Phase 1b study of safety and tolerability in patients treated with stereotactic radiotherapy combined with durvalumab and tremelimumab in stage 4 NSCLC

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To assess safety and tolerability of the combination of SBRT and combined CTLA-4/PD-L1 inhibition. In addition immune modulatory effect of the combination of an ablative dose of radiotherapy to the primary tumor and response to durvalumab/...

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

Summary

ID

NL-OMON44296

Source
ToetsingOnline

Brief title
SBRT + durvalumab + Tremelimumab in NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-small cell lung cancer (NSCLC)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Astra Zeneca,grant

Intervention

Keyword: CTLA4 inhibitor, Non-small cell lung cancer, PD-L1 inhibitor, Stereotactic radiotherapie

Outcome measures

Primary outcome

Establishing MTD in 3 sequential combination immunotherapy * radiotherapy

cohorts. Percentage of grade III/IV toxicities determined between first

radiotherapy day and 8 weeks after combination treatment.

Secondary outcome

All AEs, PFS, OS, response rate, T cell immune response (intracellular

production of IL-2, IFN-*, TNF-* and IL-4 by CD4+ en CD8+ T cells to 6

different stimuli).

Study description

Background summary

Only 20% of unselected patients with stage 4 NSCLC respond to single immunecheckpoint blockade by PD-(L)1 inhibitors. Responses to PD-1 and PD-L1 inhibitors are rapid and durable when they occur in lung cancer. High PD-L1 immunohistochemistry status enriches the population for a response. However numerically over half of patients that would respond are not selected. In addition even after enrichment 55% of patients do not repond. By blocking both PD-L1 and CTLA-4 two of four main domains of the cancer immune cycle are addressed, leading to more responding patients. Combining PD-(L)1 and CTLA-4 inhibtors is feasible and safe. Confirmed objective responses were observed for both PD-1 (38%; 95%CI 23-55) and PD-L1 inhibitors (23%; 95%CI 9-44%) independent of PD-L1 staining. By adding radiotherapy an important third additional path is addressed, possibly leading to more responses with a similar safety profile.

Study objective

To assess safety and tolerability of the combination of SBRT and combined CTLA-4/PD-L1 inhibition. In addition immune modulatory effect of the combination of an ablative dose of radiotherapy to the primary tumor and response to durvalumab/tremelimumab will be studied.

Study design

Phase 1 study with an adaptive design, n=25 patients. With sequential cohorts, first cohort starting with 1500 mg durvalumab iv day 4 ±2days before stereotactic radiotherapy (single-fraction 20 Gy, with a radiated tumor volume of 9cc (=2.5 cm diameter), SBRT) to the primary tumor and thereafter 1500 mg durvalumab iv every 4 weeks until 1 year of treatment or disease progression (cohort1 n=3). Followed by cohort 2 (n=6): tremelimumab 75 mg iv day 4 ±2days before SBRT to the primary tumor and durvalumab 1500 mg iv day 2 ±2days after radiotherapy, thereafter combined with tremelimumab 75 mg (combination only for maximum of 4 cycles) iv dose every 4 weeks until 1 year or disease progression. Followed by cohort 3 (n=6): durvalumab 1500 mg iv day 4 ±2days before SBRT to the primary tumor and day 2 ±2days after radiotherapy tremelimumab 75 mg (thereafter combination with durvalumab only for maximum of 4 cycles) iv dose and durvalumab 1500 mg iv every 4 weeks until 1 year or disease progression (see Figure1 page12). The most promising cohort (either cohort 2 or 3) will be expanded with another 10 patients for safety data.

Intervention

See Study design

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits, where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition, every 8 weeks (from week 8 until week 48) and then every 12 weeks, patients will undergo radiographic assessment of their tumors (by CT) until disease progression or treatment discontinuation whichever occurs later. Blood will also be collected at certain visits for research purposes (functional T-cell test). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Written informed consent;
- Histologically confirmed stage IIIB (without curative treatment options) and stage IV NSCLC. Tumor mutation status must be known, analyzed by next generation sequencing for specific mutations;
- A tumour tissue sample (< 6 month old);
- Any line of previous chemotherapy (but at least 1 line), with washout period of at least 4 weeks;
- At least one unidimensionally measurable lesion according to RECIST1.1 criteria;
- Age * 18 years;
- ECOG / WHO performance status of 0 or 1;
- Life expectancy of *12 weeks;
- Body weight > 30 kg;

- Adequate normal organ and bone marrow function:
- Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients.
- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women * 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >;1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
- Subject is willing and able to comply with the protocol for the duration of the study;
- Male and female patients with reproductive potential must use an approved contraceptive method, if appropriate. Female patients with childbearing potential must have a negative serum pregnancy test within 7 days prior to study enrollment.

Exclusion criteria

- Involvement in the planning and/or conduct of the study
- Participation in another clinical study with an investigational product during the last 3 months.
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
- Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) 1 month prior to the first dose of study drug (wash out period).
- Primary tumor smaller than 3 cm.
- Any unresolved toxicity NCI CTCAE Grade * 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
- Patients with Grade * 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
- Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
- Any history of radiotherapy treatment to the chest.
- Any prior radiotherapy (including palliative radiotherapy to non-target lesions) within 4 month of the first dose of study drug.
- Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.
- History of leptomeningeal carcinomatosis

- Subjects with untreated CNS metastases are excluded.
- Active or prior documented autoimmune or inflammatory disorders
- Uncontrolled intercurrent illness
- Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
- History of allogenic organ transplantation.
- History of active primary immunodeficiency
- Active infection including tuberculosis, hepatitis B, hepatitis C, or HIV. Patients with a past or resolved HBV infection and absence are eligible. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction is negative for HCV RNA
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Patients who have received any prior anti-PD-1, anti PD-L1 or anti CTLA-4.
- Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
- Judgment by the investigator that the patient is unsuitable to participate in the study
- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-11-2017

Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	NA
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	16-11-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2017-002797-39-NL
CCMO	NL62468.042.17
Other	NTR nummer 6553