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

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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...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25166

Bron
NTR

Verkorte titel
RECLAIM

Aandoening

NSCLC, stage IV, progression on chemo-immunotherapy

Ondersteuning

Primaire sponsor: AmsterdamUMC, dept Pulmonology
Overige ondersteuning: BMS

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

• 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)

Toelichting onderzoek

Achtergrond van het onderzoek

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 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.

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

Doel van het onderzoek

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.

Onderzoeksopzet

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 mature, expected DEC 2024.

Publication main results DEC 2023.

Onderzoeksproduct en/of interventie

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.

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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 ≥ 3,000/mm3
b. Absolute neutrophil count (ANC) ≥ 1500/mm3
c. Platelet count ≥ 100,000/mm3
d. Hemoglobin ≥ 6 mmol/L
e. Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥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) x weight x 1.00]/(0.81 x creat in mmol/L)
f. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome)
g. AST and ALT ≤ 3 times the upper limit of normal

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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 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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	26-08-2020
Aantal proefpersonen:	33
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	26-08-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 49121
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8857
CCMO	NL73485.029.20
OMON	NL-OMON49121

Resultaten