ISRCTN14595136 https://doi.org/10.1186/ISRCTN14595136

A study of encorafenib and binimetinib given before and after surgery, compared with standard treatment after surgery, in patients with BRAF-mutant melanoma

Submission date
12/10/2021

Recruitment status
No longer recruiting

Registration date
28/10/2021

Overall study status
Ongoing

Last Edited
16/05/2025

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-encorafenib-and-binimetinib-for-melanoma-that-has-spread-premium

Background and study aims
Patients who are planned to undergo surgery to remove melanoma that has spread to lymph nodes or other parts of their body are routinely offered a course of anticancer drug treatment after their surgery, which lasts for up to 52 weeks. This is called adjuvant therapy. The aim of this study is to determine if starting treatment before surgery is beneficial. This is called neoadjuvant therapy. Patients will be given either an 8-week course of treatment before surgery, and then up to 44 weeks further treatment after surgery (a total of 52 weeks). The study will also look at how willing patients and doctors are to take part in a trial looking at starting treatment prior to surgery compared with standard treatment given after surgery.

Who can participate?
Patients aged 18 years and over with melanoma containing a BRAF mutation and who have surgery planned

What does the study involve?
Participants will undergo a screening assessment to assess their suitability for the study. Suitable participants will be immediately go into the neoadjuvant treatment arm. Participants assigned to the treatment group will be given encorafenib and binimetinib for 8 weeks before surgery, and then for up to 44 weeks after surgery (a total of 52 weeks). Participants will need to attend all hospital appointments arranged, agree to have the tests needed for this study, agree to take the study treatment as directed, and inform the study team of any other medications being taken and of any side effects experienced. Participants must use two reliable forms of contraception for the entire duration of treatment and for at least 1 month after the last treatment dose.

What are the possible benefits and risks of participating?
There is no guarantee that participants will benefit but they may experience an improvement in their disease outcome. There are known side effects to both encorafenib and binimetinib, and all participants will receive information on these side effects and will be monitored closely throughout the study. As response rates to the treatment are so high, the researchers do not expect this will be harmful and it should improve patients' chances of successful surgery. However, there is a very small risk that the cancer could spread during the time between being invited to take part in the study and surgery being undertaken. Patients may experience discomfort and/or bruising in their arm from the blood tests. Wherever possible, study blood samples will be taken at the same time as any routine blood tests to minimise discomfort.

Where is the study run from?
Cambridge Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
August 2018 to February 2027

Who is funding the study?
Les Laboratories Pierre Fabre (France)

Who is the main contact?
Dr Pippa Corrie, philippa.corrie@nhs.net

Contact information

Type(s)
Scientific

Contact name
Dr Pippa Corrie

Contact details
Oncology Centre, Box 193
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 274013
philippa.corrie@nhs.net

Type(s)
Scientific

Contact name
Mr Samuel Resendez

Contact details
Cambridge Clinical Trials Unit - Cancer Theme
S4, Box279
Addenbrooke's Hospital

Hills Road
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 216083
cuh.cctu.premium@nhs.net

Additional identifiers

Clinical Trials Information System (CTIS)
2019-004855-35

Integrated Research Application System (IRAS)
278086

ClinicalTrials.gov (NCT)
NCT05097378

Protocol serial number
CPMS 47424

Study information

Scientific Title
PeRioperative Encorafinib+binimetinib in BRAFV600 MUtant clinically detected AJCC stage III (B/C/D) or oligometastatic stage IV Melanoma (PREMIUM)

Acronym
PREMIUM

Study objectives
The aim of this trial is to assess the pathological complete response rate in patients receiving pre-operative and postoperative treatment with encorafenib and binimetinib, compared to standard treatment only given after surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/11/2021, East of England - Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; 020 7104 8057; Essex.REC@hra.nhs.uk), ref:21/EE/0200

Study design
Single-arm; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Melanoma

Interventions
Current interventions as of 16/05/2025:

Target population:
The target population will be male and female participants aged 18 and over with stage III (B/C /D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma. Patients will be provided with information regarding the trial both through conversation with investigators and research nurses and in writing via a patient information sheet. Patients will be given time to ask questions and discuss with family/support structures before deciding to participate. If the patient agrees to take part, they will be asked to provide written consent and will be provided with a copy of the patient information sheet and informed consent form signed by themselves and the local investigator to keep.

Visit schedule for consenting patients:

Screening:
Consenting patients will enter the screening/baseline phase, which will be completed within 28 days prior to enrolment. This will include assessing the patient against inclusion & exclusion criteria, including BRAF status assessment, pregnancy test, ECHO, ECG, disease assessment, questionnaires and lymphoedema assessment.

Randomisation:
If eligible, patients will go into the EncoBini Arm.
EncoBini Arm: Participants will be asked to self-administer EncoBini pre- and post-surgery: Encorafenib 450 mg once daily + binimetinib 45 mg twice daily for 8 weeks, followed by a minimum 2-week break before surgery, then EncoBini restarted at least 2 weeks after surgery, to continue for up to 44 weeks. IMP will be dispensed to the patients on day 1 of week 1 and day 1 of week 5 for pre-surgery, and on day 1 of each treatment cycle post-surgery.

Pre-operative treatment:
Weeks 1 & 5 (day 1) - During the pre-operative treatment participants will attend the hospital where they will have a clinical assessment, routine laboratory assessment and a research blood sample collected. An ECG will also be performed on day 1 of week 5. Participants will also be asked to bring their diary card and any leftover drug to be checked by a member of the research team.
Week 3 - the patients will receive a phone call from the research team to perform an adverse event and drug compliance assessment.
Week 9 (day 1) - Patient will attend the clinic to undergo disease and Lymphoedema assessments, complete the trial questionnaires and provide a research blood sample. A drug compliance assessment will also be performed.

Surgical resection:
Patients on both arms will attend the hospital for the surgical resection of their tumour, during which a tumour sample will be provided for the research. EncoBini patients will undergo surgical resection within 2 weeks of the last IMP dose administered prior to surgery, assuming the pre-surgery scan confirms resectability of the tumour.

Post-operative treatment:
Patients will restart EncoBini at least 2 weeks after and within 12 weeks of surgery and continue for up to 44 weeks (11 x 4-week cycles).

On day 1 of each treatment cycle, a clinical review, a routine laboratory assessment and a drug compliance assessment will be performed.

Post-operative monitoring visits - patients will attend 3-monthly hospital visits to undergo a disease assessment, patients will also complete the trial questionnaires, provide a research blood sample and undergo a lymphoedema assessment (appropriate stage III participants only and at 6- and 12-monthly visits only).

An ECG will also be carried out for participants on both arms during screening and throughout the trial for those participants in the EncoBini arm only.

End of treatment:
Within 30 days of the date of the last treatment dose, patients will attend the clinic to undergo a clinical review, a routine laboratory assessment and a drug compliance assessment.

On disease progression/recurrence:
Within 30 days of disease progression or recurrence, patients will attend the clinic to undergo a clinical review, routine laboratory assessment and drug compliance assessment. A disease assessment will be performed and a research blood and tumour (if possible) sample will be taken.

Follow-up after progression during pre-operative treatment:
Participants will be followed up via a telephone call to collect data on their subsequent surgery /systemic treatment and overall survival until study closure.

Follow-up if stopping treatment after surgery due to disease recurrence:
Participants will be followed up via a telephone call every 3 months, to collect data on their subsequent surgery/systemic treatment and overall survival until study closure.

Follow-up if stopping for toxicity:
Participants will attend the clinic every 3 months until resolution of the toxicity, disease recurrence or study closure (whichever is sooner) to undergo a clinical review, disease assessment, and provide a research blood sample. Once the toxicity has resolved, participants should attend the clinic every 3 months until disease recurrence or study closure (whichever is sooner) for disease assessment. If recurrence occurs, follow-up will be as if stopping for disease recurrence, as described above.

Follow-up after completing planned adjuvant therapy (both arms):
Participants will attend the clinic approximately every 3 - 6 months depending on local practice, until disease recurrence or study closure, whichever is sooner.

Trial procedures:

BRAF status assessment:
BRAF mutation status of potential trial participants will be determined as part of standard of care, prior to their consent to take part in this clinical trial. A validated test (utilising either NGS or PCR methodology) for a specific gene BRAF V600 mutation must be used, as per local clinical practice.

Clinical assessment:
Patients will be reviewed by the trial team to check how well they are tolerating the drug and the patients' health after they have stopped taking the drug. This will involve taking a full medical history (at screening only), recording any medications they may be taking, and any symptoms and/or side effects they may have. Patients will also have a physical examination, and assessment of blood pressure and body weight as part of this review, and the clinical team will assess the patient's clinical status using ECOG and Karnofsky performance status scales.

Pregnancy test:
Women of childbearing potential will have a pregnancy test at screening to ensure they are not pregnant and are therefore able to receive the trial drugs.

Electrocardiogram (ECG):
An ECG test is required before starting the trial to ensure that the patient is fit enough to receive the trial drugs, and whilst the participant is on EncoBini treatment to ensure they are tolerating the drugs well.

Echocardiogram (ECHO):
An ECHO is required prior to starting the trial. This will check that the patient's heart is working well enough to receive the trial drug. ECHOs will subsequently be performed intermittently as standard of care to ensure that patients are tolerating the trial drug well.

Routine laboratory assessment:
Patients will be asked to have routine blood tests (haematology and biochemistry) to ensure that they are fit enough for the trial, and that they are tolerating the drug well. These blood samples will be taken at clinic visits during screening, pre-operative treatment and post-operative treatment, at the end of treatment visit and upon disease progression or recurrence.

Research blood samples:
Patients will be asked to give extra blood for research related to this trial. The samples will be used to look at BRAF mutations in the participants DNA and the response of the immune system to the treatment.

Disease assessment (CT, PET/CT and/or MRI, plus RECIST):
Participants will have CT. PET-CT or MRI, according to the standard of care at each site. The scans will be used to carry out RECIST reporting to monitor the response of the tumour/tumour excision site to treatment.

Drug compliance assessment:
Whilst on treatment, participants will be asked to complete a diary card. During treatment, at each clinical visit the participants will be asked to bring their medication along with their diary card. The clinical team will record how many tablets remain and how many tablets have been taken. The participants will be asked to record in the diary card the date and time when they take their medication. Both of these activities will be used to assess their compliance with the treatment regimen.

Quality of life questionnaires:
All patients will be asked to fill in questionnaires to report their quality of life.

Tumour tissue collection:
Upon starting treatment, patients will be asked to donate previously archived tissue. When

patients undergo surgical resection or biopsy for progressive disease or the development of a new lesion, a tumour sample will be requested for this research.

Lymphoedema assessment
Appropriate stage III participants will undergo circumferential limb measurements, to assess lymphoedema and be asked to complete a questionnaire to report on their condition.

Previous interventions:

Target population:
The target population will be male and female participants aged 18 and over with stage III (B/C /D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma.
Patients will be provided with information regarding the trial both through conversation with investigators and research nurses and in writing via a patient information sheet. Patients will be given time to ask questions and discuss with family/support structures before deciding to participate. If the patient agrees to take part, they will be asked to provide written consent and will be provided with a copy of the patient information sheet and informed consent form signed by themselves and the local investigator to keep.

Visit schedule for consenting patients:

Screening:
Consenting patients will enter the screening/baseline phase, which will be completed within 28 days prior to registration. This will include assessing the patient against inclusion & exclusion criteria, including BRAF status assessment, pregnancy test, ECHO, ECG, disease assessment, questionnaires and lymphoedema assessment.

Registration:
If eligible, participants will be asked to self-administer EncoBini pre- and post-surgery: Encorafenib 450mg once daily + binimetinib 45mg twice daily for 8 weeks, followed by a minimum 2 week break and maximum 5 week break before surgery, then EncoBini restarted at least 2 weeks after surgery, to continue for up to 44 weeks. IMP will be dispensed to the patients on day 1 of week 1 and day 1 of week 5 for pre-surgery, and on day 1 of each treatment cycle post-surgery.

Pre-operative treatment:
Weeks 1 & 5 (day 1) - During the pre-operative treatment participants will attend the hospital where they will have a clinical assessment, routine laboratory assessment and a research blood sample collected. An ECG will also be performed on day 1 of week 5. Participants will also be asked to bring their diary card and any leftover drug to be checked by a member of the research team.
Week 3 - the patients will receive a phone call from the research team to perform an adverse event and drug compliance assessment.
Week 9 (day 1) - Patient will attend the clinic to undergo disease and Lymphoedema assessments, complete the trial questionnaires and provide a research blood sample. A drug compliance assessment will also be performed.

Surgical resection:
Patients on both arms will attend the hospital for the surgical resection of their tumour, during which a tumour sample will be provided for the research. EncoBini patients will undergo surgical resection within 2 weeks of the last IMP dose administered prior to surgery, assuming the pre-surgery scan confirms resectability of the tumour.

Post-operative treatment:

Patients will restart EncoBini at least 2 weeks after and within 12 weeks of surgery and continue for up to 44 weeks (11 x 4-week cycles).

On day 1 of each treatment cycle , a clinical review, a routine laboratory assessment and a drug compliance assessment will be performed.

Post-operative monitoring visits (both arms) - patients will attend 3-monthly hospital visits to undergo a disease assessment, patients will also complete the trial questionnaires, provide a research blood sample and undergo a lymphoedema assessment (appropriate stage III participants only and at 6- and 12-monthly visits only).

An ECG will also be carried out for those participants.

End of treatment:
Within 30 days of the date of the last treatment dose, patients will attend the clinic to undergo a clinical review, a routine laboratory assessment and a drug compliance assessment.

On disease progression/recurrence (both arms):
Within 30 days of disease progression (EncoBini arm only) or recurrence (both arms), patients will attend the clinic to undergo a clinical review, routine laboratory assessment and drug compliance assessment. A disease assessment will be performed and a research blood and tumour (if possible) sample will be taken.

Follow-up after progression during pre-operative treatment:
Participants will be followed up via a telephone call to collect data on their subsequent surgery /systemic treatment and overall survival until study closure.

Follow-up if stopping treatment after surgery due to disease recurrence:
Participants will be followed up via a telephone call every 3 months, to collect data on their subsequent surgery/systemic treatment and overall survival until study closure.

Follow-up if stopping for toxicity:
Participants will attend the clinic every 3 months until resolution of the toxicity, disease recurrence or study closure (whichever is sooner) to undergo a clinical review, disease assessment, and provide a research blood sample. Once the toxicity has resolved, participants should attend the clinic every 3 months until disease recurrence or study closure (whichever is sooner) for disease assessment. If recurrence occurs, follow-up will be as if stopping for disease recurrence, as described above.

Follow-up after completing planned adjuvant therapy (both arms):
Participants will attend the clinic approximately every 3 - 6 months depending on local practice, until disease recurrence or study closure, whichever is sooner.

Trial procedures:

BRAF status assessment:
BRAF mutation status will be confirmed for all participants at registration. Where

immunohistochemistry is used, subsequent confirmation of BRAF mutation status will be performed using either next-generation sequencing or polymerase chain reaction. This may be carried out after registration.

Clinical assessment:
Patients will be reviewed by the trial team to check how well they are tolerating the drug and the patients' health after they have stopped taking the drug. This will involve taking a full medical history (at screening only), recording any medications they may be taking, and any symptoms and/or side-effects they may have. Patients will also have a physical examination, and assessment of blood pressure and body weight as part of this review, and the clinical team will assess the patient's clinical status using ECOG and Karnofsky performance status scales.

Pregnancy test:
Women of childbearing potential will have a pregnancy test at screening to ensure they are not pregnant and are therefore able to receive the trial drugs.

Electrocardiogram (ECG):
An ECG test is required before starting the trial to ensure that the patient is fit enough to receive the trial drugs, and whilst the participant is on EncoBini treatment to ensure they are tolerating the drugs well.

Echocardiogram (ECHO):
An ECHO is required prior to starting the trial. This will check that the patient's heart is working well enough to receive the trial drug. ECHOs will subsequently be performed intermittently as standard of care to ensure that patients are tolerating the trial drug well.

Routine laboratory assessment:
Patients will be asked to have routine blood tests (haematology and biochemistry) to ensure that they are fit enough for the trial, and that they are tolerating the drug well. These blood samples will be taken at clinic visits during screening, pre-operative treatment and post-operative treatment, at the end of treatment visit and upon disease progression or recurrence.

Research blood samples:
Patients will be asked to give extra blood for research related to this trial. The samples will be used to look at BRAF mutations in the participants DNA and the response of the immune system to the treatment.

Disease assessment (CT, PET/CT and/or MRI, plus RECIST):
Participants will have CT. PET-CT or MRI, according to the standard of care at each site. The scans will be used to carry out RECIST reporting to monitor the response of the tumour/tumour excision site to treatment.

Drug compliance assessment:
Whilst on treatment, participants will be asked to complete a diary card. During treatment, at each clinical visit the participants will be asked to bring their medication along with their diary card. The clinical team will record how many tablets remain and how many tablets have been taken. The participants will be asked to record in the diary card the date and time when they take their medication. Both of these activities will be used to assess their compliance with the treatment regimen.

Quality of life questionnaires:
All patients will be asked to fill in questionnaires to report their quality of life.

Tumour tissue collection:
Upon starting treatment, patients will be asked to donate previously archived tissue. When patients undergo surgical resection or biopsy for progressive disease or the development of a new lesion, a tumour sample will be requested for this research.

Lymphoedema assessment
Appropriate stage III participants will undergo circumferential limb measurements, to assess lymphoedema and be asked to complete a questionnaire to report on their condition.

_____

Previous interventions as of 14/06/2022:

Target population:
The target population will be male and female participants aged 18 and over with stage III (B/C /D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma. Patients will be provided with information regarding the trial both through conversation with investigators and research nurses and in writing via a patient information sheet. Patients will be given time to ask questions and discuss with family/support structures before deciding to participate. If the patient agrees to take part, they will be asked to provide written consent and will be provided with a copy of the patient information sheet and informed consent form signed by themselves and the local investigator to keep.

Visit schedule for consenting patients:

Screening:
Consenting patients will enter the screening/baseline phase, which will be completed within 28 days prior to randomisation. This will include assessing the patient against inclusion & exclusion criteria, including BRAF status assessment, pregnancy test, ECHO, ECG, disease assessment, questionnaires and lymphoedema assessment.

Randomisation:
If eligible, patients will be randomly assigned to either treatment arm via a web-based randomisation system, Sealed Envelope, to allocate a unique study ID and treatment arm. They will be randomised on a 2:1 (EncoBini: standard) basis to one of two arms:
EncoBini Arm: Participants will be asked to self-administer EncoBini pre- and post-surgery: Encorafenib 450 mg once daily + binimetinib 45 mg twice daily for 8 weeks, followed by a minimum 2-week break before surgery, then EncoBini restarted at least 2 weeks after surgery, to continue for up to 44 weeks. IMP will be dispensed to the patients on day 1 of week 1 and day 1 of week 5 for pre-surgery, and on day 1 of each treatment cycle post-surgery.
Standard Arm: Participants will undergo immediate surgery within 31 days of randomisation, followed by the Investigator's choice of standard adjuvant therapy to commence within 12 weeks of surgery and to continue for up to 52 weeks. The adjuvant therapy drugs will be dispensed to the patients on day 1 of each treatment cycle post-surgery.

Pre-operative treatment (EncoBini arm only):
Weeks 1 & 5 (day 1) - During the pre-operative treatment participants will attend the hospital where they will have a clinical assessment, routine laboratory assessment and a research blood sample collected. An ECG will also be performed on day 1 of week 5. Participants will also be asked to bring their diary card and any leftover drug to be checked by a member of the research team.

Week 3 - the patients will receive a phone call from the research team to perform an adverse event and drug compliance assessment.
Week 9 (day 1) - Patient will attend the clinic to undergo disease and Lymphoedema assessments, complete the trial questionnaires and provide a research blood sample. A drug compliance assessment will also be performed.

Pre-operative visit (standard arm only):
Participants randomised to the standard arm will attend the hospital for their usual pre-operative visit. During this visit a research blood sample will be taken.

Surgical resection (both arms):
Patients on both arms will attend the hospital for the surgical resection of their tumour, during which a tumour sample will be provided for the research. EncoBini patients will undergo surgical resection within 2 weeks of the last IMP dose administered prior to surgery, assuming the pre-surgery scan confirms resectability of the tumour. Patients on the standard arm will undergo surgical resection within 31 days of randomisation, a cancer waiting time requirement.

Post-operative treatment:
EncoBini Arm: patients will restart EncoBini at least 2 weeks after and within 12 weeks of surgery and continue for up to 44 weeks (11 x 4-week cycles).
Standard Arm: patients will start standard adjuvant therapy within 12 weeks of surgery and continue for up to 52 weeks.

On day 1 of each treatment cycle, for participants on both arms, a clinical review, a routine laboratory assessment and a drug compliance assessment will be performed.

Post-operative monitoring visits (both arms) - patients will attend 3-monthly hospital visits to undergo a disease assessment, patients will also complete the trial questionnaires, provide a research blood sample and undergo a lymphoedema assessment (appropriate stage III participants only and at 6- and 12-monthly visits only).

An ECG will also be carried out for participants on both arms during screening and throughout the trial for those participants in the EncoBini arm only.

End of treatment (both arms):
Within 30 days of the date of the last treatment dose, patients will attend the clinic to undergo a clinical review, a routine laboratory assessment and a drug compliance assessment.

On disease progression/recurrence (both arms):
Within 14 days of disease progression (EncoBini arm only) or recurrence (both arms), patients will attend the clinic to undergo a clinical review, routine laboratory assessment and drug compliance assessment. A disease assessment will be performed and a research blood and tumour (if possible) sample will be taken.

Follow-up after progression during pre-operative treatment (EncoBini arm only):
Participants will be followed up via a telephone call to collect data on their subsequent surgery /systemic treatment and overall survival until study closure.

Follow-up if stopping treatment after surgery due to disease recurrence (both arms):
Participants will be followed up via a telephone call every 3 months, to collect data on their subsequent surgery/systemic treatment and overall survival until study closure.

Follow-up if stopping for toxicity (both arms):
Participants will attend the clinic every 3 months until resolution of the toxicity, disease recurrence or study closure (whichever is sooner) to undergo a clinical review, disease assessment, and provide a research blood sample. Once the toxicity has resolved, participants should attend the clinic every 3 months until disease recurrence or study closure (whichever is sooner) for disease assessment. If recurrence occurs, follow-up will be as if stopping for disease recurrence, as described above.

Follow-up after completing planned adjuvant therapy (both arms):
Participants will attend the clinic approximately every 3 - 6 months depending on local practice, until disease recurrence or study closure, whichever is sooner.

Trial procedures:

BRAF status assessment:
BRAF mutation status of potential trial participants will be determined as part of standard of care, prior to their consent to take part in this clinical trial. A validated test (utilising either NGS or PCR methodology) for a specific gene BRAF V600 mutation must be used, as per local clinical practice.

Clinical assessment:
Patients will be reviewed by the trial team to check how well they are tolerating the drug and the patients' health after they have stopped taking the drug. This will involve taking a full medical history (at screening only), recording any medications they may be taking, and any symptoms and/or side effects they may have. Patients will also have a physical examination, and assessment of blood pressure and body weight as part of this review, and the clinical team will assess the patient's clinical status using ECOG and Karnofsky performance status scales.

Pregnancy test:
Women of childbearing potential will have a pregnancy test at screening to ensure they are not pregnant and are therefore able to receive the trial drugs.

Electrocardiogram (ECG):
An ECG test is required before starting the trial to ensure that the patient is fit enough to receive the trial drugs, and whilst the participant is on EncoBini treatment to ensure they are tolerating the drugs well.

Echocardiogram (ECHO):
An ECHO is required prior to starting the trial. This will check that the patient's heart is working well enough to receive the trial drug. ECHOs will subsequently be performed intermittently as standard of care to ensure that patients are tolerating the trial drug well.

Routine laboratory assessment:
Patients will be asked to have routine blood tests (haematology and biochemistry) to ensure that they are fit enough for the trial, and that they are tolerating the drug well. These blood samples will be taken at clinic visits during screening, pre-operative treatment and post-operative treatment, at the end of treatment visit and upon disease progression or recurrence.

Research blood samples:
Patients will be asked to give extra blood for research related to this trial. The samples will be used to look at BRAF mutations in the participants DNA and the response of the immune system to the treatment.

Disease assessment (CT, PET/CT and/or MRI, plus RECIST):
Participants will have CT. PET-CT or MRI, according to the standard of care at each site. The scans will be used to carry out RECIST reporting to monitor the response of the tumour/tumour excision site to treatment.

Drug compliance assessment:
Whilst on treatment, participants will be asked to complete a diary card. During treatment, at each clinical visit the participants will be asked to bring their medication along with their diary card. The clinical team will record how many tablets remain and how many tablets have been taken. The participants will be asked to record in the diary card the date and time when they take their medication. Both of these activities will be used to assess their compliance with the treatment regimen.

Quality of life questionnaires:
All patients will be asked to fill in questionnaires to report their quality of life.

Tumour tissue collection:
Upon starting treatment, patients will be asked to donate previously archived tissue. When patients undergo surgical resection or biopsy for progressive disease or the development of a new lesion, a tumour sample will be requested for this research.

Lymphoedema assessment
Appropriate stage III participants will undergo circumferential limb measurements, to assess lymphoedema and be asked to complete a questionnaire to report on their condition.

Previous interventions:

Target population:
The target population will be male and female participants aged 18 and over with stage III (B/C /D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma.
Patients will be provided with information regarding the trial both through conversation with investigators and research nurses and in writing via a patient information sheet. Patients will be given time to ask questions and discuss with family/support structures before deciding to participate. If the patient agrees to take part, they will be asked to provide written consent and will be provided with a copy of the patient information sheet and informed consent form signed by themselves and the local investigator to keep.

Visit schedule for consenting patients:

Screening:
Consenting patients will enter the screening/baseline phase, which will be completed within 28 days prior to randomisation. This will include assessing the patient against inclusion & exclusion criteria, including BRAF status assessment, pregnancy test, ECHO, ECG, disease assessment, questionnaires and lymphoedema assessment.

Randomisation:
If eligible, patients will be randomly assigned to either treatment arms using a pre-defined randomisation list, provided by the trial statistician. They will be randomised on a 2:1 (EncoBini: standard) basis to one of two arms:

EncoBini Arm: Participants will be asked to self-administer EncoBini pre- and post-surgery: Encorafenib 450mg once daily + binimetinib 45mg twice daily for 8 weeks, followed by a minimum 2-week break before surgery, then EncoBini restarted at least 2 weeks after surgery, to continue for up to 44 weeks. IMP will be dispensed to the patients on day 1 of week 1 and day 1 of week 5 for pre-surgery, and on day 1 of each treatment cycle post-surgery.

Standard Arm: Participants will undergo immediate surgery within 31 days of randomisation, followed by the Investigator's choice of standard adjuvant therapy to commence within 12 weeks of surgery and to continue for up to 52 weeks. The adjuvant therapy drugs will be dispensed to the patients on day 1 of each treatment cycle post-surgery.

Pre-operative treatment (EncoBini arm only):
Weeks 1 & 5 (day 1) - During the pre-operative treatment participants will attend the hospital where they will have a clinical assessment, routine laboratory assessment and a research blood sample collected. An ECG will also be performed on day 1 of week 5. Participants will also be asked to bring their diary card and any leftover drug to be checked by a member of the research team.
Week 3 - the patients will receive a phone call from the research team to perform an adverse event and drug compliance assessment.
Week 9 (day 1) - Patient will attend the clinic to undergo disease and Lymphoedema assessments, complete the trial questionnaires and provide a research blood sample. A drug compliance assessment will also be performed.

Pre-operative visit (standard arm only):
Participants randomised to the standard arm will attend the hospital for their usual pre-operative visit. During this visit a research blood sample will be taken.

Surgical resection (both arms):
Patients on both arms will attend the hospital for the surgical resection of their tumour, during which a tumour sample will be provided for the research. EncoBini patients will undergo surgical resection within 2 weeks of the last IMP dose administered prior to surgery, assuming the pre-surgery scan confirms resectability of the tumour. Patients on the standard arm will undergo surgical resection within 31 days of randomisation, a cancer waiting time requirement.

Post-operative treatment:

EncoBini Arm: patients will restart EncoBini at least 2 weeks after and within 12 weeks of surgery and continue for up to 44 weeks (11 x 4-week cycles).

Standard Arm: patients will start standard adjuvant therapy within 12 weeks of surgery and continue for up to 52 weeks.

On day 1 of each treatment cycle, for participants on both arms, a clinical review, a routine laboratory assessment and a drug compliance assessment will be performed.

Post-operative monitoring visits (both arms) - patients will attend 3-monthly hospital visits to undergo a disease assessment, patients will also complete the trial questionnaires, provide a research blood sample and undergo a lymphoedema assessment (appropriate stage III participants only and at 6- and 12-monthly visits only).

An ECG will also be carried out for those participants in the EncoBini arm only.

End of treatment (both arms):
Within 30 days of the date of the last treatment dose, patients will attend the clinic to undergo a clinical review, a routine laboratory assessment and a drug compliance assessment.

On disease progression/recurrence (both arms):
Within 14 days of disease progression (EncoBini arm only) or recurrence (both arms), patients will attend the clinic to undergo a clinical review, routine laboratory assessment and drug compliance assessment. A disease assessment will be performed and a research blood and tumour (if possible) sample will be taken.

Follow-up after progression during pre-operative treatment (EncoBini arm only):
Participants will be followed up via a telephone call to collect data on their subsequent surgery /systemic treatment and overall survival until study closure.

Follow-up if stopping treatment after surgery due to disease recurrence (both arms):
Participants will be followed up via a telephone call every 3 months, to collect data on their subsequent surgery/systemic treatment and overall survival until study closure.

Follow-up if stopping for toxicity (both arms):
Participants will attend the clinic every 3 months until resolution of the toxicity, disease recurrence or study closure (whichever is sooner) to undergo a clinical review, disease assessment, and provide a research blood sample. Once the toxicity has resolved, participants should attend the clinic every 3 months until disease recurrence or study closure (whichever is sooner) for disease assessment. If recurrence occurs, follow-up will be as if stopping for disease recurrence, as described above.

Follow-up after completing planned adjuvant therapy (both arms):
Participants will attend the clinic approximately every 3 - 6 months depending on local practice, until disease recurrence or study closure, whichever is sooner.

Trial procedures:

BRAF status assessment:
BRAF mutation status will be confirmed for all participants at registration. Where immunohistochemistry is used, subsequent confirmation of BRAF mutation status will be performed using either next-generation sequencing or polymerase chain reaction. This may be carried out after randomisation.

Clinical assessment:
Patients will be reviewed by the trial team to check how well they are tolerating the drug and the patients' health after they have stopped taking the drug. This will involve taking a full medical history (at screening only), recording any medications they may be taking, and any symptoms and/or side-effects they may have. Patients will also have a physical examination, and assessment of blood pressure and body weight as part of this review, and the clinical team will assess the patient's clinical status using ECOG and Karnofsky performance status scales.

Pregnancy test:
Women of childbearing potential will have a pregnancy test at screening to ensure they are not pregnant and are therefore able to receive the trial drugs.

Electrocardiogram (ECG):
An ECG test is required before starting the trial to ensure that the patient is fit enough to

receive the trial drugs, and whilst the participant is on EncoBini treatment to ensure they are tolerating the drugs well.

Echocardiogram (ECHO):
An ECHO is required prior to starting the trial. This will check that the patient's heart is working well enough to receive the trial drug. ECHOs will subsequently be performed intermittently as standard of care to ensure that patients are tolerating the trial drug well.

Routine laboratory assessment:
Patients will be asked to have routine blood tests (haematology and biochemistry) to ensure that they are fit enough for the trial, and that they are tolerating the drug well. These blood samples will be taken at clinic visits during screening, pre-operative treatment and post-operative treatment, at the end of treatment visit and upon disease progression or recurrence.

Research blood samples:
Patients will be asked to give extra blood for research related to this trial. The samples will be used to look at BRAF mutations in the participants DNA and the response of the immune system to the treatment.

Disease assessment (CT, PET/CT and/or MRI, plus RECIST):
Participants will have CT. PET-CT or MRI, according to the standard of care at each site. The scans will be used to carry out RECIST reporting to monitor the response of the tumour/tumour excision site to treatment.

Drug compliance assessment:
Whilst on treatment, participants will be asked to complete a diary card. During treatment, at each clinical visit the participants will be asked to bring their medication along with their diary card. The clinical team will record how many tablets remain and how many tablets have been taken. The participants will be asked to record in the diary card the date and time when they take their medication. Both of these activities will be used to assess their compliance with the treatment regimen.

Quality of life questionnaires:
All patients will be asked to fill in questionnaires to report their quality of life.

Tumour tissue collection:
Upon starting treatment, patients will be asked to donate previously archived tissue. When patients undergo surgical resection or biopsy for progressive disease or the development of a new lesion, a tumour sample will be requested for this research.

Lymphoedema assessment
Appropriate stage III participants will undergo circumferential limb measurements, to assess lymphoedema and be asked to complete a questionnaire to report on their condition.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)

Current primary outcome measure as of 16/05/2025:

The primary outcome measure is pathological complete response, in patients who complete 8 weeks of pre-operative EncoBini and undergo complete surgical resection.

———

Previous primary outcome measure as of 14/06/2022:
Pathological complete response of the resected tumour (defined as an absence of residual viable malignant cells on H&E staining), in patients randomised to the EncoBini arm, who complete 8 weeks of pre-operative EncoBini and undergo complete surgical resection (R0).

Previous primary outcome measure:
Pathological complete response, measured by the absence of residual viable malignant cells on Haemotoxylin and Eosin (H&E) staining of tumour removed at surgery, in patients randomised to the EncoBini arm, who complete 8 weeks of pre-operative EncoBini and undergo complete surgical resection; Timepoint(s): Week 8

Key secondary outcome(s))

Current secondary outcome measures as of 16/05/2025:

1. Treatment compliance will be defined as the percentage of total planned doses of encorafenib and binimetinib received before and after surgery.
2. Pre-operative radiological response will be assessed on imaging undertaken at 8 weeks, according to Response Evaluation Criteria In Solid Tumours (RECIST v1.1, Appendix 1)
3. Pathological overall (complete, near-complete, partial and non-response) response will be assessed by pathological assessment of resected tumour specimens
4. Adverse drug reactions will be assessed using the standard cancer National Cancer Institute (NCI) CTCAE v5.0 criteria
5. Surgical adverse events will be captured up until 30 days after surgery
6. Lymphoedema events: lymphoedema affecting upper or lower limbs will be assessed in patients undergoing either axillary/supraclavicular lymphadenectomy, or inguinal/pelvic lymphadenectomy. Lymphoedema events will be determined by comparing serial limb circumference measurements (as a surrogate marker for post-operative lymphoedema) pre- and post-surgery. Lymphoedema is defined as >16% increase in the circumference of the limb associated with the nodal field that underwent lymphadenectomy at 6 and 12 months after the date of surgery compared with pre-surgery measurement.
7. EFS: Event-free survival is defined as the time from trial enrolment to disease progression or recurrence (local or distant disease development, or death), whichever occurs first, assessed by the treating investigators. Patients who remained alive without disease progression/recurrence at the time of data analyses are censored at their last date of clinical follow-up for progression /recurrence.
8. RFS: Relapse-free survival is defined as the time from surgery to disease recurrence (local or distant disease development, or death), whichever occurs first, assessed by the treating investigators. Patients who remained alive without disease recurrence at the time of data analyses are censored at their last date of clinical follow-up for recurrence.
9. DMFS: DMFS is defined as the time from trial enrolment to development of documented distant metastatic disease outside the loco-regional site of the primary tumour or lymph node metastasis, or death, whichever occurs first, assessed by treating investigators. Patients who remained alive without distant metastasis at the time of analyses are censored at their last date

of clinical follow-up for progression.
10. OS: OS is defined as the time from trial enrolment to death. Patients who remain alive are censored at their last contact date for overall survival.Loco-regional recurrence rate: loco-regional recurrence interval is defined as the time from surgery to development of documented local disease development. Patients without local recurrence at the time of analyses are censored at their last date of clinical follow-up for recurrence, date of distant metastatic, or death, whichever occurs first.
11. Incomplete surgical resection is defined by R1 (incomplete) resection status
12. Overall QoL will be measured using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) questionnaire
13. Recruitment rate is defined as the average monthly recruitment achieved during the last 6 months of the trial recruitment period

_____

Previous secondary outcome measures as of 14/06/2022:
1. Treatment compliance will be defined as the percentage of total planned doses of encorafenib and binimetinib received before and after surgery in the EncoBini arm.
2. Pre-operative radiological response will be assessed in the EncoBini arm on imaging undertaken at 8 weeks, according to Response Evaluation Criteria In Solid Tumours (RECIST v1.1, Appendix 1)
3. Pathological overall (complete, near-complete and partial) response will be assessed by pathological assessment of resected tumour specimens in the EncoBini arm only
4. Adverse drug reactions will be assessed using the standard cancer National Cancer Institute (NCI) CTCAE v5.0 criteria
5. Surgical adverse events will be captured up until 30 days after surgery
6. Lymphoedema events: lymphoedema affecting upper or lower limbs will be assessed in patients undergoing either axillary/supraclavicular lymphadenectomy, or inguinal/pelvic lymphadenectomy. Lymphoedema events will be determined by comparing serial limb circumference measurements (as a surrogate marker for post-operative lymphoedema) pre- and post-surgery. Lymphoedema is defined as >16% increase in the circumference of the limb associated with the nodal field that underwent lymphadenectomy at 6 and 12 months after the date of surgery compared with pre-surgery measurement.
7. EFS: Event-free survival is defined as the time from randomisation to disease progression or recurrence (local or distant disease development, or death), whichever occurs first, assessed by the treating investigators. Patients who remained alive without disease progression/recurrence at the time of data analyses are censored at their last date of clinical follow-up for progression /recurrence.
8. RFS: Relapse-free survival is defined as the time from surgery to disease recurrence (local or distant disease development, or death), whichever occurs first, assessed by the treating investigators. Patients who remained alive without disease recurrence at the time of data analyses are censored at their last date of clinical follow-up for recurrence.
9. DMFS: DMFS is defined as the time from randomisation to development of documented distant metastatic disease outside the loco-regional site of the primary tumour or lymph node metastasis, or death, whichever occurs first, assessed by treating investigators. Patients who remained alive without distant metastasis at the time of analyses are censored at their last date of clinical follow-up for progression.
10. OS: OS is defined as the time from randomisation to death. Patients who remain alive are censored at their last contact date for overall survival.Loco-regional recurrence rate: loco-regional recurrence interval is defined as the time from surgery to development of documented local disease development. Patients without local recurrence at the time of analyses are censored at their last date of clinical follow-up for recurrence, date of distant metastatic, or

death, whichever occurs first.
11. Incomplete surgical resection is defined by R1 (incomplete) resection status
12. Overall QoL will be measured using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) questionnaire
13. Recruitment rate is defined as the average monthly recruitment achieved during the last 6 months of the trial recruitment period

Previous secondary outcome measures:
1. Treatment compliance as a percentage of total planned doses of encorafenib and binimetinib received before and after surgery
2. Pre-operative radiological response measured using Response Evaluation Criteria In Solid Tumours (RECIST v1.1) at 8 weeks
3. Pathological overall response measured by pathological assessment of resected tumour specimens at surgery
4. Adverse drug reactions and surgical adverse events measured using the standard cancer National Cancer Institute (NCI) CTCAE v5.0 criteria every cycle during treatment, at surgery and 3 months after stopping treatment
5. Lymphoedema measured using serial limb circumference measurements pre-surgery and at 6 and 12 months after the date of surgery
6. Event-free and relapse-free survival measured through clinical assessments every cycle during treatment from randomisation to disease progression or recurrence
7. Distant-metastases-free-survival measured using Response Evaluation Criteria In Solid Tumours (RECIST v1.1) every 3 months from randomisation to development of documented distant metastatic disease outside the loco-regional site of the primary tumour or lymph node metastasis, or death
8. Overall survival assessed as the date of death from randomisation to death
9. Loco-regional recurrence rate measured using Response Evaluation Criteria In Solid Tumours (RECIST v1.1) every 3 months from randomisation to development of documented local disease development
10. Incomplete surgical resection defined by R1 (incomplete) resection status at surgery
11. Overall quality of life measured using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) questionnaire pre-surgery and post-surgery
12. Recruitment rate measured using the average monthly recruitment achieved during the last 6 months of the trial recruitment period

Completion date
28/02/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/05/2025:

1. Written informed consent to participate
2. Aged ≥18 years old
3. AJCC 8th edition stage III (B/C/D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma, based on histological/cytological and radiological assessments for which surgery is planned, and resection is expected to remove all known tumour(s) with R0 resection margins. 'Oligometastatic stage IV' is defined for the purpose of this trial as M stage disease confined to a single body organ excluding the brain that can be readily removed surgically with anticipated clear margins

4. For stage III patients, confirmation of no evidence of distant metastatic disease using preferred imaging modalities including CT body or PET/CT and CT or MRI head
5. For stage IV patients, confirmation of no evidence of unresectable metastatic disease, or metastatic disease in more than 1 body organ, using preferred imaging modalities including CT body or PET/CT and CT or MRI head. The site of metastasis should not be in bone, or CNS, or in any other body site where complete resection is not feasible
6. The planned resectable disease must be radiologically measurable using standard imaging modalities
7. Baseline tumour assessments must be done within 28 days prior to registration
8. BRAF V600 mutation confirmed by PCR or NGS
9. Received no prior BRAF or MEK inhibitors
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 3 – Karnofsky and ECOG Performance Status Scale)
11. Predicted life expectancy >12 months
12. Normal QTc interval (<480 msec) on ECG and left ventricular ejection fraction within normal limits, assessed by echocardiogram or MUGA
13. Adequate bone marrow function defined as:
13.1. Absolute neutrophil count (ANC) ≥1.5 x 10e9/l
13.2. Haemoglobin (Hb) ≥90 g/l
13.3. Platelets ≥100 x 10e9 /l
14. Adequate liver function defined as:
14.1. Aspartate aminotransferase (AST) and/or alanine transaminase (ALT) ≤2.5 x upper limit of normal range (ULN)
14.2. Total bilirubin <1.5 x ULN (except if the patient has Gilbert Syndrome or liver metastases, in which case the bilirubin must be <3 x ULN)
15. Adequate renal function defined as:
15.1. Serum creatinine ≤1.5 x ULN or
15.2. Calculated creatinine clearance by Cockcroft-Gault of ≥40 ml/min
16. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, completion of QoL and PROM questionnaires and other procedures described in the protocol
17. Women of child-bearing potential (WCBP) and all sexually active male patients must agree to use effective contraception methods throughout treatment as per section 11.10 of this protocol
18. Ability to swallow the trial medication
19. Confirmation of adequate diagnostic tumour tissue available for research studies (see laboratory manual to confirm minimum tissue requirements)

———

Previous inclusion criteria:

1. Written informed consent to participate
2. Aged ≥18 years old
3. AJCC 8th edition stage III (B/C/D), or extracranial oligometastatic stage IV BRAFV600 mutant melanoma, based on histological/cytological and radiological assessments for which surgery is planned, and resection is expected to remove all known tumour(s) with R0 resection margins. ‘Oligometastatic stage IV’ is defined for the purpose of this trial as M stage disease confined to a single body organ excluding the brain that can be readily removed surgically with anticipated clear margins
4. For stage III patients, confirmation of no evidence of distant metastatic disease using preferred imaging modalities including CT body or PET/CT and CT or MRI head
5. For stage IV patients, confirmation of no evidence of unresectable metastatic disease, or metastatic disease in more than 1 body organ, using preferred imaging modalities including CT

body or PET/CT and CT or MRI head. The site of metastasis should not be in bone, or CNS, or in any other body site where complete resection is not feasible
6. The planned resectable disease must be radiologically measurable using standard imaging modalities
7. Baseline tumour assessments must be done within 28 days prior to randomisation
8. BRAF V600 mutation confirmed by PCR or NGS
9. Received no prior BRAF or MEK inhibitors
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix 2 – Karnofsky and ECOG Performance Status Scale)
11. Predicted life expectancy >12 months
12. Normal QTc interval (<480 msec) on ECG and left ventricular ejection fraction within normal limits, assessed by echocardiogram or MUGA
13. Adequate bone marrow function defined as:
13.1. Absolute neutrophil count (ANC) ≥1.5 x 10e9/l
13.2. Haemoglobin (Hb) ≥90 g/l
13.3. Platelets ≥100 x 10e9 /l
14. Adequate liver function defined as:
14.1. Aspartate aminotransferase (AST) and/or alanine transaminase (ALT) ≤2.5 x upper limit of normal range (ULN)
14.2. Total bilirubin <1.5 x ULN (except if the patient has Gilbert Syndrome or liver metastases, in which case the bilirubin must be <3 x ULN)
15. Adequate renal function defined as:
15.1. Serum creatinine ≤1.5 x ULN or
15.2. Calculated creatinine clearance by Cockcroft-Gault of ≥40 ml/min
16. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, completion of QoL and PROM questionnaires and other procedures described in the protocol
17. Women of child-bearing potential (WCBP) and all sexually active male patients must agree to use effective contraception methods throughout treatment as per section 11.9 of this protocol
18. Be able to swallow the trial medication
19. Confirmation of adequate diagnostic tumour tissue available for research studies (see laboratory manual to confirm minimum tissue requirements)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 16/05/2025:

1. Prior adjuvant therapy for resected primary or locoregional melanoma
2. Other invasive malignancies diagnosed within the last 2 years which are not in complete remission, or for which additional therapy is required
3. Brain or bone metastases
4. Non-cutaneous primary site of melanoma
5. Prior radiotherapy to the site planned for surgery
6. History or current evidence of retinal vein occlusion (RVO) or risk factors for RVO (uncontrolled glaucoma, ocular hypertension, history of hyperviscosity, or hypercoagulability syndromes)
7. Left ventricular function < 50%
8. Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality which in the judgment of the investigator would place the patient at undue risk or interfere with the trial. Examples include, but are not limited to:
8.1. Patients with uncontrolled ischaemic heart or other cardiovascular event (myocardial infarction (MI), new angina, stroke transient ischaemic attack (TIA), or new congestive cardiac failure (CCF)) within the last 6 months
8.2. Uncontrolled hypertension
8.3. Patients with stable but significant cardiovascular disease defined by heart failure (New York Heart Association Functional Classification (NYHA) III or IV, see Appendix 4) or frequent angina
8.4. Patients with baseline QTC interval > 480 msec on electrocardiogram (ECG)
8.5. Left ventricular ejection fraction below the lower limit of normal
8.6. Presence of active infection
8.7. Cirrhotic liver disease, known chronic active or acute hepatitis B, or hepatitis C
9. Known allergy or hypersensitivity to Encorafenib or Binimetinib, or their excipients. Binimetinib contains lactose, so patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption will be excluded
10. Women who are pregnant, plan to become pregnant or are lactating during the trial period
11. Use of other investigational anti-cancer drugs (a washout period of 28 days would be required)
12. Use of strong inducers and inhibitors of CYP3A4 (Appendix 5 – Prohibited Medication)
13. Known HIV or active Hep B or Hep C infection
14. Patients who have neuromuscular disorders associated with elevated creatine phosphokinase (CK, e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
15. Autoimmune conditions requiring regular or intermittent use of any systemic steroid or immunosuppressive drugs, with the exception of steroid inhalers
16. Any immunotherapy in the last 3 months
17. Prior radiotherapy to the site of disease planned for resection
18. Concurrent participation in an interventional clinical trial (observational studies are allowed)

———

Previous exclusion criteria:

1. Prior adjuvant therapy for resected primary or locoregional melanoma
2. Other invasive malignancies diagnosed within the last 2 years which are not in complete remission, or for which additional therapy is required
3. Brain or bone metastases
4. Non-cutaneous primary site of melanoma
5. Prior radiotherapy to the site planned for surgery
6. History or current evidence of retinal vein occlusion (RVO) or risk factors for RVO

(uncontrolled glaucoma, ocular hypertension, history of hyperviscosity, or hypercoagulability syndromes)
7. Left ventricular function < 50%
8. Significant acute or chronic medical or psychiatric condition, disease or laboratory abnormality which in the judgment of the investigator would place the patient at undue risk or interfere with the trial. Examples include, but are not limited to:
8.1. Patients with uncontrolled ischaemic heart or other cardiovascular event (myocardial infarction (MI), new angina, stroke transient ischaemic attack (TIA), or new congestive cardiac failure (CCF)) within the last 6 months
8.2. Uncontrolled hypertension
8.3. Patients with stable but significant cardiovascular disease defined by heart failure (New York Heart Association Functional Classification (NYHF) III or IV, see Appendix 3) or frequent angina
8.4. Patients with baseline QTC interval > 480 msec on electrocardiogram (ECG)
8.5. Left ventricular ejection fraction below the lower limit of normal
8.6. Presence of active infection
8.7. Cirrhotic liver disease, known chronic active or acute hepatitis B, or hepatitis C
9. Known allergy or hypersensitivity to Encorafenib or Binimetinib, or their excipients. Binimetinib contains lactose, so patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption will be excluded
10. Women who are pregnant, plan to become pregnant or are lactating during the trial period
11. Use of other investigational anti-cancer drugs (a washout period of 28 days would be required)
12. Use of strong inducers and inhibitors of CYP3A4 (Appendix 4 – Prohibited Medication)
13. Known HIV or active Hep B or Hep C infection
14. Patients who have neuromuscular disorders associated with elevated creatine phosphokinase (CK, e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy)
15. Autoimmune conditions requiring regular or intermittent use of any systemic steroid or immunosuppressive drugs, with the exception of steroid inhalers
16. Any immunotherapy in the last 3 months
17. Prior radiotherapy to the site of disease planned for resection
18. Concurrent participation in an interventional clinical trial (observational studies allowed)

Date of first enrolment
27/02/2023

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

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

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

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

Study participating centre
South Eastern Health & Social Care
Top Floor
Thompson House Hospital
19/21 Magheralave Road
Belfast
United Kingdom
BT28 3BP

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

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

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Industry

Funder Name
Les Laboratories Pierre Fabre

Alternative Name(s)
Pierre Fabre Laboratories, Pierre Fabre, Pierre Fabre S.A., Pierre Fabre Group, Groupe Pierre Fabre

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
France

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

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?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes