of the following criteria will be excluded from participation in this study:

1. Patients with fast progressive disease as per judgement of the treating physician.

2. Patients who had received any radiotherapy during previous treatment with chemopembrolizumab.

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 type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	26-08-2020
Enrollment:	33
Туре:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion	
Date:	26-08-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49121 Bron: ToetsingOnline Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

ID
NL8857
NL73485.029.20
NL-OMON49121

Study results