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

Submission date	Recruitment status No longer recruiting	Prospectively registered		
26/05/2020		[X] Protocol		
Registration date 07/06/2020	Overall study status Completed	Statistical analysis plan		
		Results		
Last Edited	Condition category Cancer	Individual participant data		
22/01/2025		[X] 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? Mrs N Thieme immunosabr@maastrichtuniversity.nl

Contact information

Type(s)

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)

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. \leq 5 metastatic lesions and \leq 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 $\geq 1.0 \times 109$ /l, platelet count $\geq 100 \times 109$ /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 \leq 1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase \leq 2.5 x ULN for the institution or \leq 5 in case of liver metastasis)

- 5. Adequate renal function (evaluated in the local lab): creatinine clearance of \geq 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

Study participating centre Maastricht University Medical Center+ (MUMC+)

P. Debyelaan 25 Maastricht Netherlands 6229HX

Study participating centre Netherlands Cancer Institute (AvL/NKI)

Plesmanlaan 121 Amsterdam Netherlands 1066 CX

Study participating centre Radboud University Medical Centre

Geert Grooteplein Zuid 10 Nijmegen Netherlands 6525 GA

Study participating centre Erasmus Medical Centre

Dr. Molewaterplein 40

Rotterdam Netherlands 3015 GD

Study participating centre University College London Hospital

235 Euston Road London United Kingdom NW1 2BU

Study participating centre University Hospital Carl Gustav Carus

Fetscherstraße 74 Dresden Germany 01307

Study participating centre Klinikum der Universität Heidelberg

Im Neuenheimer Feld 400 Heidelberg Germany 69120

Study participating centre University Hospital Tübingen

Hoppe-Seyler-Straße 3 Tübingen Germany 72076

Study participating centre Centre Oscar Lambret Lille

3 Rue Frédéric Combemale Lille France 59000

Study participating centre The Montpellier Cancer Institute (ICM) - VAL d'AURELLE

208, Avenue des Apothicaires Parc Euromédecine Montpellier France 34298

Study participating centre Saint-Luc University Clinics

Avenue Hippocrate 10 Brussel Belgium 1200

Study participating centre UZ Gent

Corneel Heymanslaan 10 Gent Belgium 9000

Study participating centre UZ Leuven

Herestraat 49 Leuven Belgium 3000

Study participating centre GZA Hospital Sint-Augustinus

Oosterveldlaan 24 Wilrijk Belgium 2610

Sponsor information

Organisation

Maastricht University

ROR

https://ror.org/02jz4aj89

Funder(s)

Funder type

Government

Funder Name

H2020-EU.3.1.3. - Treating and managing disease

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