ISRCTN14643179 https://doi.org/10.1186/ISRCTN14643179

Assessing if stopping and starting standard of care medication for later stage melanoma can reduce the body's resistance to the treatment

Submission date 28/05/2022	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 18/08/2023	**Overall study status** Ongoing	
Last Edited 21/10/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Encorafenib and binimetinib given in combination is a standard of care treatment in the UK for late-stage cutaneous melanoma, a skin cancer that starts in the cells that produce skin pigmentation. 'Late stage' means it can't be surgically removed or has spread. The treatment is taken daily. Resistance to the treatment can develop after about 12-15 months. During this period, the treatment will kill the less resistant cells, meaning the tumour has a greater proportion of cells that are resistant to the treatment. This study aims to investigate if the patient having breaks in their treatment allows the less resistant cells to continue to grow, this would result in a tumour with a lower proportion of resistant cells, making the tumour as a whole less resistant to the treatment, and increasing the time it takes for the disease to progress. A blood test that measures the amount of tumour DNA circulating in the patient's blood (known as ctDNA) will be conducted every 2 weeks to check if the cancer cells are still present, and if they are becoming active. The result of this test will allow doctors to monitor the activity of the tumour and judge when to pause and resume treatment. This treatment is called adaptive therapy.

Who can participate?
Patients aged 18 years and over with late-stage cutaneous melanoma

What does the study involve?
Participants are randomly allocated to receive either the standard, daily treatment or adaptive therapy. Patients will receive their allocated treatment until their cancer progresses or there is no longer clinical benefit from taking it, they or their doctor withdraw them from the study, or until the study ends, whichever happens first. As well as the fortnightly visits to the hospital, patients will be required to complete questionnaires to assess their quality of life. These will be completed before their treatment starts, after 4 weeks of treatment, every 12 weeks from when they start treatment and if their cancer progresses or they stop treatment.

What are the possible benefits and risks of participating?
Participants will delay the commencement of their treatment until all screening and baseline

procedures have been completed, which may result in them starting treatment a little later than they would if they were receiving it as routine care. However, if either the patient or treating clinician is of the opinion that this delay would be detrimental to the patient, treatment will commence immediately.
Some CT and/or PET-CT scans may be extra to those given as routine care. CT scans use ionising radiation, which may cause cancer many years or decades after exposure. However, the chances of this occurring in the patients recruited to this study are extremely small. Some CT scans require a contrast dye to be used, which may cause bruising or swelling around the injection site. Rarely do some people have an allergic reaction to the dye. Patients with disease in their limbs will undergo PET-CT scans. Patients may get a small bruise or swelling around the area where they inject the radioactive tracer (dye). There is also a risk that the tracer may leak outside of the vein, which may cause swelling and pain in the limb. Rarely, some patients have an allergic reaction to the tracer. Some patients will need to undergo an MRI scan. Being placed into the scanner can make some people feel claustrophobic.
Participants will be asked to undergo extra biopsies, but can still participate if they choose not to.
The study will be active at hospitals for a period of 3 years. Depending on when a participant commences treatment, they may be involved for between 1 day and 3 years. However, with the exception of the extra visits for blood sampling (explained below), the majority of procedures are as they would receive as part of standard care.
Those participants on adaptive therapy will have one 28-day cycle of treatment before it is then withheld, however, the frequency that blood samples are taken to monitor their health and safety will be increased to every 14 days from the standard 28 days. To allow for accurate comparison of results, this increased frequency will also be implemented for participants on the standard treatment too. Although this increase in blood sampling will require more frequent visits to the hospital, it also allows for a 100% increase in the amount of monitoring the participant will receive compared to normal care. All extra visits to the hospital have been mapped to match those for the standard of care as much as possible.
Women of childbearing potential will be required to undergo extra pregnancy tests as part of the screening procedure and again at the end of their treatment or when the study ends. This test will be done with a urine sample; however, a blood sample may be required if there is a problem with the urine test. Extra monitoring may also be used if their doctor thinks it is necessary.
In addition to those taken as part of routine care, a biopsy (sample) of the tumour will be taken before the patient commences treatment, about 6 weeks later, and again if they relapse.
Participants on adaptive therapy will receive stop/start therapy, which may cause them anxiety. They will be reassured that they will be monitored for signs of progression twice as often as they would be normally and, if their ctDNA levels show signs of increasing beyond a pre-determined threshold, they will be advised to immediately recommence the treatment using the 'reserve pack' of tablets they will have been issued.

Where is the study run from?
University of Liverpool (UK)

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

Who is funding the study?
Jon Moulton Charity Trust (UK)

Who is the main contact?
DyNAMIc Trial Manager, dynamic_study@liverpool.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-using-blood-test-monitor-guide-treatment-melanoma-dynamic

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Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1004759

Central Portfolio Management System (CPMS)
55327

Protocol serial number
CFTSp175

Study information

Scientific Title
Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy

Acronym
DyNAMIc

Study objectives
Current study objectives as of 01/10/2025:
Adaptive therapy relies on the competition between drug-sensitive and drug-resistant subclones to control overall tumour growth. It aims to stabilise tumour burden by allowing a significant population of treatment-sensitive cells to survive, which suppresses the proliferation of the less fit, resistant populations.
1. Patients will have circulating tumour DNA (ctDNA) response upon re-introduction of encorafenib plus binimetinib following the first drug holiday.
2. Encorafenib plus binimetinib therapy using adaptive scheduling based on ctDNA level will improve the time to progression, reduce toxicity and enhance quality of life compared to continuous dosing in patients with stage III unresectable or stage IV melanoma.

Objectives:
To assess whether tumours respond to the re-introduction of encorafenib plus binimetinib following the first period of stopping the drugs. The researchers will do this by measuring the amount of circulating tumour DNA (ctDNA) in the plasma we obtained from the patients' blood samples, which are taken every 2 weeks.

Using data from the main objective, they intend to develop a guideline based on the ctDNA levels, to inform doctors when the adaptive treatment should stop and re-start. The researchers compare the ctDNA results from the two arms to identify the average time it takes for participants to respond to the treatment, how long they may remain stable for, or for the disease to worsen. The time it may take for participants' cancer to worsen (known as progression), will be measured at 6, 12 and 15 months from commencing treatment. Also, the

median time to the death of participants will be compared between the two arms. The researchers will also calculate the number of cycles of adaptive therapy participants on arm B completed, and use this information to establish the average. Measurements of quality of life between the participants on both arms will also be compared, as will any reactions from taking the drugs. Lastly, the researchers will measure the time it takes for the lab to provide the ctDNA result after receiving the blood sample.

Previous study objectives:
Adaptive therapy relies on the competition between drug-sensitive and drug-resistant subclones to control overall tumour growth. It aims to stabilise tumour burden by allowing a significant population of treatment-sensitive cells to survive, which suppresses the proliferation of the less fit, resistant populations.
1. Patients will have circulating tumour DNA (ctDNA) response upon re-introduction of encorafenib plus binimetinib following the first drug holiday.
2. Encorafenib plus binimetinib therapy using adaptive scheduling based on ctDNA level will improve the time to progression, reduce toxicity and enhance quality of life compared to continuous dosing in patients with stage III unresectable or stage IV melanoma.

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To assess whether tumours respond to the re-introduction of encorafenib plus binimetinib following the first period of stopping the drugs. The researchers will do this by measuring the amount of circulating tumour DNA (ctDNA) in the plasma we obtained from the patients' blood samples, which are taken every 2 weeks.

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Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 13/01/2023, London - Chelsea Research Ethics Committee (REC London Centre, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8029, +44 (0)20 7104 8064, +44 (0)207 104 8356; chelsea.rec@hra.nhs.uk), ref: 22/LO/0453

Primary study design
Interventional

Study design
Randomized parallel-arm proof-of-concept study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cutaneous melanoma

Interventions
Current interventions as of 01/10/2025:
Randomisations are processed using an online system. Both arms use encorafenib (450 mg once daily) plus binimetinib (45 mg twice daily) which are both administered orally. Arm A is standard of care (SOC) for the condition and, in line with the licence, both drugs are given continuously until progression occurs or when there is no longer clinical benefit from taking the treatment, or when the treatment ends. Arm B is adaptive treatment. This means the treatment is stopped and re-started as guided by the amount of circulating tumour DNA (ctDNA) in a patient's bloodstream; treatment on this arm will also cease upon progression or when there is no longer clinical benefit from taking the treatment, or when the treatment ends. When 'on-treatment', patients on arm B will receive the SOC dose of both drugs. All participants on arm B will commence with one SOC cycle of both drugs before switching to being 'off-treatment'. The levels of ctDNA is known as the Tumour Activity Burden (TAB). The ctDNA TAB provides guidance on the resistance levels of the tumour. Pre-defined ctDNA TAB threshold levels are used to indicate when treatment should stop/re-start. These levels will be assessed and reviewed during the trial. All participants, regardless of treatment arm, will provide blood samples for ctDNA TAB analysis every 2 weeks up to progression. Once progression occurs, all participants will be followed up every 3 months until the end of the study, withdrawal or death.

Previous interventions:
Randomisations are processed using an online system. Both arms use encorafenib (450 mg once daily) plus binimetinib (45 mg twice daily) which are both administered orally. Arm A is standard of care (SOC) for the condition and, in line with the licence, both drugs are given continuously until relapse occurs. Arm B is adaptive treatment. This means the treatment is stopped and re-started as guided by the amount of circulating tumour DNA (ctDNA) in a patient's bloodstream; treatment on this arm will also cease upon relapse. When 'on-treatment', patients on arm B will receive the SOC dose of both drugs. All participants on arm B will commence with one SOC cycle of both drugs before switching to being 'off-treatment'. The levels of ctDNA is known as the Tumour Activity Burden (TAB). The ctDNA TAB provides guidance on the resistance levels of the tumour. Pre-defined ctDNA TAB threshold levels are used to indicate when treatment should stop/re-start. These levels will be assessed and reviewed during the trial. All participants, regardless of treatment arm, will provide blood samples for ctDNA TAB analysis every 2 weeks up to progression. Once relapse occurs, all participants will be followed up every 3 months until the end of the study, withdrawal or death.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Encorafenib, binimetinib

Primary outcome(s)

Maximal reduction in percentage mutant copies/ml (ctDNA mutant BRAF copies/ml of plasma) from baseline 2 TAB level upon restart of drugs following first drug off period. Measured longitudinally throughout the study.

Key secondary outcome(s)

Current key secondary outcome(s) as of 09/06/2026:

1. ctDNA mutant BRAF copies/ml of plasma. Measured longitudinally throughout the study.
2. Maximal response (complete response (CR)/partial response (PR)/stable disease (SD) /progressive disease (PD)) using RECIST v1.1 criteria. Measured from Baseline 1 until RECIST progression/clinical deterioration.
3. Percentage of participants who have experienced disease progression or death. Progression Free Survival, defined as time from randomisation to progression (RECIST v1.1 and in Arm B defined as progression whilst on targeted therapy unless stopped due to toxicity/choice). Measured continuously throughout the study.
4. Time to clinical deterioration. Defined as either the point of progression (defined as per RECIST v1.1) or in participants treated beyond progression, at the time of clinically determined deterioration, defined at the discretion of the treating clinician, specifically due to progression of the underlying cancer. Measured continuously throughout the study.
5. Overall survival, defined as time from randomisation until death from any cause. Measured continuously throughout the study.
6. Overall survival, defined as time from randomisation until death from melanoma. Measured continuously throughout the study.
7. Number of adaptive therapy cycles completed. Measured longitudinally throughout the study.
8. Median duration of adaptive therapy cycles. Measured longitudinally throughout the study.
9. Percentage of ctDNA results reported within 5 days from sample receipt into the laboratory. Measured longitudinally throughout the study.
10. EORTC QLQ-C30 and PRO-CTCAE. Measured longitudinally throughout the study.
11. Adverse Events and Serious Adverse Events defined by CTCAE version 5. Measured continuously throughout the study.
12. Number and location of sites of progression. At disease progression on imaging

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Previous secondary outcome measures as of 01/10/2025:

1. ctDNA mutant BRAF copies/ml of plasma. Measured longitudinally throughout the study.
2. Maximal radiological response (complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)) using RECIST v1.1 criteria. Measured from Baseline 1 until RECIST progression/clinical deterioration.
3. Percentage of participants who have experienced disease progression or death. Progression Free Survival, defined as time from randomisation to progression (RECIST v1.1 and in Arm B defined as progression whilst on targeted therapy unless stopped due to toxicity/choice). Measured continuously throughout the study.
4. Time to clinical deterioration. Defined as either the point of progression (defined as per RECIST v1.1) or in participants treated beyond progression, at the time of clinically determined deterioration, defined at the discretion of the treating clinician, specifically due to progression of the underlying cancer. Measured continuously throughout the study.
5. Overall survival, defined as time from randomisation until death from any cause. Measured continuously throughout the study.
6. Overall survival, defined as time from randomisation until death from melanoma. Measured continuously throughout the study.

7. Number of adaptive therapy cycles completed. Measured longitudinally throughout the study.
8. Median duration of adaptive therapy cycles. Measured longitudinally throughout the study.
9. Percentage of ctDNA results reported within 5 days from sample receipt into the laboratory. Measured longitudinally throughout the study.
10. EORTC QLQ-C30 and PRO-CTCAE. Measured longitudinally throughout the study.
11. Adverse Events and Serious Adverse Events defined by CTCAE version 5. Measured continuously throughout the study.
12. Number and location of sites of progression on imaging. At disease progression on imaging

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Previous secondary outcome measures:

1. Optimised thresholds of percentage reduction in ctDNA mutant BRAF copies/ml as a measure of response to stop drugs and the percentage and/or minimum increase in BRAF mutant copies /ml as a decision to restart drugs, measured longitudinally throughout the study
2. Maximal radiological response (complete response [CR]/partial response [PR]/stable disease [SD]/progressive disease [PD]) to therapy in Arm A vs Arm B measured using RECIST (v1.1) criteria
3. Progression-free survival (PFS) defined as the time from randomisation to radiological progression (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity/choice) on Arm A vs Arm B
4. PFS defined as time from randomisation to radiological progression (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity /choice) at 6, 12 and 15 months on Arm A vs Arm B
5. Overall survival (OS) defined as the time from randomisation until death in Arm A vs Arm B
6. Number of adaptive therapy cycles completed, recorded longitudinally throughout the study
7. Median duration of adaptive therapy cycles, measured using completed adaptive therapy date longitudinally throughout the study
8. Number and location of sites of disease progression, recorded continuously throughout the study
9. Percentage of ctDNA results provided within 5 working days from sample receipt into CBC, recorded longitudinally throughout the study
10. Maximal reduction in ctDNA mutant BRAF copies/ml for each adaptive cycle, recorded longitudinally throughout the study
11. Rise in ctDNA mutant BRAF copies/ml during drug off period for each patient, recorded longitudinally throughout the study
12. Incidence of CTCAE all grade adverse events in Arm A vs Arm B defined by CTCAE version 5 continuously throughout the study
13. Quality of life measured using EORTC QLQ-C30 and PRO-CTCAE longitudinally throughout the study

The study is expected to last for 3 years, analyses of the secondary endpoints will commence once the trial ends.

Completion date
30/09/2027

Eligibility

Key inclusion criteria

Current key inclusion criteria as of 09/06/2026:

At screening:
1. Written and informed consent obtained from the participant and agreement of the participant to comply with the requirements of the study
2. Histological confirmation of cutaneous melanoma, including acral
3. ≥18 years of age
4. Stage III un-resectable/ IV disease
5. Measurable disease on CT (thorax, abdomen and pelvis, ± neck if indicated) and/or PET-CT, or clinically accurately measurable (RECIST v1.1)
6. BRAF p.V600E/K/R/D mutation confirmed (exact point mutation must be known)
7. ECOG performance status 0/1/2
8. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drugs
9. Adequate organ function enabling safe administration of the study treatment
10. Women of childbearing potential participating in the study (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug
11. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 1 month 28 days following last dose of drug (either encorafenib or binimetinib)
12. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) from last dose of drug (either encorafenib or binimetinib)
Prior to randomisation:
13. BRAF ctDNA level of ≥7 copies/ml of plasma. (If there is a discrepancy between the screening and baseline 1 ctDNA TAB levels this should be discussed via the DyNAMIc trial team at the LCTC.)
14. Left Ventricular Ejection fraction (LVEF) ≥50% of ≥LLN by ECHO

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Previous key inclusion criteria as of 01/10/2025:

At screening:
1. Written and informed consent obtained from the participant and agreement of the participant to comply with the requirements of the study
2. Histological confirmation of cutaneous melanoma, including acral
3. ≥18 years of age
4. Stage III un-resectable/ IV disease
5. Measurable disease on CT (thorax, abdomen and pelvis, ± neck if indicated) and/or PET-CT (RECIST v1.1)
6. BRAF p.V600E/K/R/D mutation confirmed (exact point mutation must be known)
7. ECOG performance status 0/1/2
8. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drugs
9. Adequate organ function as defined below:
9.1. Haemoglobin ≥9 g/dL
9.2. White blood count ≥2 x 10^(9)/L
9.3. ANC ≥1.2 x 10(9)/L
9.4. Platelet count ≥75 x 10^(9)/L
9.5. Albumin ≥2.5 g/dL

9.6. Total bilirubinb ≤1.5 x ULN
9.7. AST or ALT ≤3 x ULN
9.8. Calculated creatinine clearance ≥30 ml/min
10. Women of childbearing potential participating in the study (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug
11. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 1 month 28 days following last dose of drug (either encorafenib or binimetinib)
12. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) from last dose of drug (either encorafenib or binimetinib)
At randomisation:
13. BRAF ctDNA level of ≥7 copies/ml of plasma
14. Left Ventricular Ejection fraction (LVEF) ≥50% of ≥LLN by ECHO

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Previous key inclusion criteria:

Patients eligible for the trial must comply with all of the following at randomisation:
1. Written and informed consent obtained from participant and agreement of participant to comply with the requirements of the study
2. Histological confirmation of cutaneous melanoma
3. ≥18 years of age
4. Stage III un-resectable/ IV disease
5. Measurable disease on CT (thorax, abdomen and pelvis, ± neck if indicated) and/or PET-CT, and CT or MRI (brain) scan (RECIST v1.1)
6. BRAF p.V600E/K/R mutation confirmed (exact point mutation must be known)
7. BRAF ctDNA TAB level of ≥15 copies/ml of plasma
8. ECOG performance status 0/1/2
9. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drugs
10. Adequate organ function as defined below:
10.1. Haemoglobin ≥9 g/dL
10.2. White blood count ≥2 x 10(9)/L
10.3. ANC ≥1.2 x 10(9)/L
10.4. Platelet count ≥75 x 10(9)/L
10.5. Albumin ≥2.5 g/dL
10.6. Total bilirubinb ≤1.5 x ULN
10.7. AST or ALT ≤3 x ULN
10.8. Calculated creatinine clearance ≥30 ml/min
10.9. Left Ventricular Ejection fraction (LVEF) ≥50% or ≥LLN by ECHO
11. Women of childbearing potential participating in the study (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug
12. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 1 month following last dose of drug (either encorafenib or binimetinib)
13. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) from last dose of drug (either encorafenib or binimetinib)

14. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP participating in the study who are continuously not heterosexually active must still undergo pregnancy testing (as described in inclusion criterion 11)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 09/06/2026:

1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥26 weeks following discontinuation of drugs)
2. BRAF wild-type malignant melanoma
3. Current evidence of active metastasis to the brain or leptomeninges (the designation of “active metastasis” should be determined by the local clinical care team in discussion with the DyNAMIc study team at LCTC if needed and informed by recent imaging.)
4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics
5. Hypersensitivity to the active substance or to any of the excipients of encorafenib or binimetinib
6. Current use of a prohibited medication as described in the protocol
7. History of another malignancy. Exception: Patients who have been disease-free for 3 years, (i. e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study. Discussion via the DyNAMIc trial team at LCTC as to whether they can be included in the study is allowed and the outcome of the discussion will determine entry.
8. 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
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus

(HCV) infection
10. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (as described in the protocol)
11. Prisoners or patients who are involuntarily incarcerated
12. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

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Previous key exclusion criteria as of 15/10/2025:

1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥26 weeks following discontinuation of drugs)
2. BRAF wild-type malignant melanoma
3. Current evidence of active metastasis to the brain or leptomeninges (patients with prior definitive treatment with immune therapy/radiotherapy (including SRS) or surgery), with no evidence of progression in the last 3 months, can be included
4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics
5. Hypersensitivity to the active substance or to any of the excipients of encorafenib or binimetinib
6. Current use of a prohibited medication as described in the protocol
7. History of another malignancy. Exception: Patients who have been disease-free for 3 years, (i. e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study
8. 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
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection
10. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
11. Child-Pugh B or C liver disease
12. Coronary syndromes (including myocardial infarction within 6 months or unstable angina)
13. A history or evidence of current ≥Class II congestive heart failure as defined by the NYHA guidelines with an ejection fraction of <50%
14. Treatment refractory hypertension defined as a blood pressure of systolic >150 mmHg and /or diastolic >95 mmHg on >3 occasions which cannot be controlled by anti-hypertensive therapy
15. Uncorrectable electrolyte abnormalities >CTCAE v5 Grade 1 (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome (baseline 1 QTC interval ≥480 msec) or taking medicinal products known to prolong the QT interval
16. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes)
17. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (as described in the protocol)
18. Prisoners or patients who are involuntarily incarcerated
19. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

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Previous key exclusion criteria as of 01/10/2025:

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:
1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥6 months ≥26 weeks following discontinuation of drugs)
2. BRAF wild-type malignant melanoma
3. Current evidence of active metastasis to the brain or leptomeninges (patients with prior definitive treatment with immune therapy/radiotherapy (including SRS) or surgery), with no evidence of progression in the last 3 months, can be included
4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics
5. Hypersensitivity to the active substance or to any of the excipients of encorafenib or binimetinib
6. Current use of a prohibited medication as described in the protocol
7. History of another malignancy. Exception: Patients who have been disease-free for 3 years, (i. e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study
8. 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
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection
10. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
11. Child-Pugh B or C liver disease
12. Coronary syndromes (including myocardial infarction within 6 months or unstable angina)
13. A history or evidence of current ≥Class II congestive heart failure as defined by the NYHA guidelines with an ejection fraction of <50%
14. Treatment refractory hypertension defined as a blood pressure of systolic >150 mmHg and /or diastolic >95 mmHg on >3 occasions which cannot be controlled by anti-hypertensive therapy
15. Uncorrectable electrolyte abnormalities >CTCAE v5 Grade 1 (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome (baseline 1 QTC interval ≥480 msec) or taking medicinal products known to prolong the QT interval
16. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes)
17. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (as described in the protocol)
18. Prisoners or patients who are involuntarily incarcerated
19. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

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Previous key exclusion criteria:

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:
1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥6 months following discontinuation of drugs)
2. BRAF wild-type malignant melanoma
3. Metastasis to the brain or leptomeninges
4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics
5. Hypersensitivity to the active substance or to any of the excipients of encorafenib or binimetinib
6. Current use of a prohibited medication as described in the protocol
7. History of another malignancy. Exception: Patients who have been disease-free for 3 years, (i. e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study
8. 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
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection
10. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
11. Child-Pugh B or C liver disease
12. Coronary syndromes (including myocardial infarction within 6 months or unstable angina)
13. A history or evidence of current ≥Class II congestive heart failure as defined by the NYHA guidelines with an ejection fraction of <50%
14. Treatment refractory hypertension defined as a blood pressure of systolic >150 mmHg and /or diastolic >95 mmHg on >3 occasions which cannot be controlled by anti-hypertensive therapy
15. Uncorrectable electrolyte abnormalities >CTCAE v5 Grade 1 (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome (baseline QTC interval ≥480 msec) or taking medicinal products known to prolong the QT interval
16. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes)
17. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (as described in the protocol)
18. Prisoners or patients who are involuntarily incarcerated
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Date of first enrolment
29/11/2024

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Guys Hospital
Guys Hospital
Great Maze Pond
London
England
SE1 9RT

Study participating centre
Royal Preston Hospital
Sharoe Green Lane
Fulwood
Preston
England
PR2 9HT

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
England
NE7 7DN

Study participating centre
Queens Medical Centre
Nottingham University Hospital
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

Study participating centre
Christie Hospital
Wilmslow Road
Manchester
England
M20 4BX

Study participating centre
Clatterbridge Cancer Centre
65 Pembroke PLACE
Liverpool
England
L7 8YA

Study participating centre
Royal Marsden Hospital
Royal Marsden Hospital
Downs Road
Surrey
England
SM2 5PT

Study participating centre
Southampton
Southampton General Hospital

Tremona Road
Southampton
England
SO16 6YD

Study participating centre
Velindre Cancer Centre
Velindre Road
Cardiff
Wales
CF14 2TL

Study participating centre
The Royal Marsden Hospital
Fulham Road
London
England
SW3 6JJ

Study participating centre
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
England
BH7 7DW

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
Scotland
G12 0YN

Study participating centre
Royal Free Hospital
Pond Street
London
England
NW3 2QG

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
England
BA1 3NG

Study participating centre
Poole Hospital
Longfleet Road
Poole
England
BH15 2JB

Sponsor information

Organisation
The Christie NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Charity

Funder Name
Jon Moulton Charity Trust

Alternative Name(s)
The Jon Moulton Charity Trust

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 3.0		27/06/2023	No	No
Protocol file	version 4.0	27/03/2023	01/10/2025	No	No
Protocol file	version 5.0	21/05/2024	01/10/2025	No	No
Protocol file	version 6.0	05/03/2025	01/10/2025	No	No
Protocol file	version 7.0	23/06/2025	01/10/2025	No	No
Protocol file	version 8.0	14/01/2026	09/06/2026	No	No