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Radiotherapy combined with immunotherapy in metastatic non-small cell lung cancer patients

Submission date
26/05/2020

Recruitment status
No longer recruiting

Registration date
07/06/2020

Overall study status
Completed

Last Edited
22/01/2025

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The aim of this study is to verify whether immunotherapy (the study medication L19-IL2) after a standard treatment such as radiotherapy, is more effective than the current standard treatment alone in fighting advanced lung cancer, specifically non-small cell lung cancer that has spread beyond the lungs.

By giving the study medication L19-IL2 after the radiation therapy, a large number of the cancer cells will first be killed by radiation and then the immune system will give an additional boost which may improve control of the cancer. Unlike other anticancer treatments (such as chemotherapy) immunotherapy does not directly fight the cancer cells themselves. Immunotherapy stimulates the immune system, so that it can better recognise, attack and destroy the cancer cells. IL2 (Interleukin-2) is a signalling substance which activates immune cells directed against the tumour. In this way the immune system may become strong enough to fight the tumour. In order to take IL2 directly to the tumour sites, it is linked to a protein, L19 to form the study medication. This protein binds to newly formed blood vessels. Many types of cancer cause the development of newly-formed blood vessels to feed the tumour and allow it to grow. The protein L19 takes the signalling substance IL2 to the centre of the tumour where the immune cells will become activated.

In the past, the study medication L19-IL2 has been studied in patients with different types of cancer, both alone and in combination with chemotherapy. The medicine can be administered alone or in combination with chemotherapy and radiotherapy and does not cause unacceptable side effects in these combinations. Previous research on animals appears to show that the combination of radiation and the study medication L19-IL2 works much better than each of the treatments separately (radiation alone, or immunotherapy alone).

In this study, the outcomes of patients receiving standard care in a number of European hospitals will be compared to the outcomes of patients at the same hospitals receiving standard care followed by the study medication L19-IL2 as immunotherapy.

Who can participate?
Adult patients with stage IV non-small cell lung cancer

What does the study involve?
Participants will be randomly allocated to either receive standard care alone, or standard care followed by the study medication L19-IL2.

The standard treatment for patients with maximum 5 metastases (tumours at distant sites, additional to the original/primary tumour) involves of high-dose (SABR) radiotherapy and potentially therapy with chemotherapy, immunotherapy or a combination of both. The standard treatment for patients with 6 to 10 metastases usually receive treatment with chemotherapy, immunotherapy or a combination of both. They may also receive radiotherapy. Radiation will be applied to a maximum of 5 metastases for patients. The research doctors in this study will provide standard treatment following their local guidelines as this may vary between countries.

What are the possible benefits and risks of participating?
It is not clear whether there will be any individual participant benefits from participating in this study. A possible benefit is that the combination of radiotherapy with immunotherapy could keep the disease under
control for a longer period of time, and it could be possible that it could disappear completely.

The possible risks of participating are the possible side effects of the study medication L19-IL2. Additionally, there may be disruptions caused due to not being allowed to become pregnant during the study period, and the time spent attending appointments and receiving additional tests and investigations. It is, therefore, possible that participants could experience negative side effects only, and do not benefit at all from the proposed study treatment.

Where is the study run from?
The study is run from Maastricht University (lead centre) and 3 other hospitals in the Netherlands, 4 hospitals in Belgium, 2 hospitals in France, 3 hospitals in Germany, and 1 hospital in the United Kingdom.

When is the study starting and how long is it expected to run for?
From January 2017 to January 2025

Who is funding the study?
H2020 European Research Council (EU)

Who is the main contact?
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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-002583-11

Integrated Research Application System (IRAS)
261785

ClinicalTrials.gov (NCT)
NCT03705403

Protocol serial number
IRAS 261785 , 18-068

Study information

Scientific Title
Multicentre, randomised, phase II study examining the activity of L19-IL2 immunotherapy and Stereotactic ABlative Radiotherapy in metastatic non-small cell lung cancer: ImmunoSABR

Acronym
ImmunoSABR

Study objectives
Combining Immunocytokines with (Stereotactic Ablative Body) Radiotherapy (SAB)R will lead to:
1. A direct cytotoxic effect of SABR to all irradiated metastatic lesions in the irradiation field

2. An immunogenic cell death (ICD) induced by radiation which will, in combination with L19-IL2, create a systemic out of field radio-immune (OFRI) effect thus eliminating micrometastases and macrometastases outside the irradiation field (watch the animation on https://youtu.be/6wDE6RkrikA)
3. A memory effect, induced by the ICD, subsequently leading to less long term relapses

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/04/2019, Medical Ethical Committee of Academic hospital Maastricht (University of Maastricht, Postbus 5800, 6202 AZ Maastricht, Netherlands; secretariaat.metc@mumc.nl;+31(0)43-3876009), ref: NL67629.068.18

Study design
Multicentre randomized controlled open-label phase II trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Advanced non-small cell lung cancer, stage IV

Interventions
The patients included in the trial will be stratified for the metastatic load (oligo; max 5 or diffuse; 6-10 metastases). After randomisation, patients will be assigned either to the experimental arm or the standard of care (SOC) arm. Depending on the metastatic load, patients with (max 5 metastases) will receive in the experimental arm SABR to all lesions followed by L19-IL2 (+ aPD(L)1 if SOC). Patients with more extensive metastatic disease (6 to up to 10 metastasis) in the experimental arm will be included following first or second line treatment with a platinum doublet and receive radiotherapy to at least one (symptomatic) lesion, followed by L19-IL2 (+ aPD(L)1 if SOC).Control: standard of care (SABR/conventional radiotherapy and/or chemotherapy and/or immunotherapy)
Experimental: SABR combined with 6 cycles of L19-IL2 (15 MIO IU; IV injection over 3 hours) immunocytokine treatment (+ aPD(L)1 if SOC).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Darleukin

Primary outcome(s)
Progression Free Survival (PFS) at 1.5 years after randomisation

Key secondary outcome(s))
1. Progression Free Survival (PFS) at 5 years after randomisation
2. Overall survival at 5 years after randomisation
3. Toxicity measured using the Common Terminology Criteria for Adverse Events (CTCAE v5.0) at 1.5 years after randomisation
4. Quality of Life measured using the Quality of Life Questionnaire Core 30 Items (QLQ-C30 v3.0) and the Quality of Life Questionnaire Lung Cancer Module (QLQ-LC13) (by the European Organization for Research and Treatment of Cancer Quality of Life Group), and the EuroQol Group EQ-5D at 1.5 years after randomisation
5. The occurrence of an Out of Field Radio-Immune (OFRI) response/the abscopal effect using imaging, based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria at 1.5 years after randomisation
6. The occurrence of an In Field Radio-Immune (IFRI) response, based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria at 1.5 years after randomisation

Completion date
06/01/2025

Eligibility

Key inclusion criteria
Oligometastatic disease participants:
1. Histological/cytological confirmed limited metastatic adult NSCLC patients, regardless of the PD-L1 status
2. ≤5 metastatic lesions and ≤2 brain lesions with a total cumulative diameter of 5 cm
3. In patients with 2 lung tumours, it can be unclear if the patient has 2 concurrent primary tumours or a primary lung tumour with 1 metastasis. Whether the patient has an M1 disease or not will be at the discretion of the local multidisciplinary tumour board.
4. Prior cancer treatments must have been discontinued for ≥4 weeks before randomisation. In case of maintenance chemotherapy, this therapy will only be started after the end of the L19-IL2 treatment or only in case of Anti-PD(L)1 treatment, during L19-IL2 therapy.

Poly-metastatic disease participants:
1. Histological/cytological confirmed limited metastatic adult NSCLC patients, regardless of the PD-L1 status
2. Between 6 and 10 metastatic lesions, inclusive, and ≤2 brain lesion with a total cumulative diameter of 5cm
3. Last administration of chemo and/or immunotherapy (given as a first or second-line standard of care treatment) ≥4 weeks before randomisation. In case of maintenance chemotherapy, this therapy will only be started after the end of the L19-IL2 treatment or only in case of Anti-PD(L)1 treatment, during L19-IL2 therapy.

All participants:
1. Aged ≥18 years
2. WHO performance status 0-1
3. Adequate bone marrow function, evaluated in the local laboratory (Lab): Absolute Neutrophil Count (ANC) of ≥1.0 x 109 /l, platelet count ≥100 x 109 /l, Haemoglobin (Hb) ≥6.0 mmol/l (or 9.67 g/dl) (it is allowed to give a blood transfusion if Hb is initially too low)
4. Adequate hepatic function (evaluated in the local lab): total bilirubin ≤1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase ≤2.5 x ULN for the institution or ≤5 in case of liver metastasis)

5. Adequate renal function (evaluated in the local lab): creatinine clearance of ≥40 ml/min
5. Capable of complying with study procedures
6. Life expectancy of ≥12 weeks
7. Negative serum pregnancy test for females of childbearing potential.
8. Ability to comply with contraception requirements:
8.1. Non-sterilised, sexually active male patient with a female partner who is of child-bearing age, must use two acceptable birth control methods like a condom combined with spermicidal cream or gel from the first dose of study medication, during the study and at least up to 12 weeks after the last administration of the study medicine and up to 5 months after the last dose of the medicine with anti-PDL)1 as an action mechanism (if you get this product besides the study medicine)
8.2. Women of childbearing potential (WOCBP) and WOCBP partners of male patients must be using, from the screening to three months following the last study drug administration and 5 months after last dose of anti-PD(L)1 maintenance treatment, effective contraception methods as defined by the "Recommendations for contraception and pregnancy testing in clinical trials" issued by the Head of Medicine Agencies' Clinical Trial Facilitation Group (www.hma.eu/ctfg.html):
8.2.1. IUD (IUD) or intrauterine hormone delivery system (IUS)
8.2.2. Combined (with estrogen and progesterone) hormonal contraception associated with ovulation inhibition (oral, intravaginal, transdermal)
8.2.3. Hormonal contraception with progesterone-only associated with ovulation inhibition (oral, injectable, implantable)
9. Signed and dated written informed consent given

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
88

Key exclusion criteria
1. ≥10 metastatic lesions
2. ≥2 brain metastatic lesions
3. 2 brain metastases with a cumulative diameter ≥5 cm
4. Patients with non-infectious pneumonitis, uncontrolled thyroid disease, pleuritis, pericarditis and peritonitis carcinomatosis
5. Received live vaccines ≤30 days prior to enrolment
6. Already actively participating in another study
7. Requiring simultaneous radiation on the primary tumour and metastatic lesion(s). For these

patients, it might be an option to treat the primary tumour first, although this is not mandatory for this study.
8. Whole-brain radiotherapy (WBRT) is not allowed, although it is accepted when given at ≤4 weeks prior to randomisation or after the treatment period. Patients with stable brain metastases are not excluded.
9. Previous radiotherapy to an area that would be re-treated by (SAB)R, resulting in overlap of the high dose areas.
10. Maintenance therapy with Anti-PD(L)1 treatment combined with chemotherapy during treatment ((SAB)R and L19-IL2 cycles)
11. Other active malignancy or malignancy within the last 2 years (except localised skin basal /squamous cell carcinoma, non-muscle invasive carcinoma of the bladder or in situ carcinoma from any site)
12. Concomitantly administered glucocorticoids (these may decrease the activity of IL2 and therefore should be avoided). However, patients who develop life-threatening signs or symptoms may be treated with dexamethasone until toxicity resolves or reduces to an acceptable level (generally grade 1 and 2, however, must be based at the research physician's discretion).
13. History of allergy to intravenously administered proteins/peptides/antibodies/ radiographic contrast media
14. HIV positive, active HIV infection, or active hepatitis B or C (assessed in local lab)
15. Systemic treatment with either corticosteroid (>10 mg daily prednisone equivalents) or Interferon alpha or immunosuppressive medications ≤14 days prior to randomisation. Topical or inhalation steroids are allowed. If a patient needs to take unexpectedly immunosuppressive medication during the trial, it will be allowed but decreasing the dose as soon as possible is strongly advised.
16. Prior history of organ transplant, including autologous stem cell transplant
17. Acute or sub-acute coronary syndromes within the last year, acute inflammatory heart disease, heart insufficiency NYHA >2, or irreversible cardiac arrhythmias
18. A known impaired cardiac function defined as left ventricular ejection fraction (LVEF) <50% (or below the study site's lower limit of normal) as measured by MUGA or ECHO
19. Uncontrolled hypertensive disease: systolic blood pressure (SBP) ≥160 or diastolic blood pressure (DBP) ≥100 mmHg during two measurements
20. History or evidence of active autoimmune disease
21. Severe diabetic retinopathy (neoangiogenesis targeted by L19 outside the tumour)
22. Major trauma, including oncologic surgery, but excluding smaller procedures like the placement of porth-à-cath or surgical biopsy, ≤4 weeks prior to randomisation (neoangiogenesis targeted by L19 outside a tumour)
23. Any underlying mental, medical, or psychiatric condition which, in the opinion of the investigator, will make administration of study drug hazardous or hinder the interpretation of study results
24. Unstable or serious concurrent uncontrolled medical conditions
25. Pregnancy or breastfeeding. It is well known that ED-B, the target of both L19IL2, is expressed in a variety of foetal tissues. Furthermore, anti-PD(L)1 treatment may increase the risk of immune-mediated disorders. Therefore, it will be contra-indicated for pregnant or lactating women.

Date of first enrolment
03/04/2019

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
United Kingdom

England

Belgium

France

Germany

Italy

Netherlands

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Maastricht University Medical Center+ (MUMC+)
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Study participating centre
Netherlands Cancer Institute (AvL/NKI)
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Sponsor information

Organisation

Maastricht University

ROR
https://ror.org/02jz4aj89

Funder(s)

Funder type
Government

Funder Name
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Funder Name
H2020 European Research Council

Alternative Name(s)
H2020 Excellent Science - European Research Council, European Research Council, EXCELLENT SCIENCE - European Research Council, H2020 Ciencia Excelente - Consejo Europeo de Investigación (CEI), CIENCIA EXCELENTE - Consejo Europeo de Investigación, H2020 Wissenschaftsexzellenz - Für das Einzelziel 'Europäischer Forschungsrat (ERC)', WISSENSCHAFTSEXZELLENZ - Für das Einzelziel 'Europäischer Forschungsrat, H2020 Excellence Scientifique - Conseil européen de la recherche (CER), EXCELLENCE SCIENTIFIQUE - Conseil européen de la recherche, ECCELLENZA SCIENTIFICA - Consiglio europeo della ricerca, H2020 Eccellenza Scientifica - Consiglio europeo della ricerca (CER), ERC, CEI, CER

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol article	protocol	15/06/2020	17/06/2020	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes