NL NVALT2017 / Translational research for immune modulating and targeted therapy in non-small cell lung cancer, an exploratory NVALT study

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* To explore baseline predictive biomarkers for tumor response to immune modulating and targeted treatment in patients with NSCLC.* To develop biomarkers of therapy resistance to anti-PD-1 treatment in patients with NSCLC.* To explore patterns of...

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

Summary

ID

NL-OMON45514

Source
ToetsingOnline

Brief title
Translational research for immune modulating and targeted therapy in NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: ZonMw;Tango project

Intervention

Keyword: Biomarkers, NSCLC

Outcome measures

Primary outcome

- Relation between adaptive and innate immune status and tumor response rate, PFS and OS.

- Relation between gate keeper mutations and complex mutations with tumor response rate, PFS and OS on treatments used by treating physician.

- Correlation of the baseline ctDNA level with tumor response rate, PFS and OS

- Correlation of the change in ctDNA level after six weeks of treatment to ORR, PFS and OS.

- Validated tumor educated platelet algorithm that is associated with increased ORR, PFS and OS.

- Validated tumor educated platelet algorithm that is associated with therapy resistance.

- Correlation of STM-panel based response assessment with radiological response assessment as performed by CT-thorax.

- Correlation of PBMC FACS parameters of lymphoid and myeloid subsets in peripheral blood to tumor response rate, PFS and OS.

- Correlation of rare mutation profile, as assessed by NGS on tumor tissue, to tumor response rate, PFS and OS.

- Correlation of tumor tissue IHC parameters to tumor response rate, PFS and OS.

- Correlation of RNAseq on fresh frozen tumor tissue to tumor response rate,

PFS and OS.

- Correlation of CT based parameters to tissue parameters and tumor response

rate, PFS and OS.

- Correlation of differences between CT based (textural) parameters and tissue

parameters and tumor response rate.

Secondary outcome

na

Study description

Background summary

An effective and sustainable immune response against NSCLC is dependent on several immunological processes described by the cancer immune cycle. This cascade begins with the release of cancer cell antigens, followed by dendritic cell antigen capture and processing, T cell priming in the lymph node, T cell trafficking to tumors, and finally by CD8 positive T cells recognition and killing of cancer cells. In this last process the PD-1/PDL-1 checkpoint axis is important and recently effective check point inhibitors have become available for the treatment of lung cancer. Phase III studies showed that immunotherapy with nivolumab, pembrolizumab and atezolizumab provide a prolonged survival compared with docetaxel as second line treatment in advanced non-small cell lung cancer (NSCLC). Pembrolizumab also showed activity as first line treatment in advanced NSCLC in those patients who had *50% PD-L1 positive tumor cells and improved survival compared to chemotherapy.
Another group of patients of interest are those with advanced NSCLC that have a targetable gene mutation and are being treated with specific drugs. The incidence of these DNA aberrations in the total population of NSCLC is less than 5%. Resistant EGFR mutations such as T790M, HER-2 amplifications or mutations, cMET amplifications, mutations, exon 14 skipping, and translocations such as ALK, ROS1, RET are just examples where targeted drugs are biologically active and need specific knowledge how to treat and follow these patients.

Checkpoint and first line targeted drug resistant tumor cells will be present at the start of treatment or may develop during treatment. Many resistance mechanisms have been described on the basis of associations in only small resistant patient cohorts.
To determine patterns of signal transduction or changes in gate keeper

mutations, blood samples at baseline, in week 2 or 3, 6, 12 and at progression or recurrence of disease and tumor biopsies at baseline, optional at 6 weeks and at progression or recurrence of disease are gathered from patients that are registered in the NVALT *Dure Geneesmiddelen* Registry.

Moreover, results from especially immunotherapy trials show that we are in need of better biomarkers. The drugs are expensive and identification of a patient group that does not benefit could reduce healthcare expenses and auto-immune related toxicity. Similarly, the contribution of drug-induced resistance mechanisms in patients treated with targeted therapy should be further explored with comprehensive methods.

Study objective

* To explore baseline predictive biomarkers for tumor response to immune modulating and targeted treatment in patients with NSCLC.
* To develop biomarkers of therapy resistance to anti-PD-1 treatment in patients with NSCLC.
* To explore patterns of resistance in patients with NSCLC.

Study design

For this study, the PRoBE design principles will be followed. The PRoBE guidelines are an application of standard principles of good population science to the special case of biomarker research. In this descriptive study, somatic tumor phenotypic changes and their underlying genotype will be explored. Phenotypes are described by patient and tumor characteristics using clinical observations e.g. responders versus non-reponders and genotypes by targeted DNA and RNA seq methods. Patients will be treated on an outpatient basis with immune checkpoint inhibitors according to label and targeted treatment according to *Stand van de Wetenschap*. These patients will be registered at NVALT *Dure Geneesmiddelen* Registry.
Baseline examination will include a (PET-) CT scan of the thorax and upper abdomen for tumor size and textural measurements, blood sampling for ctDNA, PBMC, plasma, protein and thrombocyte extraction and a tissue sample for IHC, DNA and RNA analyses.
During treatment blood will be drawn according to a standard protocol (week 2 or 3, 6, 12 and at progression of disease) and CT scan of the thorax and upper abdomen every six to eight weeks to evaluate tumor response. Tumor biopsy will be performed before, at 6 weeks (optional) and upon progression of disease and/or disease recurrence. Origin of the biopsy, i.e. whether it is taken from the primary tumor or from a metastasis, will be reported. Except for the extra blood samples and tumor biopsies, all investigations are standard diagnostic procedures for the evaluation of a NSCLC patient.

Study burden and risks

Baseline blood sampling, tissue biopsy and (PET-)CT imaging is part of routine diagnostic workup of non-small cell lung cancer before treatment initiation. As is follow-up with a CT scan every twelve weeks upon treatment. For the purpose of this study extra blood will be drawn at regularly planned visits (week 0, 2 or 3, 6, 12 and at progression or recurrence of disease). Two EDTA blood tubes (20 ml), one serum tube (10 ml) and 1 tube of whole blood (10 ml) will be taken for PBMC isolation.
The tumor biopsy at baseline and upon disease progression is routine clinical practice, six weeks after the first PD-1/PD-L1 infusion tumor or start of TKI, biopsy is optional but recommended and should be discussed with patients. Biopsies will be taken from the most easily accessible tumor site and will be performed by means of bronchoscopy, CT or ultrasound guidance biopsy (no cytology) by an experienced radiologist or pulmonologist.
In this study, tumor and germline DNA will be analyzed using sequencing techniques. Therefore, there is a small possibility of detection of unsolicited findings, i.e. germline DNA variants that confer an increased risk of developing malignancies or other diseases both for the patient and his/her family. Patients should be informed in case of clinically relevant and medically actionable genetic alterations. We will consult a medical genetist for counseling. The analysis of ctDNA / ctRNA is not part of an established workflow and methods have not been validated yet. Therefore, we will not report such data to the patient.

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

1. Eligible for immunotherapy or targeted treatment.
2. Written informed consent for registry of patient data and extra blood and tumor biopsy.
3. Age * 18 years.

Exclusion criteria

1. Without written informed consent patient will be adopted anonymously in the registry and will not take part of the study.
2. Patients with written informed consent for registry of patient data but no consent for extra blood and tumor biopsy will be excluded from the study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2017
Enrollment:	300

Type:	Anticipated

Ethics review

Approved WMO Date:	29-09-2017
Application type:	First submission
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
CCMO	NL61370.042.17
Other	volgt