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DETECTION Trial: Using blood tests to guide early treatment of relapse in early stage melanoma

Submission date 09/07/2021	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 17/08/2021	**Overall study status** Stopped	
Last Edited 06/03/2023	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-a-blood-test-to-monitor-for-early-signs-of-melanoma-coming-back-detection (added 26/01/2022)

Background and study aims
We are looking for new and better ways to treat melanoma. We have developed a blood test that tells us whether cancer cells are still present or cancer is becoming active, even if a scan looks normal. The test looks for pieces of DNA that are known to have come from the cancer, which we call 'circulating tumour DNA', or ctDNA. If we do not find ctDNA patients will stay on the study having blood tests either until the study ends (and we have not found ctDNA in their blood) or until we find ctDNA in the blood. If we find ctDNA, patients will be allocated to either receive the standard of care, which is ongoing follow up or nivolumab, an immune-boosting drug which we know is effective at treating melanoma. A doctor will inform patients of the possible benefits and risks when taking nivolumab. We do not know whether treating early with nivolumab, on the evidence of ctDNA alone, is of benefit to patients, and this is what we need to find out.

Who can participate?
Patients who have been diagnosed with early-stage melanoma which has been removed by surgery.

What does the study involve?
The study will begin with screening to check that it is safe for participants to be involved in the trial.
Then the primary tumour (tissue removed from your recent melanoma surgery) will be tested for the presence of faulty genes. If faulty genes are present then participants will undergo regular blood tests for the presence of ctDNA every 3 months. If ctDNA is detected participants will be allocated into 1 of 2 groups (Arm A or Arm B) Participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin).

For the first 3 years participants in Arm A will receive medical assessment (physical examination, vital signs, weight) and blood tests for ctDNA every 3 months; scans and questionnaires every 6 months; and an ECG and urine test yearly. In years 4 and 5 of the study participants in Arm A will receive medical assessment, ctDNA blood test, scans, and questionnaires every 6 months, and the ECG and urine test yearly. At the last visit there will be final a medical assessment, ctDNA blood test, ECG and urine test.

Over 2 years, participants in Arm B will receive medical assessments, administration of nivolumab (over a period of 1 h), ctDNA blood test every 4 weeks, scans and questionnaire every 6 months and ECG and urine test yearly. After the 2 year period of receiving nivolumab participants will receive medical assessments, ctDNA test, urine test, ECG, then scan and questionnaires every 6 months and ECG and urine test yearly.. At the last visit there will be final a medical assessment, ctDNA blood test, ECG and urine test.

What are the possible benefits and risks of participating?
We hope the treatments (nivolumab) will help you. The information from the study may help improve future treatments of patients with early-stage melanoma.

There is a small possibility that ctDNA could be detected with no disease and therefore nivolumab could be administered unnecessarily. There are side effects associated with treatment with nivolumab, exposure to radiation during CT scanning, MRI scans, and having blood tests taken.

Where is the study run from?
The Christie NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
From November 2019 to April 2029

Who is funding the study?
Cancer Research UK

Who is the main contact?
Professor Paul Lorigan
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Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT4901988

Clinical Trials Information System (CTIS)
2020-000234-17

Integrated Research Application System (IRAS)
270318

Central Portfolio Management System (CPMS)
48994

Protocol serial number
Grant codes C26937/A28891

Study information

Scientific Title
Circulating tumour DNA guidEd Therapy for stage IIB/C mElanoma after surgiCal resecTION (DETECTION)

Acronym
DETECTION

Study objectives
1. Null Hypothesis: Treating with immune therapy at the point of ctDNA detection has no impact on overall survival
2. Alternative Hypothesis: Treating with immune therapy at the point of ctDNA detection improves overall survival with a hazard ratio of 0.7

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/07/2021, London Harrow Research Ethics Committee (**Currently being held remotely via Teleconference/ZOOM** Education Centre, Northwick Park Hospital, HA1 3UJ; +44 (0)207 104 8098, +44 (0)207 104 8306, +44 (0)207 104 8356; harrow.rec@hra.nhs.uk), ref: 21/LO/0318

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Skin Cancer

Interventions
DETECTION will regularly test patients who have had their cancer removed by surgery (every three months for three years and then every six months for a further two years) using blood tests to check for ctDNA. If we do not find ctDNA, the patient will stay on the study having blood tests either until the study ends (and we have not found ctDNA in their blood) or until we do find ctDNA. If we find ctDNA, the patient will be randomised into one of two Arms.

Arm A will continue to have blood tests for ctDNA, and also scans and appointments as part of normal care. Patients will only get treatment if their scan shows that the cancer has returned as part of normal patient care. The patient and their doctor will not be told that the test has shown ctDNA in the blood. We need an equal number of patients to those receiving treatment to NOT receive treatment to compare our results against (controls). We do not know whether the presence of ctDNA in the blood means that cancer will return or not. Arm A must be treated in the same way as a patient not on the trial and knowing that ctDNA is present may mean patients act differently, for example requesting extra checkups. We also want to avoid these patients from having additional anxiety.

Arm B will have checks to see if it is safe for them to start receiving treatment and the patient will have a discussion with their doctor to see if they are still happy to take part in the trial. If it is safe to do so, patients will receive a drug called nivolumab 480mg intravenously every 4 weeks for 2 years.

Trial visits:
All Patients will have the following type of visits: screening, baseline, ctDNA monitoring, and Last visit/Withdrawal.

If the ctDNA test comes back negative the patient will continue on the trial having visits and procedures. If they relapse they will be managed with standard of care therapy.

Arm A – Standard Care:
If the patient is randomised into Arm A, neither they nor their doctor will be told that ctDNA has been detected. Patients will continue coming to hospital for visits as per the same schedule to prior to the randomisation. The doctor will only offer further treatment if the melanoma re-appears on scan or is observed to have reappeared on the skin.

Arm B – Early treatment based on the ctDNA result:
If a patient is randomised into Arm B, they will be telephoned by the clinical team to return to the clinic, where they will be told the results of their ctDNA blood test. They will receive early treatment for melanoma with a drug that helps the immune system kill the cancer called nivolumab for 2 years. They will have the drug through the vein, every 4 weeks for 2 years. They will be monitored for side effects from the treatment as well as for any sign of the cancer returning. They will also continue to have blood taken for ctDNA testing to assess the response in hte blood. In addition they will continue to have a CT scan every 6 months on the maintaining the original timings of every 6 months from when they started on the study.

End of Treatment due to side effects or choice (Arm B only):
If the patient has any severe side effects from the drug or if they choose to stop treatment they will no longer receive therapy. They will continue to attend visits (post treatment follow-up) every 3 months for 3 years and then every 6 months for a further 2 years after that until the trial closes. If their melanoma returns they will have standard of care therapy.

Follow-up after return of melanoma for all study patients:
If the patient is on Arm B and the disease re-appears whilst patients are receiving treatment they will stop having nivolumab. They will have further therapy according to the standard of care. If they have already completed nivolumab they will also have treatment according to standard of care.

If the patient is on Arm A and their melanoma re-appears they will be managed as standard of care and will continue to have bloods for ctDNA taken at the start of each treatment cycle until they progress on that first treatment.

For both arms, we will continue to collect data about the health and the treatments received by the patients along with their response to these treatments. We will collect this data through their regular clinic appointment or through telephone conversations with them and clinical note review.

In addition, in order to understand better why the melanoma came back to improve our management we will take further blood tests at the time of relapse and if the patient is planned to have surgery to remove the melanoma we will collect left-over tissue for our research.

Intervention Type
Drug

Phase

Not Applicable

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

Primary outcome(s)
Overall Survival (OS) defined as the time from randomisation until death from any cause measured as the incidence of death at follow up after relapse (every 12 weeks after the date of confirmed relapse)

Key secondary outcome(s)
1. Recurrence free survival (RFS) defined as the time from randomisation to radiological or clinical progression measured using scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
2. Distant metastasis-free survival (DMFS) defined as the time from randomisation to distant metastatic relapse or death measured using scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
3. Progression Free Survival (PFS) for participants on first-line therapy (from relapse for participants in Arm A, from randomisation for participants in Arm B) defined as the time from start of treatment (day of the first dose) until disease progression as clinical or radiological progression or death measured using scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
4. Time from randomisation to disease progression of first-line therapy (from relapse for participants in Arm A, from randomisation for participants in Arm B) measured using scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
5. Radiological response in Arm A (Complete Response, Partial Response, Stable Disease, and Progressive Disease) vs no Progressive Disease in Arm B to first-line systemic therapy measured using scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need
6. Time from registration to ctDNA detection measured using ctDNA test every three months for years 1 to 3, and every 6 months for years 4 to 5
7. Number of participants with undetectable ctDNA but clinical/radiological progression and site of progression measured using ctDNA test every three months for years 1 to 3, and every 6 months for years 4 to 5; and scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
8. RFS of participants with undetectable ctDNA (not randomised) compared to participants with detectable ctDNA in Arm A measured using ctDNA test every three months for years 1 to 3, and every 6 months for years 4 to 5; and scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e.

biopsies) when clinically indicated
9. DMFS of participants with undetectable ctDNA (not randomised) compared to participants with detectable ctDNA in Arm A measured using ctDNA test every three months for years 1 to 3, and every 6 months for years 4 to 5; and scans evaluated using the RECIST v1.1 criteria at screening, every 6 months for years 1 to 5, and at follow up from the date of confirmed relapse as part of standard of care, with up to 3 per year after this based on clinical need; or histological data (i.e. biopsies) when clinically indicated
10. OS defined as time from registration (commenced on study) until death of participants with undetectable ctDNA (not randomised) compared to participants in Arm A measured as the incidence of death at follow up after relapse (every 12 weeks after the date of confirmed relapse)
11. Treatment-free survival as defined as area between Kaplan-Meier curves between time from initiation of first-line therapy until its cessation and time from initiation of first-line therapy and subsequent therapy initiation or death in Arm A compared to Arm B S calculated during statistical analysis at interim and final study analyses
12. Toxicity measured according to Common Terminology Criteria for Adverse Events (CTCAE v5. 0) at pre-randomisation for all participants; at baseline, every 3 months for years 1 to 3, every 6 months for years 4 to 5, within 28 days of confirmed disease relapse and at the end of the study for participants in Arm A; and at the post-randomisation visit, every 4 weeks in years 1 to 2, at the end of treatment, every 6 months during follow up in years 3 to 5, within 28 days of confirmed disease relapse, and at the end of study for participants in Arm B
13. Health economics assessment by the EuroQol 5-dimension 5-level quality of life questionnaire (EQ-5D-5L) and resource use questionnaires at baseline, every 3 months for years 1 to 5, within 28 days of confirmed disease relapse, then every 6 months during follow up, and at the end of the study for participants in Arm A; and at the post-randomisation visit, every 4 weeks in years 1 to 2, every 6 months during follow up in years 3 to 5, and within 28 days of confirmed disease relapse for participants in Arm B

Completion date
30/04/2029

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Signed written informed consent
2. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study
3. Histological confirmation of cutaneous melanoma
4. Age ≥18 years
5. Stage IIB or IIC melanoma (sentinel lymph node (SNLB) staged) according to AJCC version 8 (4)
6. Complete resection (including SNLB) must have been performed within 12 weeks prior to registration
7. Disease-free status documented both clinically and radiologically within 4 weeks prior to registration
8. Mutation confirmed in at least one of the following BRAF (p.V600E/p.V600K/p.V600R) /NRAS (p.Q61R/p.Q61K, p.Q61L/p.G12D), which can be tracked in ctDNA with exact point mutation known
9. ECOG performance status 0/1

10. Adequate organ function and screening laboratory values must meet the following criteria: WBC ≥ 2.0x109/L, Absolute neutrophil count (ANC) ≥1.5x10⁹/l, Platelets ≥100 x10⁹/l, Haemoglobin ≥90 g/l, Creatinine ≤1.5 x ULN or creatinine clearance >30 ml/min using Cockcroft-Gault, AST ≤1.5 x ULN, ALT ≤1.5 x ULN, Bilirubin ≤1.5 x ULN unless the patient has familial hyperbilirubinaemia
11. LDH ≤1.5 x ULN as per local institution parameters
12. Patients who are pregnant or breastfeeding will be eligible to join the trial. However, if they are allocated to Arm B, women of childbearing potential (WOCBP) must agree to have a serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) and must be withdrawn if pregnant or breastfeeding. WOCBP and males who are sexually active with WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment plus 5 months if randomised to Arm B (or while receiving any systemic treatment and to follow local guidance if given on Arm A).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
8

Key exclusion criteria
1. If previously received prior immunotherapy, chemotherapy, cancer directed vaccine therapy or BRAF/MEK targeted therapy for cancer
2. Patients with active, known or suspected autoimmune disease. Patients with type 1 diabetes mellitus, rheumatoid arthritis not requiring disease modifying drugs, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger will be permitted to enrol.
3. Current other malignancy or history of another malignancy within the last 3 years. Patients who have been disease-free for 3 years, (i.e. patients with second malignancies that have been definitively treated at least 3 years ago) or patients with a history of completely resected non-melanoma skin cancer are eligible
4. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures
5. Patients with a condition requiring ongoing/long-term (> 3 months) systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications. Inhaled or topical steroids and adrenal replacement steroid doses ≤10 mg daily prednisolone equivalent are permitted in the absence of active autoimmune disease

6. Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
7. History of allergies or adverse drug reaction to any of the study drug components or to any monoclonal antibody
8. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection
9. Prisoners or patients who are involuntarily incarcerated

Date of first enrolment
20/10/2021

Date of final enrolment
31/08/2026

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

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

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

Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

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

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

Study participating centre
Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
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Study participating centre
East And North Hertfordshire NHS Trust
Lister Hospital
Coreys Mill Lane
Stevenage
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SG1 4AB

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
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LE1 5WW

Study participating centre
Lancashire Teaching Hospitals NHS Foundation Trust
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SE1 7EH

Study participating centre

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J B Russell House
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Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
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LS9 7TF

Study participating centre
Royal Surrey County Hospital NHS Foundation Trust
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GU2 7XX

Study participating centre
Belfast Health & Social Care Trust
Knockbracken Healthcare Park
Saintfield Road
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BT8 8BH

Sponsor information

Organisation
Christie Hospital NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Industry

Funder Name
Bristol-Myers Squibb

Alternative Name(s)
Bristol-Myers Squibb Company, Bristol Myers Squibb, Bristol-Myers Company, BMS

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

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

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from detection@liverpool.ac.uk at the end of the trial after primary results have been published, and after review from an internal committee at LCTC and discussion with the CI. It must also be authorised by the Sponsor.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version 5.0	14/07/2021	17/08/2021	No	Yes