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Reduced frequency pembrolizumab immunotherapy: can the frequency of pembrolizumab treatment for non-small cell lung cancer be reduced without reducing its effectiveness?

Submission date 21/01/2022	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 10/03/2022	**Overall study status** Ongoing	
Last Edited 22/10/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-how-often-to-give-pembrolizumab-for-non-small-lung-cancer-refine-lung

Background and study aims
Lung cancer is the most common cause of cancer death. Things have improved with the use of drugs like pembrolizumab, which is often used following a diagnosis of advanced non-small cell lung cancer (NSCLC). Pembrolizumab uses the immune system, the body's natural defence. The immune system sends cells called T cells to fight infections and diseases. Cancer cells hide in the 'PD-1/PD-L1 pathway', allowing them to grow and spread. Pembrolizumab blocks the pathway. This prevents cancer cells from hiding, meaning they can be killed by T cells. The cancer may shrink or disappear as a result.
Treatment is usually every 6 weeks, sometimes with chemotherapy. Treatment can last 2 years, and this may be too much. Research has not shown that length increases benefit, and many people who stop before 2 years continue to benefit from pembrolizumab after it has finished. There is a possibility that researchers can reduce treatment frequency without effectiveness being reduced. This is the main aim of REFINE-Lung.

Who can participate?
Eligible participants will be about to or already receiving pembrolizumab as first treatment for NSCLC.

What does the study involve?
Participants will be randomly allocated to one of the following with or without chemotherapy until the cancer grows significantly:
- Pembrolizumab 6 weekly – the 'control' group, or standard treatment;
- Pembrolizumab 12 weekly.

After 150 participants are recruited, the researchers will see if 12 weekly is similar to 6 weekly, and if so 3 further groups will be opened:
- Pembrolizumab 9 weekly;
- Pembrolizumab 15 weekly;
- Pembrolizumab 18 weekly.

Up to 350 participants will be recruited into each group from up to 45 participating UK hospitals, 1750 in total. Each participant will be followed up for 18 months.

What are the possible benefits and risks of participating?
Benefits:
Similar effectiveness but fewer side effects
Improved quality of life
Fewer visits to and savings by hospitals
Risks:
CT Scans: The risk of causing cancer from one scan is around 1 in 1,000, in a healthy person. The dose from a scan is similar to 9 years of background radiation. Subjects would receive the scans as part of their normal care and the risks are considered low because of their existing condition. The patient may find the CT scanner claustrophobic. A contrast dye may be used which may cause discomfort, bruising, swelling and sometimes an allergic reaction. Severe reactions are very rare.
Blood collection: There is a possibility of redness, swelling and bruising after collection and participants may feel lightheaded or faint. The blood samples collected are not above those that would be performed routinely.
Pembrolizumab: Pembrolizumab is a common treatment for NSCLC. The common side effects are related to the immune system and include itching/rash, diarrhoea, cough, muscle/joint pain, fever, abdominal pain, sickness, headache and tiredness. The research arms reduce the treatment frequency which may reduce the side effects and reduce the burden on patients. Participants may be hesitant about this causing disease progression, hence we have allowed re-escalation to 6-weekly treatment.
Pregnancy: The risks are unknown, however, patients are aware of this having been on this treatment for the previous 6 months. Women who become pregnant will be withdrawn and female and male subjects must agree to take appropriate precautions to avoid pregnancy or fathering a child.
Data Protection: Agreements will be in place prior to the transfer of data externally and pseudo-anonymised will be sent to avoid participant identification.
COVID-19: Patients are included in the at-risk categories but the study aims to reduce the required visits. It is recommended that the vaccine be given as per current guidance for immunotherapy.
Additional visits: The patients will not have to attend hospital more than normal, except for an additional two visits for the screening and end of treatment.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
January 2022 to August 2028

Who is funding the study?
The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (UK).

Who is the main contact?
refine-lung@imperial.ac.uk

Contact information

Type(s)
Principal investigator

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-004908-18

Integrated Research Application System (IRAS)
1004165

ClinicalTrials.gov (NCT)
NCT05085028

Protocol serial number
C/41/2021, IRAS 1004165, CPMS 52203

Study information

Scientific Title
A randomised open-label Phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

Acronym
REFINE-Lung

Study objectives
To determine the optimal dose frequency of pembrolizumab amongst patients with NSCLC who have benefited from and completed 6 months of standard therapy.

To determine the longest frequency of pembrolizumab treatment that has similar effectiveness in terms of the following when compared to standard 6 weekly pembrolizumab in NSCLC patients who have completed and benefitted from 6 months of standard treatment:
• Overall survival (OS)
• Progression-free survival (PFS), or the length of time that a participant is alive and the cancer has not come back or grown significantly
• Overall response rate (ORR), or the proportion of participants for whom the cancer either disappears or shrinks significantly
• Duration of response (DoR), or, in the proportion of patients for whom the cancer either disappears or shrinks significantly, the length of time between the disappearance or shrinking significantly and the shrinking stopping or the cancer coming back or growing significantly
• Safety and tolerability, or the side effects that are related to pembrolizumab
• Quality of life (QoL)
• Cost-effectiveness

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/03/2022, North West - Haydock Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 2071048248; haydock.rec@hra.nhs.uk), ref: 22/NW/0037

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Lung cancer

Interventions

1. Pembrolizumab (400mg) every 6 weeks for up to 18 months from randomisation. Patients will be followed up for 18 months from randomisation if they stop treatment prior to this date.
2. Pembrolizumab (400mg) every 12 weeks for up to 18 months from randomisation. Patients will be followed up for 18 months from randomisation if they stop treatment prior to this date.
3. Pembrolizumab(400mg) every 9 weeks for up to 18 months from randomisation. Patients will be followed up for 18 months from randomisation if they stop treatment prior to this date.
4. Pembrolizumab (400mg) every 15 weeks for up to 18 months from randomisation. Patients will be followed up for 18 months from randomisation if they stop treatment prior to this date.
5. Pembrolizumab (400mg) every 18 weeks for up to 18 months from randomisation. Patients will be followed up for 18 months from randomisation if they stop treatment prior to this date.
Randomisation will occur electronically through the eCRF system, OpenClinica.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Overall survival at 2 years, or whether each participant is alive or deceased due to any cause 2 years from initiation of pembrolizumab treatment measured using patient records at 2 years from initiation of pembrolizumab treatment i.e. 18 months from randomisation

Key secondary outcome(s))
1. Median overall survival, or whether each participant is alive or deceased due to any cause measured using patient records throughout the study
2. Median progression free survival, or the length of time a participant is alive without the cancer getting significantly worse as defined by RECIST v1.1 or deceased due to any cause measured using patient records at baseline and then every 12 weeks for a maximum of 2 years from initiation of pembrolizumab
3. Overall response rate, or the proportion of participants with cancer that shows a complete or partial response as defined by RECIST v1.1 measured using patient records at baseline and then every 12 weeks for a maximum of 2 years from initiation of pembrolizumab
4. Median duration of response, or the length of time between a participant with cancer showing a complete or partial response and the cancer getting significantly worse as defined by RECIST v1.1 or death due to any cause measured using patient records at baseline and then every 12 weeks for a maximum of 2 years from initiation of pembrolizumab
5. Safety and tolerability, as defined by adverse events in the Common Terminology Criteria for Adverse Events version 5.0 measured from baseline until the end of treatment visit
6. Quality of life, as defined by the validated EORTC questionnaires QLQ C30 and QLQ LC13 measured from baseline until 2 years from initiation of pembrolizumab
7. Cost effectiveness, as defined by the validated EuroQol EQ-5D measured from baseline until 2 years from initiation of pembrolizumab

Completion date
31/08/2028

Eligibility

Key inclusion criteria
1. Written informed consent prior to initiation of any study procedures and willingness and ability to comply with the study schedule
2. Any patient ≥18 years who has received 6 months of pembrolizumab treatment, with or without chemotherapy, for advanced NSCLC who is planned to continue immunotherapy every 6 weeks, or because of continued benefit.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Disease progression or not tolerating treatment at 6 months into therapy
2. Clinician does not intend to continue immunotherapy
3. Is currently receiving an investigational agent or has participated in a study of an investigational agent and or used an investigational device within 28 days of randomisation

Added 04/07/2023:
4. Any patient with a synchronous primary cancer. This includes any new cancer diagnoses or relapse of previously treated cancer since starting pembrolizumab treatment.

Date of first enrolment
20/06/2022

Date of final enrolment
28/02/2027

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
United Kingdom
W6 8RF

Study participating centre
Weston Park Hospital
Whitham Road
Sheffield
United Kingdom
S10 2SJ

Study participating centre
Royal Surrey County Hospital
Egerton Road
Guildford
United Kingdom
GU2 7XX

Study participating centre
The Royal Marsden Hospital (surrey)
Downs Road
Sutton
United Kingdom
SM2 5PT

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre

New Victoria Hospital
52 Grange Rd
Glasgow
United Kingdom
G42 9LF

Study participating centre
Guys and St Thomas' NHS Foundation Trust
249 Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Velindre Cancer Centre
Velindre Rd
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Colchester General Hospital
Colchester District General Hosp.
Charter Way
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Ipswich Hospital
Heath Road
Ipswich
United Kingdom
IP4 5PD

Study participating centre
Clatterbridge Cancer Centre - Liverpool
Royal Liverpool University Hospital
Prescot Street
Liverpool

United Kingdom
L7 8XP

Study participating centre
Bristol Haematology & Oncology Centre
Horfield Road
Bristol
United Kingdom
BS2 8ED

Study participating centre
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Lothian
United Kingdom
EH4 2XU

Study participating centre
Forth Valley Royal Hospital
Stirling Road
Larbert
United Kingdom
FK5 4WR

Study participating centre
Christie Hospital
Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Kent and Canterbury Hospital
Ethelbert Road
Canterbury
United Kingdom
CT1 3NG

Study participating centre
Peterborough City Hospital
Edith Cavell Campus
Bretton Gate
Bretton
Peterborough
United Kingdom
PE3 9GZ

Study participating centre
Queens Hospital
Rom Valley Way
Romford
United Kingdom
RM7 0AG

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital

Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Royal Cornwall Hospital (treliske)
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre
Royal Sussex County Hospital
Eastern Road
Brighton
United Kingdom
BN2 5BE

Study participating centre
Royal Bournemouth General Hospital
Castle Lane East
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United Kingdom
BH7 7DW

Study participating centre
Kettering General Hospital
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United Kingdom
NN16 8UZ

Study participating centre
North Middlesex Hospital
Sterling Way
London
United Kingdom
N18 1QX

Study participating centre
Yeovil District Hospital NHS Foundation Trust
Higher Kingston
Yeovil
United Kingdom
BA21 4AT

Study participating centre
Barts Health NHS Trust
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Northampton General Hospital NHS Trust
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Calderdale and Huddersfield NHS Foundation Trust
Trust Headquarters
Acre Street
Lindley
Huddersfield
United Kingdom
HD3 3EA

Study participating centre
St John's Hospital
Howden West

Livingston
Lothian
United Kingdom
EH54 6PP

Study participating centre
North Devon District Hospital
Raleigh Park
Barnstaple
United Kingdom
EX31 4JB

Study participating centre
The Royal Marsden Hospital
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Kingston Hospital
Galsworthy Road
Kingston upon Thames
United Kingdom
KT2 7QB

Study participating centre
Worthing Hospital
Lyndhurst Road
Worthing
United Kingdom
BN11 2DH

Study participating centre
Poole General Hospital
Longfleet Road
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BH15 2JB

Study participating centre
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Study participating centre
Addenbrooke's Hospital
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request. Requests should be sent to REFINE-Lung@imperial.ac.uk and will be considered by the TMG and other relevant committees depending on the timing of the request. Consent has been obtained to share data with other researchers for future research. All data shared will be pseudonymised and only identifiable by the trial ID. The researchers requesting data will not be able to identify the participants. Data will not be available until the study has been published. Access criteria has not yet been defined by the TMG.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version 2.0	21/02/2022	10/03/2022	No	Yes
Participant information sheet	version 2.2	12/07/2022	29/09/2022	No	Yes
Participant information sheet	version 3.0	05/10/2022	23/03/2023	No	Yes
Participant information sheet	version 3.1	10/03/2023	04/07/2023	No	Yes
Protocol file	version 2.0	21/02/2022	10/03/2022	No	No
Protocol file	version 4.0	05/07/2022	29/09/2022	No	No
Protocol file	version 5.0	19/10/2022	23/03/2023	No	No
Protocol file	version 6.0	10/03/2023	04/07/2023	No	No
Protocol file	version 8.0	12/11/2024	22/10/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes