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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The primary objective of this study is to identify biomarkers predictive for response to chemo-immunotherapy in patients with lungcancer with a known driver mutation.Secondary endpoints are overall survival; time to biological progression, defined…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational non invasive

Summary

ID

NL-OMON54889

Source
ToetsingOnline

Brief title
Biomarker by minimal invasive techniques of response to chemo-immunotherapy

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Lung Cancer, Non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Hoffmann-La Roche

Intervention

Keyword: Biomarker, checkpoint inhibitors, chemotherapy, resistance

Outcome measures

Primary outcome

Primary Endpoint:

Response to treatment defined as Progression Free Survival (PFS) in months

according to RECIST v1.1 and divided into the following subgroups of response:

- primary resistance (PFS < 6 mo);

- acquired resistance (PFS >= 6 mo).

Primary predictor variable:

The change in level of ctDNA measured by ddPCR in blood between week 12 (end of

chemotherapy) and week 18.

Secondary outcome

Secondary endpoints:

1. Overall survival

2. Time to biological progression, defined as an increase of >= 30% in the

levels of the specific mutation from the lowest value achieved, measured in

ctDNA in blood using ddPCR.

3. Immune related adverse events (irAE).

4. Quality of life and symptom scores.

Study description

Background summary

This will be an exploratory multicenter biomarker study to identify possible new biomarkers by minimally invasive diagnostic tools (blood, urine, stools and exhaled air). The study will be carried out in patients with stage 4 non-small cell lung cancer with a known driver mutation. Patient population will mainly consist of patients with a known EGFR and ALK translocation resistant to standard TKI treatment, who are eligible for chemo-immunotherapy.
Up to now no good biomarker is available that predicts response to treatment in this population. By minimally invasive techniques (blood, urine, stools and exhaled air) biomarkers will be studied for that purpose.
In addition, mechanisms of resistance will be studied. This may help to timely stop treatments that are not effective and to gain insight in possible new treatments.

Study objective

The primary objective of this study is to identify biomarkers predictive for response to chemo-immunotherapy in patients with lungcancer with a known driver mutation.
Secondary endpoints are overall survival; time to biological progression, defined as an increase of >= 20% in the levels of the specific mutation from the lowest value achieved, measured in ctDNA in blood using ddPCR; immune related adverse events (irAE).

Study design

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

Study burden and risks

This study is considered a low burden study: At fixed treatment time points (see Appendix 2) when regular blood is drawn 50 ml extra blood and 45 ml urine will be allocated for this study per patient. At these fixed time points a SpiroNose will be performed as well to collect exhaled breath data. All visits will be regular visits for treatment; no extra visits will be scheduled. Only in the first 18 weeks we will ask patients to have a (few) visit more when measurements according to the timing of the protocol can not be performed on the day of a regular visit, for example when the treatment is posponed. Stools will be collected maximally 4 times by patient him/herself (together with a nutrition questionnaire).
Every 12 weeks the QLQC30 and LC13 questionnaire will have to be filled in by

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. 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, HER 2).
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 confirmed by a pathologist). If the tumor specimen reveals a possible new targetable driver than that has to be discussed with the subject as an option next to this study.

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:
o ANC >=1500 cells/µL (without granulocyte colony-stimulating factor support)
o WBC counts >2500/µL
o Lymphocyte count >=500/µL
o Platelet count >=100,000/µL (without transfusion)
o Hemoglobin >=9.0 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion.
o 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
o Serum bilirubin <= 1.5 × ULN. Patients with known Gilbert disease who have serum bilirubin level <= 3 × ULN may be enrolled.
o 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.
o 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:
o Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
o 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.
o 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.

Exclusion criteria

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:
o Minimum of 6 weeks from the last dose of anti*CTLA-4
o 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.
• Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Active tuberculosis.
17. 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.
18. Signs or symptoms of infection within 2 weeks prior to inclusion of the study.
19. 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.
20. 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.
21. Prior allogeneic bone marrow transplantation or solid organ transplant.
22. 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.
• corona vaccination is allowed.
23. 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.
24. Treatment with systemic immunostimulatory agents (including but not limited

to IFNs, IL-2).
25. 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.
26. 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.

Exclusion criteria related to bevacizumab:
27. 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.
28. Prior history of hypertensive crisis or hypertensive encephalopathy
29. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
30. History of hemoptysis (>= one-half teaspoon of bright red blood per episode) within 1 month prior to randomization.
31. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation).
32. Current or recent (within 10 days of randomization) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and clostazol.
33. 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 activit

Study design

Design

Study type: Observational non invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-09-2020
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	31-03-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-12-2024
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	NL71722.042.19
Other	NTR NL8111