Validation of Pharmacokinetic and Pharmacodynamic Assays for determination of Nivolumab and Pembrolizumab concentrations, and the occupancy of their target receptor Programmed Death-1 (PD-1) on T-cells

Published: 27-10-2016
Last updated: 19-08-2024

The aim of this study is to develop and validate the ELISA and potential other assays (e.g. LC-MS), in order to measure drug concentration levels. For this, blood and other material will be collected.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON47401

Source
ToetsingOnline

Brief title
Developing Assays for Anti-PD-1 monoclonal antibodies

Condition

- Metastases

Synonym
metastasized cancer, Solid tumors

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Nederlands Kanker instituut

Intervention

Keyword: ELISA, immunotherapy, PD-1, Pharmacokinetics

Outcome measures

Primary outcome

Establish the clinical applicability as part of the validation of assays for

the determination of free and PD-1 receptor bound anti-PD-1 monoclonal

antibodies pembrolizumab and nivolumab in peripheral blood and other material.

Secondary outcome

Cross-validation between the described ELISAs and LC-MS methods.

Study description

Background summary

Programmed cell death protein 1 (PD-1) is a transmembrane immune checkpoint molecule, which is expressed on T-cells and pro-B cells. PD-1 fulfils various anti-inflammatory functions, such as promoting apoptosis of antigen specific T-cells and preventing activation of T cells. PD-1 binds two ligands: PD-1 and PD-2. PD-1 in particular is often overexpressed in many tumour types. Anti-PD-1 monoclonal antibodies are able to prevent the binding of PD-1 to its ligands and sequentially prevent inhibition of the immune system.

Anti PD-1/PD-L1 immunotherapy has quickly risen to be one of the most effective immunotherapies for various cancer types, such as non-small cell lung cancer (NSCLC), renal cell carcinoma and melanoma. Investigation on predictive and prognostic biomarkers is currently ongoing. Biomarkers in the peripheral blood, which are measured during routine clinical testing, such as lymphocyte numbers, may predict outcome but are not therapy specific. One biomarker that has received much attention is the immunologic biomarker PD-L1. PD-L1 expression

has been associated with better response rates to PD-1/PD-L1 treatment1,2. Predictiveness of clinical outcome based on PD-L1 expression varies between tumor types. PD-L1 status may have a stronger predictive value in melanoma patients compared to NSCLC3. Other markers such as T-cell infiltration, T-cell receptor clonality and somatic mutation burden are currently being investigated4.

Not one marker will suffice on predicting outcome to PD-1/PD-L1 treatment. For example, negative PD-L1 staining does not rule out a response to treatment. Combinations of different markers may be needed in order to select which patients will respond to treatment. Possible predictive individual markers for outcome are the serum free drug levels and bound drug levels of the monoclonal antibody. Upon administration, a large portion of the therapeutic drug immediately binds to its target on T-cells. The target is mainly located in peripheral tissues and therefore a large portion of nivolumab may not reach the tumor infiltrating lymphocytes (TILs). To our knowledge, it has not been described whether it is binding to the T-cells located in the peripheral blood or binding to TILs that contribute the most to tumour cell killing. This knowledge is limited due to lack of well described validated assays to measure anti-PD1 antibodies and well described pharmacokinetic and PK/PD models.

To better describe the pharmacokinetics of anti PD-1 antibodies, validated assays to measure serum concentrations of PD-1 antibodies, which can be used routinely in the clinic are needed. In our lab Enzyme-Linked Immuno Sorbent Assays are currently developed or in development. These assays use commercially available reagents to measure pembrolizumab and nivolumab. For these assays, plates are first coated with PD-1, followed by incubation of serum samples. During this step the antibody binds to PD-1. During the washing step other antibodies will be removed from the plate. Next, wells are incubated with anti-human-IgG4 antibodies, which are horseradish peroxidase conjugated. During the final step, wells are incubated with enhanced chemiluminescence reagent, which contains luminol. Horseradish peroxidase catalyses the oxidation of luminol in a product that emits light. This signal is measured with an ELISA plate reader. By comparing the sample to a standard curve, the concentration of the antibody can be calculated.

Study objective

The aim of this study is to develop and validate the ELISA and potential other assays (e.g. LC-MS), in order to measure drug concentration levels. For this, blood and other material will be collected.

Study design

For Group A: Patients who receive nivolumab or pembrolizumab treatment will be asked to participate in this study for blood sampling during treatment. Blood

will be drawn a total of 8 cycles (max 128ml). It will be discussed with the patient how many times.

For Group B: Patients who will undergo a clinically indicated necessary procedure, such as ascites/pleural fluid drainage, will be asked to donate residual material for this study. Additionally, pts will be asked to donate 8ml of blood.
.

Study burden and risks

For Group A: Patients who receive nivolumab or pembrolizumab treatment will be asked to participate in this study for blood sampling during treatment. How many and when will be discussed with the patient:
-Pre dose will be drawn from drug infusion venflon
-At the end of infusion (extra venipuncture)
-Up to 8 cycles, max 128ml blood will be drawn

Patients do not need to stay longer at the hospital and do not need to make extra visits. Optionally one extra phlebotomy will be performed at the end of infusion. The risks for this study are low: there is a chance that a bruise will be visible at the site of injection.

For group B, no extra burden exists for the donation of residual material, but patients will be asked to donate 8ml of blood.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with solid tumors who will start treatment with nivolumab or pembrolizumab and are willing to undergo blood sampling and/or donate residual material.

Exclusion criteria

Patients with known alcoholism, drug addiction, psychotic disorders in the history and/or other reasons, for which they are not amendable for adequate follow up.
Uncontrolled infectious disease or known HIV-1 or HIV-2 type patients.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-06-2017

Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	27-10-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC NedMec

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	NL58857.031.16