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A trial to find a safe dose of drug treatment combined with radiotherapy for non small cell lung cancer (CONCORDE)

Submission date
21/10/2020

Recruitment status
Recruiting

Registration date
04/11/2020

Overall study status
Ongoing

Last Edited
15/04/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] 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-of-radiotherapy-and-targeted-treatment-for-non-small-cell-lung-cancer-concorde

Background and study aims
This study will investigate if drug treatment makes radiotherapy a more effective treatment for non-small cell lung cancer (NSCLC) that has not spread beyond the chest. This study aims to see which dose of the drug is safe to use.

DNA carries the instructions for making our body. Radiotherapy works by damaging the cancer cells' DNA to the point where hopefully they can no longer survive. The cancer cell will try to repair the radiotherapy damage, so blocking these repair systems may make radiotherapy more effective.

The drugs being evaluated in this study are called DNA damage response inhibitors (DDRis), they limit the body's ability to repair damaged DNA. It is believed that this will cause the radiotherapy to kill more cancer cells. However, radiotherapy can also damage the DNA of the normal non-cancer cells surrounding the tumour. It is important to work out whether using DDRi with radiotherapy leads to increased side-effects or not. DDRis have been given with radiotherapy and chemotherapy in a number of tumour types, including lung cancer. We are also including immunotherapy treatment in some study-arms. Immunotherapy is a drug treatment administered into a vein that helps the patient's immune system fight cancer cells. Both patients and study doctors will know prior to the start of the actual treatment whether a DDRi with or without immunotherapy will be given, and if so which one.

The main purpose of the study is to find the most suitable dose of the DDRi that can be safely combined with radiotherapy. This will enable us to test this dose in larger clinical studies. This study will also be looking at whether the DDRis might improve the effectiveness of the radiotherapy in treating the cancer. Samples from participant's tumour and blood will be tested

to see if patients who might benefit from the DDRi can be identified. Several DDRis are being examined in the study, each in a separate study-arm. Participants will only be enrolled into one study arm.

Who can participate?
All study participants will have been diagnosed with non small cell lung cancer that is confined to the chest and is suitable for treatment with radiotherapy. Each participant is carefully assessed using tests to check that they are suitable for inclusion in the study. These include: blood tests, an assessment of medical history, a physical examination, lung function tests, pregnancy tests (where appropriate), chest x-ray, heart scan, CT scan and CT or MRI scan of the brain. Some of these tests would need to have been done irrespective assessment of study eligibility.All study participants will have been diagnosed with non small cell lung cancer that is confined to the chest and is suitable for treatment with radiotherapy. Each participant is carefully assessed using tests to check that they are suitable for inclusion in the study. These include: blood tests, an assessment of medical history, a physical examination, lung function tests, pregnancy tests (where appropriate), chest x-ray, heart scan, CT scan and CT or MRI scan of the brain. Some of these tests would need to have been done irrespective assessment of study eligibility.

What does the study involve?
Participants are allocated to either DDRi (study drug) and radiotherapy or radiotherapy alone. All participants will attend hospital for radiotherapy Monday to Friday for 6 weeks. Participants allocated to study drug will also take this throughout radiotherapy. Once treatment has been completed participants will attend hospital every 6 weeks for 6 months and then every 3 months until 2 years after the end of treatment, and those who are receiving immunotherapy treatment will visit for their treatment every 4 weeks for up to 12 months. Assessments will be carried out during treatment and follow up to monitor for adverse effects and to measure the effect of treatment.

What are the possible benefits and risks of participating?
There is no guarantee that participants will benefit from the treatment given in this study, but this is the same as any treatment they would have even if they did not take part in the study. Although radiotherapy is effective in treating lung cancer, as with other cancer treatments, there is no certainty that they will be effective for the participant. Nor can it be certain that the addition of the DDRi will produce any benefit. Therefore, study participation may not be of direct benefit to participants personally, but it is possible that it may be of benefit to future cancer patients. Information from this study will help doctors to learn more about the DDRi when it is used with radiotherapy, and whether this may be a step forward for the treatment of lung cancer in the future. Without research of this sort, improvements in cancer treatments are not possible. All study participants could benefit from more close monitoring than would be possible outside of the study.

Radiotherapy is a tried and tested cancer treatment. The kind of side effects that participants may have whilst being given this treatment are well known and are listed in the participant information. However, as the type of radiotherapy has only been used with a DDRi in a small numbers of patients, there is a chance that there may be side effects that are new or which differ from those which doctors would usually expect to see with radiotherapy alone. Potential adverse effects are described in the participant information provided prior to study enrolment.

Where is the study run from?
Clinical Trials Research Unit (CTRU) at the University of Leeds (UK)

When is the study starting and how long is it expected to run for?
From November 2019 to September 2028

Who is funding the study?
The National Institute for Health Research (NIHR) (UK), AstraZeneca Ltd (UK) and Cancer Research UK (UK)

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-000206-28

Integrated Research Application System (IRAS)
282001

ClinicalTrials.gov (NCT)
NCT04550104

Protocol serial number
CPMS 45504, IRAS 282001

Study information

Scientific Title
A platform study of DNA damage response inhibitors in combination with conventional radiotherapy in non small cell lung cancer

Acronym
CONCORDE

Study objectives
To find a safe dose for each DNA damage response inhibitors (DDRi) used in combination with radiotherapy in patients with non small cell lung cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/10/2020, Yorkshire and the Humber – Leeds West Research Ethics Committee (Queens Hotel, City Square, Leeds, LS1 1PJ;+44 (0)207 972 2504; leedswest.rec@hra.nhs.uk), ref: 20/YH/0280

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Non small cell lung cancer

Interventions
Current intervention as of 12/01/2024:
Participants will initially be allocated to either radiotherapy (RT)-alone, or RT + DNA damage response inhibitors (DDRi), on a 1:1 basis. Once 10 participants have been randomised to RT-alone the allocation ratio will change to 3:1 in favour of RT+DDRi. This is necessary to accrue

sufficient RT-alone patients to act as comparators in the early stages of the trial and to assess whether the target toxicity level of 0.25 in each experimental arm is reasonable. Consenting participants will be randomised between DDRi with RT or RT only, initially on a 1:1 basis in order to accumulate sufficient comparator patients in the early stages of the study and to evaluate the pre-defined DLT rate in the calibration arm. The pooling of patients receiving RT across the platform allows us to move to a 3:1 ratio to DDRi and RT combination, maximizing the patients who receive a novel agent in the study whilst developing a robust calibrator cohort to allow interpretation of any toxicities seen on the study. If the calibration arm DLT rate is higher than expected then the target toxicity level in the experimental arms will be adjusted accordingly. Patients are not randomised between experimental arms.

Randomisation will be performed centrally using the CTRU's 9-5 telephone randomisation system. The randomisation is open-label, therefore the patient, clinician and research team will be informed of the treatment allocation.

CONCORDE is a multi-institution, multi-arm, Phase IB study that will determine the safe dose of different DDRis when given in an open label fashion in combination with fixed-dose curative intent radiotherapy in the 'radiation phase' in patients with locally advanced non-small-cell lung cancer (NSCLC). In selected cohorts a second phase of treatment known as the 'consolidation phase' eligible participants will receive up to 12 months of consolidation durvalumab treatment with or without DDRi depending on randomisation and study-arm. The study’s primary objective is to determine the safe dose for each DDRi when given in combination with thoracic radiotherapy of 60 Gy in 30 fractions. This will be evaluated by incorporating the number of observed dose-limiting toxicities into a time to event continuous reassessment method (TiTE-CRM) model within each of the experimental arms, with a maximum of 30 patients being treated in each experimental arm. TiTE-CRM is used here to take into account longer-term toxicities up to 13.5 months post start of radiotherapy and use these to inform dose escalation decision-making.

At the time of patient identification the treating centre will be informed of the allocated study arm by Leeds CTRU following a pre-specified prioritisation schedule. The process of patient allocation will be determined by a number of logistical factors (e.g. which sites are open for which study arm). The speed of recruitment into each arm will be monitored and can be adjusted by the Safety Review Committee (SRC) should additional toxicity data/follow-up be deemed necessary prior to further allocation. The trial information will be provided to the patient and discussed so that the patient can ask questions. Written informed consent will be obtained by a suitably qualified member of the patient's healthcare team at an appropriate clinic visit.

The patients receiving RT alone will be pooled across the arms to provide contemporary data on toxicity in up to 50-60 patients, accounting for recent improvements in RT techniques and quality assurance. All patients will receive external beam RT with a planned dose of 60 Gy in 30 daily fractions. This calibration arm will aid with attribution of toxicities to the addition of DDRi to RT and will therefore aid interpretation rather than permitting formal comparison between arms. Each DDRi will be administered orally in an open-label fashion alongside the RT. The schedule and starting dose for dose escalation will be based on single agent experience in the clinic and pre-clinical safety. This is fully outlined for each agent in the relevant study arm protocol.

Toxicity will be assessed continuously throughout treatment according to Common Toxicity Criteria for Adverse Events (CTCAE) with weekly assessments until grade 2 or higher toxicities have resolved to ≤ grade 1 in severity. Subsequently, the participants will be followed up at 4, 6, 12, 18, and 24 weeks after the completion of RT, and 3 monthly thereafter until 2 years after the

completion of RT. Response to treatment, and progression-free survival will be assessed by CT scans performed at 1 month following the completion of RT and subsequently at 3, 6, 9 (only for those receiving durvalumab consolidation), 12, 18 and 24 months.

Dose limiting toxicities (DLTs) will be monitored from start of treatment up to 13.5 months post start of RT in order to capture both the acute and long term toxicities related to the drug RT combination; and participants will then be followed-up for a maximum of 2 years for safety and efficacy, as described above. DLTs will also be collected for participants randomised to RT-alone. The DLT period will be split into two stages:
1. Short DLT period which will be during DDRi and/or radiotherapy treatment and up to 4.5 months from day 1 of radiotherapy (weighted for 90% of TiTE-CRM)
2. Long DLT period which will be 4.5-13.5 months from day 1 of radiotherapy (weighted for 10% of TiTE-CRM)
Full follow-up of DLTs to 13.5 months post-start of radiotherapy (RT) will allow capture of all DLTs related to the DDRi and RT combination. Full DLT follow-up of all evaluable participants at the highest tolerable dose level will be required to confirm the recommended phase II dose (RP2D) within each DDRi treatment arm. Patients at the highest tolerable dose level may need to be replaced. The end of the DLT period aligns with the 12-month post end of RT study visit.

Dose Escalation
A separate TiTE-CRM model will be used for each DDRi independently, with dose escalation decisions driven by the occurrence of DLTs and reviewed by a SRC. Dose escalation may consist of both changes in dose and schedule to increase exposure as outlined in the relevant study arm protocols.

Each patient's dose is decided individually based on the available data at the time of recruitment, i.e. using cohorts of size 1 within the TiTE-CRM model.The dose with probability of toxicity closest to the target of 0.25, in the first instance, will be selected. This target toxicity level is based on expert clinical opinion and target DLT rates in phase I studies of novel systemic therapies. It may, however, be adjusted by the SRC following the assessment of the first 10 calibration arm patients and in light of emerging data from the patients treated with radiotherapy alone. Due to the novelty of agents used in this study, untried dose levels will not be skipped.

At least 1 patient is required to have completed the short DLT period (i.e. around 4.5 months' worth of data) from a dose level before the next dose level can be opened up and the SRC will decide whether enough follow-up has been observed in the previous patients in order to dose escalate. The RP2D will be defined as the dose level at which the toxicity probability is closest to the target DLT probability, 0.25.

During dose escalation, if the dose under assessment for any arm is reduced to dose level -1, recruitment will be restricted to approximately 1 patient per month for that arm, for at least the first three patients recruited at this dose, and additional pauses will be implemented prior to dose re-escalation, as discussed and agreed with the SRC.

If the lower limit of the credible interval for the estimated probability of unacceptable toxicity is higher than 0.3 at dose level -1, or more than 3 DLTs are observed at this dose level, then that arm will be closed to further recruitment and dose escalation.

If no DLTs are seen at any dose level, then that trial arm will close to recruitment once 10 participants have completed the late DLT assessment period at the highest dose level, and that dose level will be deemed the RP2D. The SRC can, however, override this stopping rule if more data is deemed necessary for deciding the RP2D.

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Previous intervention as of 31/03/2023:
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Intervention Type
Mixed

Primary outcome(s)
1. Dose-limiting toxicities (DLTs), within 13.5 months of starting radiotherapy, in order to establish the Recommended Phase II Dose (RP2D) of each DDR-RT combination between baseline and 13.5 months

Key secondary outcome(s))
1. Safety and toxicity reported based on the occurrence of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). Toxicity will be reported based on adverse events, as graded by Common Toxicity Criteria for Adverse Events (CTCAE v5.0), and determined by routine clinical assessments at each centre.between baseline and 2 years after the end of radiotherapy (RT)
2. Treatment compliance measured by overall radiotherapy treatment time and delays, omissions and reductions to treatment doses (both DDRi and RT) between baseline and the end of trial treatment
3. Best overall response measured as the best response (complete response, partial response or stable disease) recorded until disease progression, using Response Evaluation Criteria In Solid Tumors (RECIST v1.1), by 2 years post-RT
4. Disease control assessed using the Green Criteria by 2 years post-RT. Disease Control includes either the complete disappearance of all evidence of malignant disease or residual radiographic abnormalities assessed by chest CT scan at 3 and 6 months after completion of RT, which then remains stable for an additional 6 months or more and which then qualifies as controlled local disease.
5. Progression-free survival measured using CT scans at 1, 3, 6, 12, 18, and 24 months after the end of RT. Participants who have not progressed at the time of analysis will be censored at the last date they were known to be alive and progression-free.
6. Overall survival measured from patient notes between baseline and 2 years. Participants who have not died at the time of analysis will be censored at the last date they were known to be alive.

7. Changes from baseline in Health Related Quality of Life measured using European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), IL-73 and IL-74 at baseline, end of RT, 3, 6, 12, 18 and 24 months after the end of RT
8. Objective response rate (ORR) measured using CT scans at 1, 3, 6, 12, 18, and 24 months after the end of RT. ORR is defined as the proportion of patients who have a partial or complete response to therapy. The proportion of patients with evaluable scans that achieve at least a partial response, as defined by RECIST v1.1, will be presented with 95% confidence intervals.
9. Changes in tumour size during and following treatment with DDRi-RT compared to RT alone measured using .. at baseline and 2 years after the end of RT

Exploratory outcomes:
1. Assessment of mutations in components of DDR pathway in archival tumour and cfDNA prior to therapy assessed using using medical tests during treatment and follow up to 2 years after the end of RT
2. Assessment of T cells within the archival tumour specimens assessed using medical tests at baseline and disease progression
3. Changes in cfDNA during and following treatment with DDRi-RT compared to RT alone measured using medical tests during treatment and follow up to 2 years after the end of RT
4. Changes in circulating biomarkers of cardiac and respiratory toxicity measured during and following treatment with DDRi-RT compared to RT alone measured using medical tests during treatment and follow up to during treatment and follow up to 3 months after the end of RT
5. Changes in circulating peripheral T cell sub-sets during and following treatment with DDRi-RT compared to RT alone measured using medical tests at baseline, during treatment and follow up to disease progression
6. Changes in lung parenchyma during and following treatment with DDRi-RT compared to RT alone measured using using medical tests at baseline and 2 years after the end of RT

Completion date
01/09/2028

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/01/2024:
Core inclusion criteria (radiation phase):
1. Histologically or cytologically confirmed NSCLC (patients where the local MDT agree the diagnosis is NSCLC after review of the available pathology and imaging at MDT can be enrolled after discussion with the CI)
2. Not suitable for concurrent chemoradiotherapy/surgery due to tumour or patient factors
3. Stage IIB and III (TNM 8th Edition)
4. Planned to receive RT at curative intent doses (i.e. 60 Gy) as part of treatment plan (either with or without induction chemotherapy)
5. Patient considered suitable for radical RT by the local lung cancer multidisciplinary team and a clinical oncologist
6. If chemotherapy has been given previously, the maximum interval between the last day of chemotherapy and the start of RT <10 weeks
7. Age ≥18 years
8. Life expectancy estimated to be greater than 6 months
9. Karnofsky Performance status ≥70
10. MRC dyspnoea score <3
11. Forced expiratory volume in one second (FEV1) ≥35% predicted and diffusing capacity of the

lungs for carbon monoxide (DLCO or TLCO) ≥35% predicted
12. Patient must be fully informed about the study and have signed the informed consent form
13. Patient must be willing and able to comply with the protocol, have mental capacity and (if relevant) use effective contraception throughout treatment and for 4 months for women of childbearing potential (WOCBP)/6 months for men after trial treatment
completion. Treatment is defined as including the last dose of durvalumab or DDRi in the consolidation phase (or comply with more stringent contraceptive requirements if prescribed in the relevant study-arm protocol).
14. Adequate organ function within 28 days prior to confirmation of eligibility and 7 days of study treatment
15. Patient has body weight of >30 kg

Inclusion criteria (consolidation phase):
The following eligibility criteria must be met before participants can receive durvalumab +/- DDRi in the consolidation phase. Participants that do not meet these criteria to enter the consolidation phase, or are not in a study arm with durvalumab +/- DDRi consolidation will continue post RT follow up.
Participants randomised to RT + DDRi in the radiation phase are eligible to receive both DDRi and durvalumab in consolidation phase. Participants will not be permitted to receive DDRi alone.
Participants randomised to RT + DDRi that have a DLT and meet the consolidation eligibility criteria can receive durvalumab alone.
Participants randomised to RT-only in the radiation phase are eligible to receive durvalumab alone in the consolidation phase if they meet the following eligibility criteria.
1. A minimum of 4 and a maximum of 8 weeks have elapsed following completion of RT. (Investigators should ideally aim to start consolidation treatment within 6 weeks, following the receipt of the CT scan results to rule out progression.)
2. Any toxicities from RT have resolved to grade 1. If patient has pneumonitis following RT treatment, this must be asymptomatic (grade 1). If pneumonitis is ≥2 or requiring steroids, then participant is not eligible.
3. Karnofsky Performance status >70
4. The laboratory requirements are met
5. Patient has no known hypersensitivity to the excipients of durvalumab
6. Patient has body weight of >30kg

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Previous inclusion criteria as of 31/03/2023:
Core inclusion criteria (radiation phase):
1. Histologically or cytologically confirmed NSCLC (patients where the local MDT agree the diagnosis is NSCLC after review of the available pathology and imaging at MDT can be enrolled after discussion with the CI)
2. Not suitable for concurrent chemoradiotherapy/surgery due to tumour or patient factors
3. Stage IIB and III (TNM 8th Edition)
4. Planned to receive RT at curative intent doses (i.e. 60 Gy) as part of treatment plan (either with or without induction chemotherapy)
5. Patient considered suitable for radical RT by the local lung cancer multidisciplinary team and a clinical oncologist
6. If chemotherapy has been given previously, the maximum interval between the last day of chemotherapy and the start of RT <10 weeks
7. Age ≥18 years
8. Life expectancy estimated to be greater than 6 months
9. Karnofsky Performance status >70

10. MRC dyspnoea score <3
11. Forced expiratory volume in one second (FEV1) ≥35% predicted and diffusing capacity of the lungs for carbon monoxide (DLCO or TLCO) ≥40% predicted
12. Patient must be fully informed about the study and have signed the informed consent form
13. Patient must be willing and able to comply with the protocol, have mental capacity and (if relevant) use effective contraception throughout treatment and for 4 months for women of childbearing potential (WOCBP)/6 months for men after trial treatment completion. Treatment is defined as including the last dose of durvalumab or DDRi in the consolidation phase (or comply with more stringent contraceptive requirements if prescribed in the relevant study-arm protocol).
14. Adequate organ function within 28 days prior to confirmation of eligibility and 7 days of study treatment
15. Patient has body weight of >30 kg

Inclusion criteria (consolidation phase):
The following eligibility criteria must be met before participants can receive durvalumab +/- DDRi in the consolidation phase. Participants that do not meet these criteria to enter the consolidation phase, or are not in a study arm with durvalumab +/- DDRi consolidation will continue post RT follow up.
Participants randomised to RT + DDRi in the radiation phase are eligible to receive both DDRi and durvalumab in consolidation phase. Participants will not be permitted to receive DDRi alone. Participants randomised to RT + DDRi that have a DLT and meet the consolidation eligibility criteria can receive durvalumab alone.
Participants randomised to RT-only in the radiation phase are eligible to receive durvalumab alone in the consolidation phase if they meet the following eligibility criteria.
1. A minimum of 4 and a maximum of 8 weeks have elapsed following completion of RT. (Investigators should ideally aim to start consolidation treatment within 6 weeks, following the receipt of the CT scan results to rule out progression.)
2. Any toxicities from RT have resolved to grade 1. If patient has pneumonitis following RT treatment, this must be asymptomatic (grade 1). If pneumonitis is ≥2 or requiring steroids, then participant is not eligible.
3. Karnofsky Performance status >70
4. The laboratory requirements are met
5. Patient has no known hypersensitivity to the excipients of durvalumab
6. Patient has body weight of >30kg

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Previous inclusion criteria:
1. Histologically or cytologically confirmed non small cell lung cancer
2. Not suitable for concurrent chemoradiotherapy/surgery due to tumour or patient factors
3. Stage IIB and IIIA/IIIB (TNM 8th Edition) planned to receive radiotherapy (RT) at curative intent doses (i.e. 60 Gy) as part of treatment plan (either with or without induction chemotherapy)
4. Patient considered suitable for radical RT by the local lung cancer multidisciplinary team and a clinical oncologist
5. If chemotherapy has been given previously, the maximum interval between the last day of chemotherapy and the start of RT <8 weeks
6. Age ≥18
7. Life expectancy estimated to be greater than 6 months
8. Performance status (ECOG) 0 or 1
9. MRC dyspnoea score <3
10. Forced expiratory volume in one second (FEV1) ≥40% predicted and diffusing capacity of the

lungs for carbon monoxide (DLCO) ≥40% predicted
11. Patient must be fully informed about the study and have signed the informed consent form
12. Patient must be willing and able to comply with the protocol, have mental capacity, and (if relevant) use effective contraception throughout treatment and for 4 months after treatment completion (or comply with more stringent contraceptive requirements if prescribed in the relevant study-arm protocol)
13. Adequate organ function within 28 days prior to confirmation of eligibility and 7 days of study treatment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 31/03/2023:
Core exclusion criteria (radiation phase):
1. Mixed non-small cell and small cell tumours
2. Confirmed progressive disease according to RECIST 1.1 during induction chemotherapy
3. Participation in a study of an investigational agent or using an investigational device within 4 weeks prior to the anticipated start of treatment
4. Current or previous malignant disease which may impact on a patient's estimated life expectancy (other than NSCLC)
5. History of interstitial pneumonitis (to include diffuse alveolar damage, non-malignant causes of pneumonitis, acute respiratory
distress syndrome, alveolitis, cryptogenic organising pneumonia, obliterative bronchiolitis, non-malignant causes of pulmonary fibrosis, usual interstitial pneumonia, interstitial pulmonary fibrosis and connective tissue disorder (scleroderma, systemic lupus erythematosus))
6. Prior thoracic radiotherapy (excluding patients that have had RT for breast cancer or lung SABR to the contralateral lung providing that the overlap is minimal as per local investigator's discretion or as discussed and agreed by CI/Study Arm Lead contacted via CTRU as required)
7. Prior treatment with pneumotoxic drugs, e.g. busulfan, bleomycin, within the past year. If prior therapy in lifetime, then exclude if history of pulmonary toxicities from administration. Patients who have received treatment with nitrosoureas (e.g., carmustine, lomustine) in the year before study entry without experiencing lung toxicity are allowed on study.
8. Mean resting corrected QT interval (QTcF) >470 msec obtained from 3 electrocardiograms (ECGs) (QTc interval will be calculated using Fridericia's formula). Multiple ECGs are only required if 1st ECG QTcF >470 msec. ECGs should be at least 5 minutes apart.
9. Received a prior autologous or allogeneic organ or tissue transplantation
10. Patients unable to swallow orally administered medications or chronic gastrointestinal (GI) disease likely to interfere with absorption of IMP in the opinion of the treating investigator (e.g.

malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease, refractory nausea and vomiting etc).
11.Grade 2 or higher peripheral sensory neuropathy.
12. Known positive test for human immunodeficiency virus (HIV), history of active primary immunodeficiency, known active hepatitis B or C infection (new test not mandated for trial entry). Participants with a past or resolved hepatitis B virus infection are eligible (defined as the presence of the hepatitis B core antibody (antiHBc) and absence of the hepatitis B surface antigen (HBsAg). Participants positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
13. Positive pregnancy test (at eligibility assessment for women of childbearing potential) or breast-feeding women
14. Patients with persistent toxicities (>CTCAE grade 2) caused by previous cancer therapy, excluding alopecia
15. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML
16. Major surgery within 2 weeks of confirmation of eligibility
17. Patients considered a poor medical risk by the investigator due to a serious, uncontrolled medical disorder, non-malignant system disease or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, uncontrolled hypertension, uncontrolled atrial fibrillation, active bleeding, recent (within 3 months) myocardial infarction, major seizure, active COVID-19, known active Mycobacteria tuberculosis infection, any psychiatric disorder that prohibits obtaining informed consent.
18. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease (eg, ulcerative colitis or Crohn's disease), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis rheumatoid arthritis, hypophysitis, uveitis, etc)). The following are exceptions to this criterion: patients with vitiligo or alopecia, patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement, any chronic skin condition that does not require systemic therapy, patients without active disease in the last 5 years at enrolment may be included but only after consultation with the CI/Study arm-lead (via CTRU), patients with coeliac disease controlled by diet alone.
19. Exclusions as described in the relevant study arm protocol. Patients ineligible for a particular study arm may be considered for entry into an alternative study arm if an appropriate slot is available and they meet all the inclusion and exclusion criteria for that arm. This will need to be discussed with CTRU and the patient will be required to reconsent using the appropriate study arm PIS/ICF.

Exclusion criteria (consolidation phase):
1. Progressive disease during RT or at the end of RT treatment response assessment (4-week post RT CT scan must be reviewed prior to entry for the consolidation phase)
2. Participant declines treatment in the consolidation phase
3. Patients who have received prior anti-PD-1 or anti PD-L1 treatment
4. Major surgery within 4 weeks of confirmation of eligibility for consolidation phase
5. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion: Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection), systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent, steroids as premedication for hypersensitivity reactions or as protocol defined pre-medication (e.g. as anti-emetics for trial treatments or for CT scan premedication).
6. Patients considered a poor medical risk by the investigator due to a serious, uncontrolled medical disorder, non-malignant system disease, active GI infection or active uncontrolled infection. Examples include, but are not limited to, symptomatic congestive heart failure,

unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled hypertension, uncontrolled atrial fibrillation, active bleeding, recent (within 3 months) myocardial infarction, major seizure, active COVID-19 (defined in radiation phase eligibility criteria), known active Mycobacteria tuberculosis infection, serious chronic gastrointestinal conditions associated with diarrhoea, or any psychiatric disorder that prohibits obtaining informed consent.
7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease e.g., colitis or Crohn's disease), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc). The following are exceptions to this criterion: Patients with vitiligo or alopecia, patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement, any chronic skin condition that does not require systemic therapy, patients without active disease in the last 5 years may be included but only after consultation with the study arm lead/CI (contacted via CTRU), patients with celiac disease controlled by diet alone.

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Previous exclusion criteria:
1. Mixed non-small cell and small cell tumours
2. Confirmed progressive disease during induction chemotherapy
3. Participation in a study of an investigational agent or using an investigational device within 4 weeks prior to the anticipated start of treatment
4. Current or previous malignant disease which may impact on a patient’s estimated life expectancy (other than NSCLC)
5. History of interstitial pneumonitis
6. Prior thoracic radiotherapy (excluding patients that have had RT for breast cancer providing that the overlap is minimal as per local investigators discretion or as discussed and agreed by CI as required)
7. Prior treatment with pneumotoxic drugs, e.g. busulfan, bleomycin, within the past year. If prior therapy in lifetime, then exclude if history of pulmonary toxicities from administration. Patients who have received treatment with nitrosoureas (e.g., carmustine, lomustine) in the year before study entry without experiencing lung toxicity are allowed on study.
8. Mean resting corrected QT interval (QTcF) >470 msec obtained from 3 electrocardiograms (ECGs).
9. Received a prior autologous or allogeneic organ or tissue transplantation
10. Patients unable to swallow orally administered medications or chronic gastrointestinal (GI) disease likely to interfere with absorption of IMP in the opinion of the treating investigator (e.g. malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease etc)
11. Grade 2 or higher peripheral sensory neuropathy
12. Known positive test for human immunodeficiency virus (HIV), active hepatitis B or C infection (new test not mandated for trial entry)
13. Positive pregnancy test (at eligibility assessment for women of childbearing potential) or breast-feeding women
14. Patients with persistent toxicities (> CTCAE grade 2) caused by previous cancer therapy, excluding alopecia
15. Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML
16. Major surgery within 2 weeks of confirmation of eligibility
17. Patients considered a poor medical risk by the investigator due to a serious, uncontrolled medical disorder, non-malignant system disease or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, uncontrolled hypertension, uncontrolled atrial fibrillation, active bleeding, recent (within 3 months) myocardial infarction,

major seizure, active COVID-19, any psychiatric disorder that prohibits obtaining informed consent.
14. Gemcitabine treatment (within 6 months of assessment of eligibility
15. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease (eg, ulcerative colitis or Crohn's disease), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc)). The following are exceptions to this criterion:
15.1. Patients with vitiligo or alopecia
15.2. Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
15.3. Any chronic skin condition that does not require systemic therapy
15.4. Patients without active disease in the last 5 years at enrolment may be included but only after consultation with the CI/Study arm-lead
15.5. Patients with coeliac disease controlled by diet alone
16. Exclusions as described in the relevant study arm protocol

Date of first enrolment
16/12/2020

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester

United Kingdom
M20 4BX

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

Study participating centre
Velindre NHS Trust
Unit 2
Charnwood Court
Heol Billingsley
Cardiff
United Kingdom
CF15 7QZ

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Belfast Health and Social Care Trust
Trust Headquarters
A Floor - Belfast City Hospital
Lisburn Road
Belfast
United Kingdom
BT9 7AB

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
Birmingham Heartlands NHS Trust
Bordesley Green East
Birmingham
United Kingdom
B9 5SS

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Hospital
Clatterbridge Road
Wirral
United Kingdom
CH63 4JY

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing, and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	22/09/2020		Yes	No
HRA research summary			28/06/2023	No	No
Other publications		01/11/2022	02/12/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes