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
Registration date 10/03/2022	Overall study status Ongoing	 Statistical analysis plan Results
Last Edited 28/08/2024	Condition category Cancer	 Individual participant data [X] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-how-oftento-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 reescalation 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 pseudoanonymised will be sent to avoid participant identification.

COVID-19: Patients are included in the at-risk categories but the aim of the study is 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 May 2027

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

Study website https://www.imperial.ac.uk/department-surgery-cancer/research/cancer/research-areas/clinicaltrials/refine-lung/

Contact information

Type(s) Principal Investigator

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Additional identifiers

EudraCT/CTIS number 2021-004908-18

IRAS number 1004165

ClinicalTrials.gov number NCT05085028 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

Secondary study design Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet See additional files

Health condition(s) or problem(s) studied

Lung cancer

Interventions

 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.
 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.
 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.
 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.
 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.
 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.
 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.

Intervention Type

Drug

Phase Phase III

Drug/device/biological/vaccine name(s)

pembrolizumab

Primary outcome measure

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

Secondary outcome measures

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

Overall study start date

14/01/2022

Completion date

31/05/2027

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

Age group Adult

Lower age limit

18 Years

Sex

Both

Target number of participants 1750

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 30/11/2025

Locations

Countries of recruitment England

Scotland

United Kingdom

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

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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 Bournemouth United Kingdom BH7 7DW

Study participating centre Kettering General Hospital Rothwell Road Kettering 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 Poole United Kingdom 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

Sponsor details

Imperial Clinical Trials Unit – Cancer Cancer Research UK Convergence Science Centre Department of Surgery and Cancer Imperial College London 5th Floor Roderic Hill Building South Kensington Campus Prince Consort Road London England United Kingdom SW7 2AZ +44 (0)20 7594 2796 p.badman@imperial.ac.uk **Sponsor type** University/education

Website http://www.imperial.ac.uk/

ROR https://ror.org/041kmwe10

Funder(s)

Funder type Government

Funder Name Health Technology Assessment Programme

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

Funding Body Type Government organisation

Funding Body Subtype National government

Location United Kingdom

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals Internal report Conference presentation Publication on website Submission to regulatory authorities

Intention to publish date 31/05/2028

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?
Participant information sheet	version 2.0	21/02/2022	10/03/2022	No	Yes
Protocol file	version 2.0	21/02/2022	10/03/2022	No	No
Participant information sheet	version 2.2	12/07/2022	29/09/2022	No	Yes
Protocol file	version 4.0	05/07/2022	29/09/2022	No	No
Participant information sheet	version 3.0	05/10/2022	23/03/2023	No	Yes
Protocol file	version 5.0	19/10/2022	23/03/2023	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	version 3.1	10/03/2023	04/07/2023	No	Yes
<u>Protocol file</u>	version 6.0	10/03/2023	04/07/2023	No	No