ML41176 Unraveling tumor response and resistance to combined chemotherapy and PD-L1 inhibition with minimal invasive techniques in patients with advanced NSCLC with targetable disease

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To identify (both primary and acquired) resistance mechanisms to chemo-immunotherapy (obtained by less invasive procedures (NGS on ctDNA in blood & urine, exhaled breath or microbioma in stools alone or in combination)) and provide new insights...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21412

Bron
NTR

Verkorte titel
Biomarker by minimal invasive techniques of response to chemo-immunotherapy

Aandoening

Non-small cell lung cancer (NSCLC) with a documented driver mutation (EGFR, ALK, ROS, BRAF, MET, RET, NTRK).

Ondersteuning

Primaire sponsor: University Medical Center Groningen
Overige ondersteuning: Roche

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Predictive value of response to treatment (PFS) by blood test, with emphasis on acquired resistance mechanisms.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Chemo-immunotherapy has become the standard first line treatment of metastasized lung cancer. To date no relevant biomarker has been identified to reliably select patients for treatment.

Objective: To identify (both primary and acquired) resistance mechanisms to chemo-immunotherapy (obtained by less invasive procedures (NGS on ctDNA in blood & urine, exhaled breath or microbioma in stools alone or in combination)) and provide new insights on their predictive value for response to chemo-immunotherapy in NSCLC patients with a known driver mutation.

Study design: Explorative multicenter biomarker study, stratifying for resistance (primary resistance, acquired resistance, continuing response).

Study population: Stage 4 NSCLC patients with a tumor harboring a driver mutation and disease progression after at least one line of TKI treatment, ≥18 years old.

Intervention (if applicable): Standard chemo-immunotherapy (Atezolizumab/paclitaxel/ carboplatin/bevacizumab q3 wks iv).

Main study parameters/endpoints:
Primary Endpoint:
Predictive value of response to treatment (PFS according to RECIST v1.1 are decisive for treatment changes) by blood test, with emphasis on acquired resistance mechanisms.
Secondary endpoints:
Predictive value of response to treatment (PFS) by NGS blood test, with emphasis on acquired resistance mechanisms by the following subgroup of response:
- ctDNA profiles associated with primary resistance (PD within 6 mo);
- ctDNA profiles associated with acquired resistance (PD 6 mo-24 mo);
- ctDNA profiles associated with continuing response of 2 years and more.
Predictive value of response PFS/OS/continuing response:
- TMB and clustered Foundation One CDX genes in pretreatment biopsy.

- Predictive value of ctDNA in urine and blood.
- Predictive value of baseline and sequential microbioma.
- Predictive value of exhaled breath analysis by electronic nose (SpiroNose).
- Predictive response of combining different biomarkers together (SpiroNose, microbioma, genes from ctDNA).
- Predictive value of biomarkers for immune related AE.

Doel van het onderzoek

To identify (both primary and acquired) resistance mechanisms to chemo-immunotherapy (obtained by less invasive procedures (NGS on ctDNA in blood & urine, exhaled breath or microbioma in stools alone or in combination)) and provide new insights on their predictive value for response to chemo-immunotherapy in NSCLC patients with a known driver mutation.

Onderzoeksopzet

-Tumor Biopsy or tumor cell block at baseline and timepoint progressive disease (optional)
-Blood-, urine and exhaled breath samples will be collected at baseline, week 1, 3 thereafter 6 weekly until treatment discontinuation (2 years of treatment or progressive disease wichever comes first).
-Stool sample (microbioma) & 24h recall questionnaire for stool analysis will be collected at baseline, week 12, 42 and at treatment discontinuation (2 years of treatment or progressive disease wichever comes first).
-PET/CT-thorax/abdomen at baseline and week 12
-CT-thorax/abdomen week 6, 18 and 6 weekly until week 48, thereafter every 12 weeks until treatment discontinuation (2 years of treatment or progressive disease wichever comes first).
-EORTC QLQ-C30 & LC13 at baseline and every 12 weeks until treatment discontinuation (2 years of treatment or progressive disease wichever comes first).

Onderzoeksproduct en/of interventie

-Tumor biopsy
-Blood samples and less invasive: urine samples, stool samples and exhaled breath samples
-Atezolizumab/bevacizumab/paclitaxel/carboplatin i.v. treatment as standard of care
-PET/CT scans for response as standard of care

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Provision of signed and dated, written informed consent.
2. Female and male subjects aged at least 18 years.
3. Subjects with histologically- or cytologically-documented non squamous NSCLC with a documented driver mutation (such as EGFR, ALK, ROS, BRAF, MET, RET, NTRK1-3, KRAS, NRG1)
4. New (< 3 month old) tumor specimen (histology or cytology containing enough tumor cells and tumor DNA for at least NGS and PD-L1 staining).
Confirmation of sufficient adequate tumor material by the central reviewing pathologist (Wim Timens) is required before start.
5. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
6. Evidence of radiological disease progression following first line TKI or any subsequent treatment lines with TKI only (for EGFR treated with either osimertinib or failure of other TKIs 2nd line or later). Previous
course of chemotherapy is allowed, but not necessary as well.
7. ECOG performance status 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
8. At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except for
pathological lymph nodes they must be ≥ 15mm in short axis) with computerized tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.
9. Adequate hematologic and end organ function, defined by the following laboratory results obtained within ≤14 days prior to study treatment:
-ANC ≥1500 cells/µL (without granulocyte colony-stimulating factor support)
-WBC counts >2500/µL
-Lymphocyte count ≥500/µL
-Platelet count ≥100,000/µL (without transfusion)
-Hemoglobin ≥9.0 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion.

-AST, ALT, and alkaline phosphatase ≤ 2.5× the upper limit of normal (ULN), with the following exceptions:
-Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN
-Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN
-Serum bilirubin ≤ 1.5 × ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
-INR and aPTT ≤ 1.5 × ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
-Creatinine clearance ≥ 30 mL/min.
10. Females should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of
non-child-bearing potential by fulfilling one of the following criteria at screening:
-Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
-Women under 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with Luteinizing Hormone
(LH) and Follicle-Stimulating Hormone (FSH) levels in the post-menopausal range for the institution.
-Documentation of irreversible surgical sterilization by hysterectomy, bilateral ophorectomy or bilateral salpingectomy but not tubal ligation.
11. Male subjects should be willing to use barrier contraception ie, condoms.
12. Ability to comply with protocol.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 14 days prior to inclusion of the study.
2. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD-1, and anti−PD-L1 therapeutic antibodies.
-Patients who have had prior anti−CTLA-4 treatment may be enrolled, provided the following requirements are met:
-Minimum of 6 weeks from the last dose of anti−CTLA-4
-No history of severe immune related adverse effects from anti−CTLA-4 (CTCAE Grade 3 and 4).
3. CNS disease, treated brain metastases without the need for steroids are allowed.
4. Leptomeningeal disease.
5. Uncontrolled tumor-related pain.
-Patients requiring pain medication must be on a stable regimen at study entry.
-Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Patients should be recovered from the effects
of radiation. There is no required minimum recovery period.

-Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be
considered for loco-regional therapy if appropriate prior to enrollment.
6. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
7. Malignancies other than NSCLC within 3 years prior with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in
situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, ductal carcinoma in situ treated surgically with curative intent).
8. Pregnant and lactating women.
9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
10. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cell products or any component of the atezolizumab formulation.
11. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular
thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
-Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.
-Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
12. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
-History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
13. Positive test for HIV.
14. Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C.
15. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be
performed in these patients prior to start of study treatment.
16. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD-1, and anti−PD-L1 therapeutic antibodies.
-Patients who have had prior anti−CTLA-4 treatment may be enrolled, provided the following requirements are met:
-Minimum of 6 weeks from the last dose of anti−CTLA-4
-No history of severe immune related adverse effects from anti−CTLA-4 (CTCAE Grade 3 and 4)
-Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
17. Active tuberculosis.
18. Severe infections within 4 weeks prior to inclusion of the study, including but not limited

to hospitalization for complications of infection, bacteremia, or severe pneumonia.
19. Signs or symptoms of infection within 2 weeks prior to inclusion of the study.
20. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina.
-Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction <50% must be on a stable medical regimen that is optimized in the
opinion of the treating physician, in consultation with a cardiologist if appropriate.
21. Major surgical procedure other than for diagnosis within 28 days prior to prior to inclusion of the study, or anticipation of need for a major surgical procedure during the course of the study.
22. Prior allogeneic bone marrow transplantation or solid organ transplant.
23. Administration of a live, attenuated vaccine within 4 weeks prior to inclusion of the study, or anticipation that such a live attenuated vaccine will be required during the study.
-Influenza vaccination should be given during influenza season only (example: approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g.
FluMist®) at any time during the study.
24. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug
or that may affect the interpretation of the results or render the patient at high risk from treatment complications.
25. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, IL-2).
26. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor agents) within 2
weeks prior to inclusion of the study.
-Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by
the sponsor.
27. The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g. fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for
adrenocortical insufficiency are allowed.
28. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg). Anti-hypertensive therapy to achieve these parameters is allowable.
29. Prior history of hypertensive crisis or hypertensive encephalopathy
30. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
31. History of hemoptysis (≥ one-half teaspoon of bright red blood per episode) within 1 month prior to randomization.
32. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic

anticoagulation).
33. Current or recent (within 10 days of randomization) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol.
34. Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for > 2 weeks prior to randomization.
The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been
on a stable dose of anticoagulants for at least 2 weeks prior to randomization. Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an
INR < 1.5 × ULN and aPTT is within normal limits within 14 days prior to randomization.
Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
35. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab.
36. History of abdominal or tracheosphageal fistula or gastrointestinal perforation within 6 months prior to randomization.
37. Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.
38. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
39. Serious, non-healing wound, active ulcer, or untreated bone fracture.
40. Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection. All patients with ≥ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must
demonstrate ≤ 1 g of protein in 24 hours.
41. Known sensitivity to any component of bevacizumab.
42. Clear tumor infiltration into the thoracic great vessels is seen on imaging.
43. Clear cavitation of pulmonary lesions is seen on imaging.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	03-02-2020
Aantal proefpersonen:	100
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Toelichting
NA

Ethische beoordeling

Positief advies

Datum:	24-10-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8111
Ander register	METc UMCG : METc2019/647

Resultaten

Samenvatting resultaten
NA