Immune profiling of stage III non-small cell lung cancer patients treated with concurrent chemoradiation and adjuvant durvalumab: A prospective observational phase II trial

Published: 18-02-2021
Last updated: 12-10-2024

Primary Objective: To identify immune changes between baseline, one week of radiotherapy, end of radiotherapy and three months of durvalumab- Identification of differentially expressed proteins at all time points- Identification of differentially...

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

Summary

ID

NL-OMON52550

Source
ToetsingOnline

Brief title
Immune profiling of stage III NSCLC patients

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
immune changes, non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: KOFL grant

Intervention

Keyword: Immune profiling, Immune therapy, Non-small cell lung cancer, Radiotherapy

Outcome measures

Primary outcome

Profiling immune changes between baseline, after one week of radiotherapy, end

of radiotherapy and three months of durvalumab

Secondary outcome

- Progression-free survival

- Overall survival

- Toxicity during and after concurrent chemoradiation, also in relation to the

irradiated bone marrow volume:

o Lymphopenia and subtypes

o Neutropenia

o Anemia

o Other toxicity

o Dose and intensity of chemotherapy (i.e. dose delays/reductions)

- Toxicity of durvalumab and chemoradiation treatment:

o Pneumonitis

o Cardiac side effects

o Cognitive side effects

- Incidence and severity of adverse events (Common Terminology Criteria for

Adverse Events (CTCAE) v 5.0 and patient reported outcome (PRO)-CTCAE)

- Identify immune changes that are distinct for proton therapy compared with photon therapy

- Cardiac function: BNP, Troponins, ECG, blood pressure

- Neurocognitive function: HVALT-R, trail making test, controlled oral word association, and MOS

- Obtaining tumor material from standard diagnostic material for translational purposes

- Genetic and phenotypic tumor heterogeneity of the tumor biopsy

- Biobanking blood samples for later translational research

- Chest-CT, FDG-PET, brain imaging MRI/CT scans

- Circulating tumor DNA to determine minimal residual disease

- LC3/GABARAPL protein family in the blood

Study description

Background summary

Even with the addition of durvalumab to concurrent chemoradiation, approximately only half of the patients are alive at 3 years, and more have progressed already, either locally or distant. Not much is known regarding to identification of patients that will benefit from adjuvant durvalumab, or regarding resistance to adjuvant durvalumab after chemoradiation. Most data on immunotherapy resistance come from metastatic patients treated with monotherapy PD-(L)1 antagonists. Depending on PD-L1 expression level, 10-44% of patients respond well to PD-(L)1 antagonists. The majority of patients are either unresponsive, or experience a tumor recurrence after achieving an initial response. The development of individual immunological treatment strategies (e.g. selection of best treatment: mono- or combination ICI, ICI combined with chemotherapy, or the addition of radiotherapy) is hampered by the lack of knowledge in the best timing, sequencing, and dosing of all modalities and the lack of optimal biomarkers for monitoring the treatment response. This

highlights the need of clear biomarkers that can be used to select the best treatment for each individual patient and predict whether patients will benefit from adjuvant immunotherapy. Currently, there is only limited data available on the functional immune changes after concurrent chemoradiation in NSCLC patients. Identifying the effect of the treatment on immune cells (e.g. T-, B-, NK-cells, dendritic cells, macrophages) and what their functional consequences are is an essential first step to come to prognostic and predictive biomarkers.

Many studies investigating the role of immunomodulatory effects of treatment are carried out in either in vitro or in vivo animal models. However, identified factors frequently hamper clinical validation. In addition, as mentioned earlier, although several immunogenic factors have been shown to be released by irradiated tumor cells, so far, only a limited number of studies searched for potential predictive and prognostic immunological biomarkers (53-56).

This will be the first time that the immune effects of both treatment modalities will be studied, with, in addition, the immune changes during durvalumab treatment, which are also unknown at present. By getting more insight in the treatment-induced immunomodulatory effects, ultimately, in subsequent projects, this will allow to determine optimal immune stimulation and hence improved outcomes of subsequent durvalumab immune therapy

Hypothesis: Our hypothesis is that we can identify immune changes in stage III NSCLC patients receiving concurrent chemoradiation with protons or photons followed by durvalumab, as is done in standard clinical practice in The Netherlands.

Study objective

Primary Objective:
To identify immune changes between baseline, one week of radiotherapy, end of radiotherapy and three months of durvalumab
- Identification of differentially expressed proteins at all time points
- Identification of differentially expressed genes at all time points
- Investigate the functional immunological activity of serum samples at all time points
- Investigate the immune cell composition in blood samples from all time points

Secondary Objectives:
- To investigate the progression-free survival (PFS)
- To investigate the overall survival (OS)
- To evaluate toxicity during and after concurrent chemoradiation, also in relation to the irradiated bone marrow volume:
o Lymphopenia and subtypes
o Neutropenia
o Anemia

o Other toxicity
o Dose and intensity of chemotherapy (i.e. dose delays/reductions)
- To evaluate toxicity of durvalumab and chemoradiation treatment:
o Pneumonitis
o Cardiac side effects
o Cognitive side effects
- Incidence and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 and patient reported outcome (PRO)-CTCAE)
- To investigate immune changes that are distinct for proton therapy compared to photon therapy
- To evaluate the effects of protons versus photons on the occurrence of cancer cachexia/sarcopenia
- To evaluate whether a higher percentage of patients treated with protons will be able to receive adjuvant durvalumab, compared with photon treated patients
- Obtaining routine imaging (chest-CTs, 18FDG-PET, brain MRI/CTs) for qualitative and quantitative image analyses.
- To evaluate the effect of durvalumab and chemoradiation on the cardiac function: BNP, Troponins, ECG, blood pressure
- To evaluate the effect of durvalumab and chemoradiation on neurocognitive function: HVALT-R, trail making test, controlled oral word association, and MOS
- Obtaining tumor material from standard diagnostic material for translational purposes
- To investigate the genetic and phenotypic tumor heterogeneity of the tumor biopsy
- Biobanking blood samples for later translational research
- To detect circulating tumor DNA (ctDNA) to determine minimal residual disease
- To evaluate the effect of durvalumab after photon and proton therapy on LC3/GABARAPL protein family in the blood

Study design

This is a prospective, non-randomized observational phase II non-interventional clinical trial.

Patients with stage III NSCLC who are eligible for curative intent concurrent chemotherapy and radiotherapy will be enrolled in the study. They receive standard radiotherapy (60 Gy in 30 fractions of 2 Gy) with protons or photons according to the standard of care. Eligible patients will thereafter receive standard durvalumab immune therapy for 12 months. Eligibility criteria for this study are therefore similar to those for standard of care treatment.

Study burden and risks

The risk of the investigations in this trial (ECG's, blood pressure and blood withdrawals) are minimal. The biggest burden for participants may be the time needed for these investigations.

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

• Pathological diagnosis of adequately staged (according to standard practice using chest-CT, FDG-PET, brain imaging MRI/CT) NSCLC
• Participant is willing and able to give informed consent for participation in the trial
• Male or female, aged 18 years or above
• Scheduled to receive one of the following two therapeutic strategies:
o Concurrent chemotherapy and radiotherapy with photons (60 Gy in 30 fractions of 2 Gy) in patients with stage III NSCLC
o Concurrent chemotherapy and radiotherapy with protons (60 Gy in 30 fractions of 2 Gy) in patients with stage III NSCLC
• Is able and willing to comply with all trial requirement

Exclusion criteria

• Mixed non-small cell lung cancer with other histologies such as small cell lung cancer
• Not able to comply with the study protocol
• Less than 18 years* old
• Pregnancy or not able to comply with adequate contraception in women with child baring potential
• Previous radiotherapy to the chest for benign or malignant conditions, including radiation for breast cancer
• Previous malignancy treated with chemotherapy, immune therapy or radiotherapy (irrespective of when this happened)
• Previous malignancies treated with surgery only are allowed if 2 years or more before inclusion in the present study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2021
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	18-02-2021

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT04432142
CCMO	NL74399.068.20

Study results

Date completed: 01-07-2024

Summary results
Trial ended prematurely