CA209-759: Blood-borne biomarkers for tumor response to Nivolumab in KRAS-mutated non-small cell lung cancer, an exploratory study

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Predictive value of patient specific KRAS mutation in ctDNA in serial blood samples (trajectories) and a durable clinical response to nivolumab.

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

Summary

ID

NL-OMON45880

Source
ToetsingOnline

Brief title
Biomarkers for tumor response to PD-1 inhibitors

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: Bristol-Myers Squibb,grant

Intervention

Keyword: Biomarkers, KRAS, Nivolumab, NSCLC

Outcome measures

Primary outcome

To discriminate, early in treatment, responders from non-responders to nivolumab in KRAS positive NSCLC.

Secondary outcome

-Tumor response according RECIST1.1

-To test (blood-borne and stool) biomarkers during nivolumab treatment to explore the predictive value for early tumor response (with one year survival as readout of response).

-To develop a simple, affordable, diagnostic test using these data that can be rapidly adopted in clinical practice (e.g. ctDNA as biomarker in blood, calprotectin level in both stool and serum, peptides shared between the microbiota and the tumor that are identified by 16s RNA sequencing at baseline, serum IL-8, CRP, I-FABP, endotoxin and CRP-levels, or a combination).

Study description

Background summary

To date there is no discriminating biomarker that predicts response to checkpoint inhibitors. KRAS mutated DNA is shed in the blood and can be measured by digital droplet PCR (ddPCR). Clinical outcome in advanced NSCLC patients with KRAS mutations treated with nivolumab can be measured by CT imaging, but plasma ctDNA may provide an earlier and better biomarker for response and 1-year survival than CT. The study in this patient group will be used as proof of principal for the clinical use of ctDNA in a broader setting, since the KRAS mutation is encountered in lung cancer in up to 30% of patients

and only 12 different KRAS mutations may be present (limited number of primers needed).

Study objective

Predictive value of patient specific KRAS mutation in ctDNA in serial blood samples (trajectories) and a durable clinical response to nivolumab.

Study design

For the exploratory biomarker study, n=40 patients with tumors failing first line treatment with a platinum containing doublet and harboring a mutation in exon 12, 13 or 61 of the KRAS gene determined by routine NGS analysis in ISO15189-accreditated laboratory.
-Plasma for ctDNA will be collected and stored at baseline, 1, 2, 4 and 6 weeks upon starting nivolumab, and thereafter at similar intervals as radiographic imaging is done.
-KRAS mutation levels in plasma ctDNA will determined with ddPCR detection using patient specific KRAS mutations.
-PET/CT imaging will be performed every 6 weeks until week 49 then every 12 weeks until disease progression
-Stools will be collected at baseline and progression or 1 year whichever comes first.
Patients will be followed up for at least one year.

Intervention

The medical intervention includes nivolumab. Nivolumab is given intravenously every 2 weeks. Continuing will depend on subject's response.

Study burden and risks

As part of the trial, patients will be expected to attend several clinic visits, where they will undergo physical examinations, vital sign measurements (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition, every 6 weeks (from week 6 until week 49) and then every 12 weeks, patients will undergo radiographic assessment of their tumours (by PET/CT) until disease progression or clinical benefit. Blood will also be collected at certain visits for research
purposes (biomarker). The frequency of visits and number of procedures carried out during this trial will generally be considered 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. Treatment for cancer often has side effects, including some that are life threatening.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically confirmed stage IIIB and stage IV NSCLC KRAS positive tumors only.
2. Available tumor tissue sample.
3. Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose nivolumab.
4. Any line of previous chemotherapy.
5. Nivolumab has to be the treatment that will be started.
6. At least one unidimensionally measurable lesion according to RECIST1.1 criteria.
7. Life expectancy more than 3 months.
8. ECOG PS 0-1.
9. Age18 years and older, both male and female subjects
10. Adequate organ functions
11. Signed informed consent.

12. Male and female patients with reproductive potential must use an approved contraceptive method,

Exclusion criteria

1. Previous treatment with PD-1 or PD-L1 inhibitor.
2. Lung cancer previously treated for an ALK translocation, EGFR mutation or BRAF mutation
3. Pregnant or lactating women.
4. Patients who are poor medical risks because of non-malignant disease as well as those with active uncontrolled infection.
5. Patients without plasma sample at baseline (before treatment).
6. Patients are excluded if they have active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
7. Subjects with carcinomatous meningitis.
8. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.
9. Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded 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.
10. Other active malignancy requiring concurrent intervention.
11. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
12. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
13. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
14. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
15. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-08-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	17-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-06-2019
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
CCMO	NL57963.042.17