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

No registrations found.

| | |
|---|---|
| **Ethical review** | Not applicable |
| **Status** | Pending |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON25545

**Source**
Nationaal Trial Register

**Brief title**
Biomarkers for tumor response to PD-1 inhibitors

**Health condition**

Non-small cell lung cancer, KRAS mutation
Niet-kleincellig longkanker, KRAS mutatie

### Sponsors and support

**Primary sponsor:** University Medical Center Groningen
**Source(s) of monetary or material Support:** Bristol-Myers Squibb

### Intervention

### 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**

Immunotherapy by a checkpoint inhibitor is a promising new treatment in lung cancer (and other solid tumors). When patients respond to PD-1 inhibition, prognosis is markedly increased with 3-year survival rates being realistic in these responders. The responders are characterized by a so-called durable clinical benefit1. However, only 20% of patients seem to belong to this category. Up to date there is no biomarker to select only these 20% of patients that benefit from this therapy.

Nivolumab has recently been registered for second line treatment for all patients with non-small cell lung cancer (NSCLC). Current practice is that all patients (without a known driver mutation and accompanied targeted therapy) progressing after first line (chemo)therapy and with a performance score 0-1, are eligible for treatment with nivolumab. For 80% of these patients this treatment will have no favorable effect in terms of long-term survival. These patients should be identified as soon as possible to offer a different treatment strategy (either chemotherapy or strictly palliative care). Treatment response is currently monitored by imaging (RECIST criteria). However, imaging during nivolumab treatment is far less guiding than for other treatments (e.g. chemotherapy or EGFR-TKI). Patients may show a so called “pseudo-progression response”, meaning that according to RECIST criteria they show progression of disease, while the patients general condition improves, so in fact has a favorable clinical response.

The primary objective of this study is to validate an easy-to-use blood borne biomarker that accurately predicts the response to nivolumab early in treatment. Such a marker will enable us to select patients that do respond and for whom treatment should be continued versus those non/poor-responders where treatment could be stopped soon after start of therapy.

Our hypothesis is that in patients with KRAS mutated lung cancer the presence or absence of circulating tumor DNA (ctDNA) with this tumor-specific mutation present in the cell-free blood plasma fraction can be used as an early biomarker for a durable response to nivolumab as

well as to monitor disease in responders.
Our primary outcome will be ctDNA to predict a durable clinical response at one year of nivolumab treatment based on quantification of tumor-specific (KRAS) mutation in ctDNA of plasma samples collected regularly.

Forty patients harboring a KRAS mutation progressing after at least one line of platinum containing chemotherapy will be treated with nivolumab and have blood drawn at baseline, the first weeks and thereafter at same rate as routine CT guided imaging. The presence of the tumor-specific KRAS mutation in ctDNA will be tested and quantified using analytical sensitive plasma-based PCR assays.

Another area of research within the UMCG is the so called “gut-microbiome”, that has been related to checkpoint inhibitors. This possible biomarker will be taken into account as a secondary outcome parameter.

**Study objective**

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 design**

-Blood samples (biomarker) will be drawn at baseline, week 1, 2, 4 and 6. Thereafter 6 weekly simultaneously with radiographic tumor assessment.

-Nivolumab 3 mg/kg i.v. 2-weekly until disease progression as standard of care

-PET/CT scans: at baseline and 6-weekly until week 49, then every 12 weeks until disease progression as standard of care

**Intervention**

-Blood samples (biomarker)

-Nivolumab i.v. treatment as standard of care

-PET/CT scans for response measurment as standard of care

# Contacts

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# Eligibility criteria

## Inclusion criteria

1. Histologically confirmed stage IIIB and stage IV NSCLC KRAS positive tumors only. Tumor mutation analyzed by next generation sequencing for specific KRAS mutation.

2. The tumor tissue sample must be fresh, preferably fresh frozen, in addition to routine FFPE-tissue processing from the primary tumor, core needle biopsy, excisional or incisional biopsies are accepted. Fine needle biopsies and drainage of pleural effusions with cytospins are considered adequate for this biomarker study, but a KRAS mutation must be present and verified.

3. Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose nivolumab.

4. Any line of previous chemotherapy.

5. At least one unidimensionally measurable lesion according to RECIST1.1 criteria.

6. Life expectancy more than 3 months.

7. ECOG PS 0/1.

8. Age 18 years and older, both male and female subjects.

9. Adequate organ functions, including:

a. Adequate bone marrow reserve: Hb > 9.0 g/L WBC ¡Ý 2.0 x 109/L, ANC > 1.5 x 109/L, platelets > 100 x 109/L.

b. Hepatic: bilirubin <1.5 x ULN, AP, ALT, AST < 3.0 x ULN or AP, ALT, and AST <5 x ULN if the liver has tumor involvement.

c. Renal: serum creatinine <1.5 x ULN or calculated creatinine clearance > 40 ml/min based on the Cockroft-Gault formula.

10. Signed informed consent.

11. Male and female patients with reproductive potential must use an approved contraceptive method, with a failure rate of less than 1% per year if appropriate. Female patients with childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to study enrollment.

12. WOCBP will use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose

13. Women must not be breastfeeding

14. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of investigational product Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

## 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

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| Study type: | Interventional |

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| Intervention model: | Other |
| Allocation: | Non controlled trial |
| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-01-2017 |
| Enrollment: | 40 |
| Type: | Anticipated |

## Ethics review

Not applicable

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| Application type: | Not applicable |

## Study registrations

### Followed up by the following (possibly more current) registration

ID: 45681
Bron: ToetsingOnline
Titel:

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| NTR-new | NL6027 |
| NTR-old | NTR6158 |
| CCMO | NL60183.042.16 |
| OMON | NL-OMON45681 |

# Study results