ISRCTN73037722 https://doi.org/10.1186/ISRCTN73037722

LION: lifting immune checkpoints with NSAIDs

Submission date 04/03/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 02/08/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 16/04/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Cancer accounts for a quarter of UK deaths and more effective treatments are needed. One approach is to use immunotherapy drugs that can unleash a patient's immune system to attack the cancer. Immunotherapy drugs have been shown to be an effective treatment for many patients with cancer, but, even in melanoma, where these agents are most useful, not all patients respond.
Chronic inflammation can encourage cancer growth. The anti-inflammatory drug celecoxib can make immune checkpoint inhibitors more effective and better at treating cancers. Celecoxib does this by preventing the cancer from producing substances that dampen down the type of inflammation that weakens the immune response whilst encouraging ‘good’ inflammation, the type that produces an effective anti-cancer immune response.
The next step is to investigate if celecoxib given alongside routinely prescribed immune checkpoint inhibitors could be a useful treatment in the clinic for patients with newly diagnosed non-small cell lung cancer, renal cell cancer and triple-negative breast cancer. These cancer types were chosen as laboratory data suggest these may be the cancer types most likely to benefit from this approach.

Who can participate?
Newly diagnosed patients aged 18 years and over with advanced cancer, based in the UK and who have the following tumour types:
1. Inoperable or secondary triple-negative breast cancer suitable that expresses the immune marker PDL-1
2. Advanced (stage IIIB or IV) non-small cell lung cancer
3. Locally advanced or secondary renal cell cancer

What does the study involve?
Patients will be treated with the NHS-approved immunotherapy drugs for the type of cancer that they have. In the case of lung and breast cancer patients, the immunotherapy drugs are given with chemotherapy. In addition to the usual treatment for their cancer all patients will be prescribed the anti-inflammatory tablet celecoxib.
Patients will have their cancer monitored in the usual way by scans. Additional blood samples will be taken for laboratory research. Some patients will be asked to undergo a research biopsy (sample) of their cancer but this part will be optional.

What are the possible benefits and risks of treatment?
It is hoped that celecoxib will help immunotherapy to work better, but it is not known if this will be the case yet. All patients will be fully informed of the potential risks and benefits of this study before trial entry. Side effects of celecoxib include a risk of bleeding, allergic reactions, gastrointestinal upsets and heart problems. All patients will be given gastrointestinal protection with a drug called a proton-pump inhibitor. Patients with a risk of heart problems will be excluded from the study.

Where is the study from?
1. The Christie NHS Foundation Trust (UK)
2. Liverpool Clinical Trials Centre (UK)

When is the study starting and how long is it expected to run for?
February 2022 to May 2027

Who is funding the study?
1. Jon Moulton Charity Trust (UK)
2. Christie Hospital Charity (UK)

Who is the main contact?
LION Trial Coordinator, LION@liverpool.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-celecoxib-with-standard-treatment-for-certain-types-of-cancer-that-have-spread

Contact information

Type(s)
Scientific

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-005109-29

Integrated Research Application System (IRAS)
1004222

Protocol serial number
CFTSp198, IRAS 1004222

Study information

Scientific Title
Pan tumour trial of COX-inhibitor and immune checkpoint blockade

Acronym
LION

Study objectives
This clinical study will evaluate the addition of the COX-2 inhibitor, celecoxib, to the current standard of care immunotherapy regimens in the treatment of triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC). Each of these disease groups has a licensed immunotherapy regimen, and has been shown to be a promising target for manipulation of the COX-2-associated inflammatory response in pre-clinical data. This trial tests the hypothesis that combining COX-2 inhibition with immune checkpoint blockade is associated with an enhanced response.

Primary objective:
To assess the best tumour response to first-line treatment with COX-2 inhibition (celecoxib) in combination with standard of care immune checkpoint blockade (determined by each disease type).

Secondary objectives:
1. To assess overall survival
2. To assess progression-free survival
3. To assess the best overall response rate over 6 months
4. To assess time to secondary progression
5. To determine the safety and tolerability of celecoxib when given with standard of care immune checkpoint blockade combinations

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/05/2022, London - Fulham Research Ethics Committee (Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8084, +44 (0)207 104 8035, +44 (0)207 104 8109; fulham.rec@hra.nhs.uk), ref: 22/LO/0219

Study design
Non-randomized study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC)

Interventions
Current interventions as of 14/05/2024:
Interventions: ALL cohorts
IMP: Celecoxib
Form: Capsule
Dose: 200 mg twice daily for 13 weeks then 100 mg twice daily (continuous until disease progression or stopping immune therapy)
Route: Oral

TNBC:
IMP: Atezolizumab
Form: Solution for infusion
Dose: 840 mg on day 1 and day 15 of a 28-day cycle (until disease progression or unacceptable toxicity; patients who are no longer also receiving concurrent Nab-paclitaxel can receive 1680mg d1 of a 28-day cycle)
Route: intravenous (IV)

IMP: Nab-paclitaxel
Form: Powder for suspension for infusion
Dose: 100 mg/m² day 1,8,15 of a 28-day cycle (continuous until disease progression)
Route: IV

RCC:
IMP: Nivolumab
Form: Concentrate for solution for infusion
Dose: 3 mg/kg every 21 days for the first four cycles and then flat dosed at 480 mg every 28 days (continuous until disease progression)
Route: IV

IMP: Ipilimumab
Form: Concentrate for solution for infusion
Dose: 1 mg/kg every 21 days for the first four cycles
Route: IV

NSCLC:
IMP: Pembrolizumab
Form: Solution for infusion
Dose: 200 mg every 21 days or 400 mg every 42 days (maximum treatment duration 2 years)
Route: IV

Duration of treatment:
All patients will be treated until progressive disease, unacceptable toxicity, end of trial or withdrawal of patient consent. In the case of pembrolizumab patient must also stop treatment after 2 years of therapy in line with national guidelines.

Duration of follow-up:
For all cohorts a minimum follow-up of 6 months for all patients who do not experience progression prior to 6 months post start of treatment

Overall study duration: 48 months

Screening/baseline activity:
1. Written Informed Consent for the LION trial
2. Confirmation of histological diagnosis of tumour type and patient eligibility check.
3. Complete demographics and medical history including prior surgeries, systemic therapies, radiotherapy, and allergies
4. Full physical examination
5. Pregnancy test for women of child-bearing potential only. To be performed within 30 days for screening sample and within 72 hours of cycle 1 Day 1 of any trial therapy
6. Vital Signs: pulse, blood pressure, temperature, respiration and O2 saturation
7. Height and Weight
8. ECOG Performance Status
9. Haematological and Clinical Biochemistry. To be performed within 30 days for screening sample and within 72 hours of cycle 1 Day 1 of any trial therapy for baseline sample
10. CT scan reported to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
11. Availability of archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue. Collection of FFPE tumour tissue is mandatory if no archival tissue from previous surgery or biopsy, are available
12. Translational Sample Collection

13. Serum, plasma and PMBC
14. Baseline adverse events
15. Concomitant medication review and check (see Section 9.7)

The following screening/baseline assessments should be performed on the TNBC cohort:
1. HER2, ER and PR
2. PD-L1 immunohistochemistry (IHC)

The following screening/baseline assessments should be performed on the NSCLC cohort:
1. EGFR, ALK and ROS1 genetic analysis
2. PD-L1 IHC

The following screening/baseline assessments should be performed on the RCC cohort:
1. International mRCC Database Consortium (IMDC) score
2. PD-L1 IHC

Routinely collected information e.g. medical history/vital signs/relevant blood test results etc can be transcribed from the patient's medical notes into the case report form (CRF) once appropriate consent has been obtained. The patient can proceed to registration once all the baseline assessments have been completed.

On treatment activity (until disease relapse):
The following procedures will be performed at the participant visits whilst on study treatment:
1. Symptom-guided physical examination and medical review
2. ECOG Performance Status
3. Adverse Events/SAE Reporting (see Section 13)
4. Concomitant medication review and check (see Section 9.7)
5. Weight
6. Vital Signs: pulse, blood pressure, temperature, respiration and O2 saturation
7. Pregnancy test for women of child-bearing potential only (see definition in section 10.4). To be performed within 72 hours of cycle 1 Day 1 of any trial therapy
8. Haematological and clinical biochemistry
8.1. Haematology laboratory tests
8.2. Clinical chemistry (serum or plasma) laboratory tests
9. CT scan with RECIST 1.1
10. Translational sample collection. The following specimens may be collected as part of consent to the trial.
10.1. FFPE of primary tumour specimen
10.2. Blood for peripheral blood mononuclear cells (PBMCs)
10.3. Blood for cytokine/metabolomics analysis
10.4. Blood for the ctDNA analysis
10.5. Microbiome samples (stool)
10.6. Fresh biopsy of easily accessible lesions (up to a maximum of three cores per procedure), at baseline (within 6 weeks of day-7) prior to immune therapy, at 12 weeks +/- 1 week on therapy and if progression on therapy. Patients may consent to any or all of these biopsies
10.7. If a surgical resection on study occurs for clinical reasons then provided the patient has consented
11. Medical history and demographics
12. Patient Diary Cards
13. Concomitant Medications
14. ECOG
15. Pregnancy test

16. Physical examination, vital signs and clinical disease assessment
17. CT scans
18. Tumour tissue testing:
18.1. EGFR and ALK mutational analysis (lung cohort only)
18.2. PD-L1 testing
18.3. PD-L1 testing should be performed according to the standard of care guidelines for each tumour type.
18.4. HER2, PR and ER testing (breast cohort only)

Disease relapse activity:
1. Haematology and biochemistry
2. Research blood
3. Urine sample
4. Tissue collection from surgical resection (only if clinically indicated)

Follow-up activity; follow-up after relapse every 3 months (+/- 1 week):
1. AE and toxicity assessment - Final safety check to be completed at the first follow-up visit after relapse i.e. 90 days
2. Haematology and biochemistry
3. Tissue collection from surgical resection (only if clinically indicated) - tissue (FFPE and if possible a piece snap frozen) from any cancer-associated surgical procedure performed as part of routine care to be used for translational research. This can be at first and subsequent relapses following each line of treatment and prior to starting a new line of treatment.
4. Date of disease progression on each subsequent therapy
5. Subsequent treatment data
6. Survival status

Previous interventions:
Interventions: ALL cohorts
IMP: Celecoxib
Form: Capsule
Dose: 200 mg twice daily for 4 weeks then 100 mg twice daily (continuous until disease progression or stopping immune therapy)
Route: Oral

TNBC:
IMP: Atezolizumab
Form: Solution for infusion
Dose: 840 mg on day 1 and day 15 of a 28-day cycle (until disease progression or unacceptable toxicity; patients who are no longer also receiving concurrent Nab-paclitaxel can receive 1680mg d1 of a 28-day cycle)
Route: intravenous (IV)

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(continuous until disease progression)
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IMP: Ipilimumab
Form: Concentrate for solution for infusion
Dose: 1 mg/kg every 21 days for the first four cycles
Route: IV

NSCLC:
IMP: Pembrolizumab
Form: Solution for infusion
Dose: 200 mg every 21 days or 400 mg every 42 days (maximum treatment duration 2 years)
Route: IV

Duration of treatment:
All patients will be treated until progressive disease, unacceptable toxicity, end of trial or withdrawal of patient consent. In the case of pembrolizumab patient must also stop treatment after 2 years of therapy in line with national guidelines.

Duration of follow-up:
For all cohorts a minimum follow-up of 6 months for all patients who do not experience progression prior to 6 months post start of treatment

Overall study duration: 48 months

Screening/baseline activity:
1. Written Informed Consent for the LION trial
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4. Full physical examination
5. Pregnancy test for women of child-bearing potential only. To be performed within 30 days for screening sample and within 72 hours of cycle 1 Day 1 of any trial therapy
6. Vital Signs: pulse, blood pressure, temperature, respiration and O2 saturation
7. Height and Weight
8. ECOG Performance Status
9. Haematological and Clinical Biochemistry. To be performed within 30 days for screening sample and within 72 hours of cycle 1 Day 1 of any trial therapy for baseline sample
10. CT scan reported to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
11. Availability of archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue. Collection of FFPE tumour tissue is mandatory if no archival tissue from previous surgery or biopsy, are available
12. Translational Sample Collection
13. Serum, plasma and PMBC
14. Baseline adverse events
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1. HER2, ER and PR
2. PD-L1 immunohistochemistry (IHC)

The following screening/baseline assessments should be performed on the NSCLC cohort:
1. EGFR, ALK and ROS1 genetic analysis
2. PD-L1 IHC

The following screening/baseline assessments should be performed on the RCC cohort:
1. International mRCC Database Consortium (IMDC) score
2. PD-L1 IHC

Routinely collected information e.g. medical history/vital signs/relevant blood test results etc can be transcribed from the patient's medical notes into the case report form (CRF) once appropriate consent has been obtained. The patient can proceed to registration once all the baseline assessments have been completed.

On treatment activity (until disease relapse):
The following procedures will be performed at the participant visits whilst on study treatment:
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2. ECOG Performance Status
3. Adverse Events/SAE Reporting (see Section 13)
4. Concomitant medication review and check (see Section 9.7)
5. Weight
6. Vital Signs: pulse, blood pressure, temperature, respiration and O2 saturation
7. Pregnancy test for women of child-bearing potential only (see definition in section 10.4). To be performed within 72 hours of cycle 1 Day 1 of any trial therapy
8. Haematological and clinical biochemistry
8.1. Haematology laboratory tests
8.2. Clinical chemistry (serum or plasma) laboratory tests
9. CT scan with RECIST 1.1
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10.3. Blood for cytokine/metabolomics analysis
10.4. Blood for the ctDNA analysis
10.5. Microbiome samples (stool)
10.6. Fresh biopsy of easily accessible lesions (up to a maximum of three cores per procedure), at baseline (within 6 weeks of day-7) prior to immune therapy, at 12 weeks +/- 1 week on therapy and if progression on therapy. Patients may consent to any or all of these biopsies
10.7. If a surgical resection on study occurs for clinical reasons then provided the patient has consented
11. Medical history and demographics
12. Patient Diary Cards
13. Concomitant Medications
14. ECOG
15. Pregnancy test
16. Physical examination, vital signs and clinical disease assessment
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18. Tumour tissue testing:
18.1. EGFR and ALK mutational analysis (lung cohort only)
18.2. PD-L1 testing
18.3. PD-L1 testing should be performed according to the standard of care guidelines for each tumour type.
18.4. HER2, PR and ER testing (breast cohort only)

Disease relapse activity:
1. Haematology and biochemistry
2. Research blood
3. Stool sample
4. Urine sample
5. Tissue collection from surgical resection (only if clinically indicated)

Follow-up activity; follow-up after relapse every 3 months (+/- 1 week):
1. AE and toxicity assessment - Final safety check to be completed at the first follow-up visit after relapse i.e. 90 days
2. Haematology and biochemistry
3. Tissue collection from surgical resection (only if clinically indicated) - tissue (FFPE and if possible a piece snap frozen) from any cancer-associated surgical procedure performed as part of routine care to be used for translational research. This can be at first and subsequent relapses following each line of treatment and prior to starting a new line of treatment.
4. Date of disease progression on each subsequent therapy
5. Subsequent treatment data
6. Survival status

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Celecoxib, atezolizumab, nab-paclitaxel, pembrolizumab, nivolumab, ipilimumab

Primary outcome(s)
Best overall response rate (complete response plus partial response) using RECIST criteria and CT scan
during the course of follow-up. For all cohorts a minimum follow-up of 6 months for all patients who do not experience progression prior to 6 months post start of treatment

Key secondary outcome(s))
1. Overall survival measured as the time from recruitment to death by any cause using medical records during the course of follow-up
2. Progression-free survival (PFS) measured as the time from recruitment to disease progression (RECIST 1.1) or death by any cause using CT scan, medical records during the course of follow-up
3. Best overall response rate over 6 months measured by RECIST 1.1 criteria and CT scan at the 6-month follow-up visit
4. Time from initial progression defined by RECIST 1.1 to secondary progression measured using CT scan during the course of follow-up
5. Quantity and grade of toxicity observed when adding celecoxib to standard of care, assessed using all adverse events/serious adverse events Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 by clinical assessment during the course of follow-up
6. Response rate at PD-L1 expression of ≥1%, ≥5% and ≥50% measured using immunohistochemistry, CT scans during the course of follow-up
7. PFS at PD-L1 expression of ≥1%, ≥5% and ≥50% measured using immunohistochemistry, CT scans during the course of follow-up

For all cohorts a minimum follow-up of 6 months for all patients who do not experience progression prior to 6 months post start of treatment

Completion date
07/05/2027

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 14/05/2024:
All cohorts:
1. Written informed consent obtained
2. Age ≥ 18 years at the time of screening.
3. No prior treatment for metastatic or locally advanced, incurable disease.
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrolment.
5. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion at baseline.
6. Adequate organ and bone marrow function as defined below
6.1. Haemoglobin ≥ 9.0 g/dL
6.2. Absolute neutrophil count ≥ 1.5 x 109/l
6.3. Platelet count ≥ 100 x 109/l
6.4. Serum bilirubin ≤ 1.5 x ULN. In patients with a confirmed diagnosis of Gilbert's syndrome then an isolated bilirubin of ≤ 3 x ULN is permitted.
6.5. ALT and AST ≤ 2.5 x ULN
6.6. Creatinine clearance ≥ 40mL/min calculated by Cockcroft-Gault (using actual body weight) OR by measured 24-hour urine collection.
7. Provision of an FFPE tumour sample taken within 3 months of trial registration.
8. Eligible for immune-checkpoint blockade therapy according to the relevant Blueteq/NHSE eligibility criteria with approval requested and confirmed.
9. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of the study drug (see definition in section 10.4).
10. WOCBP must agree to follow instructions in Section 8.3.2 for method(s) of contraception for the duration of treatment with study drugs plus 5 months after the completion of trial therapy.
11. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 5 months after completion of treatment.
12. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, participating WOCBP must still undergo pregnancy testing.

Tumour-specific inclusion criteria:
Triple Negative Breast cohort
1. Locally confirmed TNBC determined from the most recent tumour sample taken for diagnostic purposes defined:
1.1 Negative for ER with <1% tumour cells positive for ER on IHC or IHC score (Allred) of ≤ 2
1.2. Negative for PR with <1% tumour cells positive for PR on IHC or IHC score (Allred) of ≤ 2 or PR unknown and
1.3. Negative for HER2 with 0 /1+ or 2+ and no evidence of amplification on in situ hybridisation
2. PD-L1 tumour expression of ≥1% by an approved and validated test.

3. No prior treatment for metastatic or locally advanced, inoperable TNBC. Prior treatment with curative intent for stage I-III TNBC is acceptable if chemotherapy treatment was completed ≥ 12 months before study entry.

Non-Small Cell Lung Cancer cohort
Histologically or cytologically confirmed diagnosis of stage IIIB or IV non-squamous non-small cell lung cancer.
2. Negative for EGFR mutation, ALK and ROS1 rearrangements.
3. PD-L1 testing with an approved and validated test to determine those tumours express PD-L1 (with at least a 50% tumour proportion score) has been requested and the result documented.
4. If there is a prior systemic treatment for localised disease, the last chemotherapy dose must have been >6 months from the final cycle to the diagnosis of recurrence.

Renal Cell Carcinoma Cancer cohort
1. Locally advanced or metastatic renal cell adenocarcinoma that either has a clear cell component or is a papillary RCC.
2. Intermediate or poor-risk advanced renal cell carcinoma as assessed by the International Metastatic RCC Database Consortium (IMDC) system by having at least one of the following factors:
• < 1 year from initial diagnosis of RCC
• ECOG PS < 1
• Haemoglobin ≤LLN
• Corrected Ca > 2.5 mmol/L
• Platelet count >ULN
• Absolute neutrophil count > ULN

Previous participant inclusion criteria:
All cohorts:
1. Capable of giving written informed consent and willing and able to comply with all study procedures for the duration of the study protocol
2. Age ≥18 years at the time of screening
3. No prior treatment for metastatic or locally advanced, incurable disease
4. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrollment
5. At least one lesion, nor previously irradiated, that qualifies as a RECIST 1.1 target lesion at baseline
6. Adequate organ and bone marrow function as defined below:
6.1. Haemoglobin ≥9.0 g/dl
6.2. Absolute neutrophil count ≥ 1.5 x 10e9/l
6.3. Platelet count ≥100 x 10e9/l
6.4. Serum bilirubin ≤1.5 x ULN. In patients with a confirmed diagnosis of Gilbert's syndrome then an isolated bilirubin of ≤3 x ULN is permitted.
6.5. ALT and AST ≤2.5 x ULN
6.6. Creatinine clearance ≥40 ml/min calculated by Cockcroft-Gault (using actual body weight)
7. Provision of a FFPE tumour sample taken within 3 months of trial registration
8. Eligible for immune-checkpoint blockade therapy within the according to the relevant Blueteq /NHSE eligibility criteria with approval requested and confirmed
9. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of the study drug
10. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 5 months after the completion of therapy
11. Males who are sexually active with WOCBP must agree to follow instructions for method(s)

of contraception for the duration of treatment plus 5 half-lives of the study drug as above plus 90 days (duration of sperm turnover).
12. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, participating WOCBP must still undergo pregnancy testing (see Section 10.4)

Tumour-specific inclusion criteria:
Triple-negative breast cancer cohort:
1. Locally confirmed TNBC determined from the most recent tumour sample taken for diagnostic purposes defined:
1.1. Negative for ER with <1% tumour cells positive for ER on IHC or IHC score (Allred) of ≤2
1.2. Negative for PR with <1% tumour cells positive for ER on IHC or IHC score (Allred) of ≤2 or PR unknown and
1.3. Negative for HER2 with 0 /1+ or 2+ and no evidence of amplification on in situ hybridisation
2. PD-L1 tumour expression of ≥1% by an approved and validated test
3. No prior treatment for metastatic or locally advanced, inoperable TNBC. Prior treatment with curative intent for stage I-III TNBC is acceptable if chemotherapy treatment was completed ≥12 months prior to study entry.

Non-small cell lung cancer cohort:
1. Histologically or cytologically confirmed diagnosis of stage IIIB or IV non-squamous non-small cell lung cancer
2. Negative for EGFR and ALK mutations
3. PD-L1 testing with an approved and validated test to determine the Tumour Proportion Score (tumour cell content ≥50%) has been requested and results documented

Renal cell carcinoma cohort:
1. Locally advanced or metastatic renal cell adenocarcinoma that either has a clear cell component or is a papillary RCC
2. Intermediate or poor-risk advanced renal cell carcinoma as assessed by the International Metastatic RCC Database Consortium (IMDC) system by having at least one of the following factors:
2.1. <1 year from initial diagnosis of RCC
2.2. ECOG PS <1
2.3. Haemoglobin ≤LLN
2.4. Corrected Ca >2.5 mmol/l
2.5. Platelet count >ULN
2.6. Absolute neutrophil count >ULN

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current participant exclusion criteria as of 14/05/2024:
All cohorts:
1. History of another malignancy within the last 5 years except adequately treated non-melanoma skin cancer; curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma.
2. History of leptomeningeal metastases
3. Known symptomatic CNS metastases or symptoms suspicious of CNS metastases are excluded unless:
3.1. Symptomatic lesions have been definitively treated with surgery or stereotactic surgery (whole-brain radiation may be given as adjuvant treatment), and do not require steroids for control of symptoms
3.2. Are asymptomatic without the use of steroids.
4. Current use of a prohibited medication as described in section 9.7.2.
5. Patients known to be CYP2C9-poor metabolisers.
6. Has received a live vaccine within 30 days of the first dose of study treatment.
7. Contraindications to COX-inhibitor dosing including hypersensitivity.
8. Hypersensitivity to sulphonamides.
9. Significant cardiovascular disease including a history of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months or clinically significant congestive heart failure.
10. Any other serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that in the opinion of the investigator could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures.
Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection.
12. Patients with active, known or suspected autoimmune disease. The following are exceptions to this criterion:
12.1. Patients with vitiligo or alopecia
12.2. Patients with hypothyroidism stable on hormone replacement
12.3. Patients with any chronic skin condition that does not require systemic therapy
13. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily Prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration.
14. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
15. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely in to interfere with absorption of the trial medication.
16. Females who are pregnant or breast-feeding.
17. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anti-cancer therapy with the exception of alopecia and vitiligo.
18. Active infection requiring systemic treatment.
19. Any concomitant chemotherapy, IP or biologic for cancer treatment. Bisphosphonates or Denosumab are acceptable for patients with bone metastases
20. Current or previous regular use of Aspirin (at any dose) or current use of another NSAID for any indication
21. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically

related to the study treatments.
22. Prisoners or patients who are involuntarily incarcerated.
23. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

Previous participant exclusion criteria:
All cohorts:
1. History of another malignancy within the last 5 years except adequately treated non-melanoma skin cancer; curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma.
2. History of leptomeningeal metastases
3. Known symptomatic central nervous system (CNS) metastases or symptoms suspicious of CNS metastases are excluded unless:
3.1. Symptomatic lesions have been definitively treated with surgery or stereotactic surgery (whole-brain radiation may be given as adjuvant treatment), and do not require steroids for control of symptoms
3.2. Are asymptomatic without the use of steroids
4. Current use of a prohibited medication
5. Has received a live vaccine within 30 days of the first dose of study treatment
6. Contraindications to Cox-inhibitor dosing including hypersensitivity
7. Significant cardiovascular disease including a history of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months or clinically significant congestive heart failure
8. Any other serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that in the opinion of the investigator could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures
9. Known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
10. Patients with active, known or suspected autoimmune disease. The following are exceptions to this criterion:
10.1. Patients with vitiligo or alopecia
10.2. Patients with hypothyroidism stable on hormone replacement
10.3. Patients with any chronic skin condition that does not require systemic therapy
11. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration
12. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
13. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the trial medication
14. Females who are pregnant or breastfeeding
15. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia and vitiligo
16. Active infection requiring systemic treatment
17. Any concomitant chemotherapy, IP or biologic for cancer treatment. Bisphosphonates or denosumab are acceptable for patients with bone metastases
18. Current regular use of aspirin (at any dose) or current use of another NSAID for any indication
19. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments

Date of first enrolment
08/05/2024

Date of final enrolment
10/04/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Christie
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

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

Study participating centre
Royal United Hospitals Bath
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast
United Kingdom
BT9 7AB

Study participating centre
Glan Clwd Hospital
Ysbyty Glan Clwydd
Bodelwyddan
Rhyl
United Kingdom
LL18 5UJ

Study participating centre
Colchester - the Lakes
Colchester District General Hospita
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Weston Park Hospital
Whitham Road
Sheffield
United Kingdom
S10 2SJ

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

Study participating centre
Wrexham Maelor Hospital
Croesnewydd Road
Wrexham Technology Park
Wrexham
United Kingdom
LL13 7TD

Sponsor information

Organisation
Christie Hospital NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Charity

Funder Name
Jon Moulton Charity Trust

Funder Name
Christie Charity

Alternative Name(s)
Christie Charitable Fund

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
In instances where study data is shared with other researchers for quality assurance or the design or conduct of further research, data will be provided in a pseudo-anonymised format. Potential participants will be informed of this possibility and will have the option to reject this aspect of the study and not allow their study data to be provided for this purpose.

Data will be made available following article publication. All requests for data should be addressed to the trial sponsor, The Christie (the-christie.sponsoredresearch@nhs.net). The

sponsor will process the requests by involving all applicable parties in their decision-making outcome. Data will be made available subject to independent ethical review, and resources to process the data and perform identification. Only deidentified participant data will be shared with collaborators. The Sponsor will process each data sharing request and access the needs of the researcher and resources available to prepare and transfer the datasets. The data dictionary will be publicly available on the trial website for collaborators to access. The LION protocol, case report forms, patient information sheets/consent forms and data dictionary will be available for download at https://lctc.org.uk. Additional documents can be made available on request to the sponsor. Data requests will be considered after the primary publication estimated end of 2025 with no specific end date. Applications will be reviewed by the sponsor involving all applicable parties in their decision-making outcome. New projects that result in data sharing should meet the high standards (quality, ethical and financial) maintained by the Sponsor. All data sharing will require a review of consent parameters and a data access agreement prior to sending data.

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