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REFINE - a randomised control trial testing reduced intensity immunotherapy across different cancers

Submission date 06/06/2022	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 27/07/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 04/07/2023	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
REFINE (Reduced Frequency ImmuNE checkpoint inhibition in cancers) is a clinical trial for patients who are receiving immune checkpoint inhibitors for the treatment of advanced cancers. These drugs work by stimulating the body's own immune system to fight against cancer cells. Immune checkpoint inhibitors can stop cancers growing for many months or years.

Immune checkpoint inhibitors are given to patients through an injection into a vein every 2-6 weeks in a hospital or clinic. Blood tests are needed before each injection. This means that patients spend a lot of time (and money) on hospital visits.

Clinical trials have proven the effectiveness of immune checkpoint inhibitors in the treatment of different cancers. However, the best way to give these drugs is not known. It is likely that immune checkpoint inhibitors work for a longer period of time than originally thought. This means it may be possible to give the drugs less often and still have the same effect on the cancer. The REFINE trial tests whether giving an immunotherapy drug less-often to patients with advanced cancer results in fewer side effects and improved quality of life, whilst continuing to be an effective treatment. Giving these drugs less often may also allow the NHS to deliver equally effective treatment at a lower cost.

Who can participate?
Patients aged 18 years and over with locally advanced or metastatic cancers

What does the study involve?
As part of standard of care patients can receive infusions of immune checkpoint inhibitors once every 4 weeks. Patients with kidney cancer receive ipilimumab and nivolumab (once every 4 weeks), and patients with melanoma receive ipilimumab + nivolumab (once every 4 weeks) or pembrolizumab (once every 6 weeks). The final administration of ipilimumab is at 12 weeks. Patients responding to treatment after 12 weeks will continue with treatment but are randomly allocated to receive this either at the same frequency or at a reduced frequency as the standard of care. Patients with kidney cancer randomly allocated to the reduced treatment frequency

group will receive nivolumab treatment once every 8 weeks. Patients with melanoma receive either nivolumab once every 8 weeks or pembrolizumab once every 12 weeks. Treatment will continue to week 92. Patients will be followed up for 1 year and 9 months.

What are the possible benefits and risks of participating?
Although it is hoped that the less-often schedule of immunotherapy drug used in this study will make treatment easier (i.e. less severe side effects), the researchers do not know this for certain. It is possible that the less often schedule might be less good at controlling the cancer. If this happens participants will have the chance to have their treatment increased back to the normal 'more-often' schedule. Participants will also undergo routine assessments which are typical for cancer patients and will require scans and sample collection. The researchers will take a small amount of the participants' blood before each treatment for the first 9 months of the study.

Where is the study run from?
MRC Clinical Trials Unit at UCL (UK)

When is the study starting and how long is it expected to run for?
October 2021 to May 2026

Who is funding the study?
JP Moulton Charity Trust (UK)
Medical Research Council (UK)

Who is the main contact?
Dr Duncan Gilbert
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https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-how-often-to-give-immunotherapy-for-cancer-that-has-spread-refine

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-002060-47

Integrated Research Application System (IRAS)
298208

ClinicalTrials.gov (NCT)
NCT04913025

Protocol serial number
RF01, IRAS 298208, CPMS 50169

Study information

Scientific Title
REduced Frequency ImmuNE checkpoint inhibition in cancers: A multi-arm phase II basket protocol testing reduced intensity immunotherapy across different cancers

Acronym
REFINE

Study objectives
Extending the interval between doses of ICI in patients with advanced cancers maintains efficacy and disease control compared to standard intensity treatment, with patient and economic benefits

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/10/2021, London - Westminster Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 207 1048236; westminster.rec@hra.nhs.uk), ref: 21/LO/0593

Study design
Randomized phase II multi-stage multi-arm basket trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treatment of multiple cancer types which are local advanced or metastatic using immune checkpoint inhibition therapies in adult patients already receiving immune checkpoint inhibitors

Interventions
As part of standard of care patients can receive infusions of immune checkpoint inhibitors once every 4 weeks. Patients with renal cancer receive ipilimumab + nivolumab (once every 4 weeks), and patients with melanoma receive ipilimumab + nivolumab (once every 4 weeks) or pembrolizumab (once every 6 weeks). The final administration of ipilimumab is at 12 weeks.

Patients responding to treatment after 12 weeks will continue with treatment but be randomised to receive this either at the same frequency or at reduced frequency as the standard of care. Patients with renal cancer randomised to the reduced treatment frequency group will receive 480 mg nivolumab treatment once every 8 weeks. Patients with melanoma receive either 480 mg nivolumab once every 8 weeks or 400 mg pembrolizumab once every 12 weeks. Treatment will continue to week 92 from the date of randomisation. Patients will be followed up for 1 year and 9 months from randomisation.

Patients are randomised using the online trial database. There is no placebo group in this trial.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Ipilimumab, nivolumab, pembrolizumab

Primary outcome(s)
Progression-free survival (time to event) from randomisation to first evidence of local recurrence, new renal primary cancer, distant metastases (new or progression of existing metastases), or death from any cause, whichever occurs first. A CT scan with contrast of the chest, abdomen and pelvis will be conducted within 42 days prior to randomisation and then every 12 weeks from the first treatment administered to assess for progression and new metastases until disease progression or treatment discontinuation, whichever occurs later.

Key secondary outcome(s))
1. Overall survival measured using mortality and follow-up data collected from sites. Survival is measured from randomisation until date of death or last follow-up.
2. Quality of Life measured using EQ-5D-5L and QLQ-C30 questionnaires every 12 weeks starting at baseline; also applying the relevant tariff to EQ-5D-5L questionnaire responses to calculate utility scores.
3. Treatment related toxicity measured using severity of all AEs and/or ARs (serious and non-serious) with the toxicity scales in NCI CTCAE v5.0 reviewed at the end of each stage and reported until trial closure.
4. Mean incremental cost per patient measured using unit costs from NHS Reference Costs, Personal Social Services Research Unit (PSSRU) and British National Formulary (BNF) prices, and applying them to health and social care resource use collected via the Client Service Receipt Inventory (CSRI), intervention medication CRF, additional treatment logs, and concomitant medication CRF, every 12 weeks starting at baseline, calculating the cost and taking the difference between arms to calculate mean incremental cost per patient (bootstrapped regression, adjusting for baseline values, jointly with QALYs).
5. Mean incremental QALYs per patient measured using utility scores calculated from EQ-5D-5L questionnaire responses collected every 12 weeks starting at baseline, and applying them to the

relevant period of follow-up to calculate quality-adjusted life-years (QALYs), and taking the difference between arms to calculate mean incremental QALYs per patient (bootstrapped regression, adjusting for baseline values, jointly with costs).
6. Cost-utility analysis assessing cost-effectiveness of reduced vs. standard frequency administration with summary result expressed as the incremental cost-effectiveness ratio (ICER), i.e. incremental cost per QALY gained, calculated by dividing incremental costs by incremental QALYs; with sensitivity analysis expressed via cost-effectiveness planes and cost-effectiveness acceptability curves to indicate probability that the intervention is cost-effective compared to the standard of care for a range of values of the cost-effectiveness threshold.
7. Feasibility of recruitment to each cohort measured using screening logs collected by site staff.

Completion date
25/05/2026

Eligibility

Key inclusion criteria
1. Patients with locally advanced or metastatic cancers for which immune checkpoint inhibitors are standards-of-care and whose clinician has determined they are candidates for treatment with this approach (see also Cohort Specific Inclusion Criteria, below).
2. WHO Performance Status 0 or 1.
3. Patients aged ≥18 years.
4. Adequate normal organ and marrow function:
4.1. Haemoglobin ≥90g/L (transfusions will be allowed within 2 weeks prior to randomisation in order to achieve the entry criteria).
4.2. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1500 per mm³).
4.3. Platelet count ≥100 x 10^9/L (≥100,000 per mm³).
4.4. Bilirubin ≤1.5 x ULN or patients with confirmed Gilbert's syndrome (i.e. persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology).
4.5. AST/ALT ≤3 x ULN.
4.6. eGFR >40mL/min by CKD-EPI formula .
5. Resting 12-lead ECG on which QTcF must be <450 ms. This will usually have been performed prior to commencement of the initial 12 weeks ICI.
6. Both men and women enrolled in this trial must be in agreement with trial policy on contraception during the treatment phase of the study. Egg donation, sperm donation and breastfeeding must be avoided.
7. Evidence of post-menopausal status or negative serum HCG pregnancy test for female pre /peri-menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
a. Women <50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy).
b. Women ≥50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Renal cohort specific inclusion criteria:
1. Patients with unresectable locally advanced or metastatic renal cell carcinoma (including clear cell and papillary histologies).
2. Intermediate or poor risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria (prior to the initial 12 weeks treatment with ICI combination).
3. Patients have received induction ipilumumab (all four doses) and nivolumab as first-line treatment as planned.
4. No evidence of progression on ipilimumab and nivolumab induction therapy and due to commence maintenance nivolumab (i.e. response or stable disease on cross sectional imaging on completion of initial 12 weeks treatment with ICI combination).

Melanoma cohort specific inclusion criteria:
1. Patients with locally advanced or metastatic melanoma.
2. No evidence of progression on ipilimumab and nivolumab induction therapy and due to commence maintenance nivolumab (i.e. response or stable disease on cross sectional imaging on completion of initial 12 weeks treatment with ICI combination).
or
Patients have received single agent pembrolizumab first line for 12 weeks, with no evidence of progression (i.e. response or stable disease) on cross sectional imaging 12 weeks after initiation of ICI, and due to commence maintenance pembrolizumab every 6 weeks.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Patients who have received ICI in a prior line of treatment.
2. Patients who have undergone any prior systemic anti-cancer treatment (previous participation in adjuvant studies allowed, providing the patient was on the observation/ placebo arm – this may require un-blinding of the patient).
3. Patients where treatment is the combination of anti-PD-1 and tyrosine kinase inhibitor (e.g. pembrolizumab+axitinib) or the combination of traditional cytotoxic chemotherapy and anti-PD-1.
4. History of another previous malignancy, except for:
4.1. Malignancy treated with curative intent and with no known active disease ≥5 years prior to the first dose of ICI.
4.2. Adequately treated non-melanoma skin cancer without evidence of current, active disease.
4.3. Adequately treated carcinoma in situ without evidence of current, active disease.
4.4. Non-muscle invasive bladder cancer.
5. Concurrent enrolment in another interventional clinical study, unless in the follow-up period,

except where approved by the CTU (see co-enrolment section for further details).
6. Current or prior use of immunosuppressive medication within 14 days of starting trial treatment, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10mg/day of prednisone, or an equivalent corticosteroid.
7. Active infection including:
7.1. Tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice).
7.2. Hepatitis B (known positive HBV surface antigen (HBsAg) result). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.
7.3. Hepatitis C. Note: Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
7.4. Human immunodeficiency virus (positive HIV 1/2 antibodies).
8. Receipt of a live attenuated vaccine within 30 days prior to the start of treatment.
Note: Patients, if enrolled, should not receive a live vaccine while receiving immune checkpoint inhibitor and up to 30 days after the last dose of immune checkpoint inhibitor.
9. Known allergy or hypersensitivity to immune checkpoint inhibitor.
10. Pregnant or breastfeeding patients.
11. Uncontrolled adrenal insufficiency.
12. Any serious or uncontrolled medical or psychiatric disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, interfere with participation and/or compliance in the trial, or interfere with the interpretation of study results.
13. Untreated brain metastases or brain metastases treated only with whole brain radiotherapy. (Patients are eligible if previous brain metastases treated with complete surgical resection, Stereotactic Brain Radiation Therapy (SBRT), or gamma knife with no subsequent evidence of progression and asymptomatic).

Date of first enrolment
25/05/2022

Date of final enrolment
25/05/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
East Yorkshire Hospitals NHS Trust (head Office)
Castle Hill Hospital

Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
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M20 4BX

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
JP Moulton Charity Trust

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
mrcctu.refine@ucl.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		26/11/2022	16/12/2022	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 5.0	03/01/2023	04/07/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes