Adjuvant encorafenib & binimetinib vs. placebo in fully resected stage IIB/C BRAF V600E/K mutated melanoma: a randomized triple-blind phase III study in collaboration with the EORTC Melanoma Group

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To characterize the safety and tolerability.1. To describe the available RFS data by treatment arm.2. To describe the available DMFS data by treatment arm.3. To describe-reported health-related quality of life (HRQoL) bytreatment arm.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52293

Source
ToetsingOnline

Brief title
W00090GE303 / EORTC-2139-MG (COLUMBUS-AD)

Condition

- Skin neoplasms malignant and unspecified

Synonym
Melanoma, skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Pierre Fabre
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Adjuvant, Binimetinib, Encorafenib, Phase III

Outcome measures

Primary outcome

•Severity of adverse events and SAEs on-study graded according to NCI CTCAE

Version 5.0

•Changes from baseline and worst value on-study for clinical safety laboratory

assessments, physical examinations, vital signs, ECGs, ECHO,

dermatological examinations, ophthalmic examinations and ECOG performance status

•Incidence of dose interruptions, dose modifications and discontinuation due to

AEs and incidence of AEs requiring additional therapy

Secondary outcome

1. Recurrence-free survival (RFS) RFS is defined as the time between the date

of randomization and the date of

1) first recurrence (local, regional, or a distant metastasis),

2) new melanoma that is known to be either ulcerated, thick (Breslow

thickness>1 mm) or requiring a treatment other than surgery or 3) death

(whatever the cause), whichever occurs first (i.e., the date of the earliest of

recurrence, ulcerated or thick or requiring a treatment other than surgery new

melanoma, and death minus the date of randomization plus one day). For

participants who remain alive and whose disease has not recurred, RFS will be censored on the date of last adequate disease assessment. RFS will be based on the disease assessment and date of
death provided by the local investigator. A distant metastasis of cutaneous melanoma will always be treated as an event in the RFS analysis, irrespective of the presence of a new melanoma.

2. Distant metastasis-free survival (DMFS) DMFS is defined as the time between the date of randomization and the date of first distant metastasis or date of death (whatever the cause), whichever occurs first (i.e., the date of distant metastasis for participants with a distant metastasis or the date of death for without a distant metastasis minus the date of randomization plus one day). For participants who remain alive and distant metastasis-free, DMFS will be censored on the date of last adequate disease assessment. DMFS will be based on the disease assessment and date of death provided by the local investigator. A distant metastasis of cutaneous melanoma will always be treated as an event in the DMFS analysis, irrespective of the presence of a new melanoma.

3.

• The change in the HRQoL from baseline over time and to the average of the scores during the treatment

• The change in the HRQoL from baseline for post treatment visits

Study description

Background summary

•Severity of adverse events and SAEs on-study graded according to NCI CTCAE Version 5.0
•Changes from baseline and worst value on-study for clinical safety laboratory assessments, physical examinations, vital signs, ECGs, ECHO, dermatological examinations, ophthalmic examinations and ECOG performance status
•Incidence of dose interruptions, dose modifications and discontinuation due to AEs and incidence of AEs requiring additional therapy

Study objective

To characterize the safety and tolerability.

1. To describe the available RFS data by treatment arm.
2. To describe the available DMFS data by treatment arm.
3. To describe-reported health-related quality of life (HRQoL) by treatment arm.

Study design

This is a randomized triple-blind placebo-controlled international multicenter phase III superiority clinical trial of encorafenib and binimetinib combination versus placebo in resected pT3b-4bN0 BRAF V600E/K melanoma participants.

Intervention

Subjects will be randomized 1:1 to receive either treatment with encorafenib and binimetinib or placebo. The treatment will consist of a combination of encorafenib 450 mg (6 capsules of 75 mg) once daily taken by mouth and binimetinib 45 mg (3 tablets of 15 mg) twice daily taken by mouth for 12 months or equivalent placebos for 12 months.

Study burden and risks

Participation into this phase III triple-blind clinical trial will give a burden to participants above the routine standard of care approach that is nowadays offered to these participants worldwide, which is currently simple sequential follow-up surveillance. The frequency of this surveillance in terms of amount of visits / intervals and if there is or not any imaging offered (and if so, the frequency of this surveillance imaging) differs greatly across countries and guidelines. Thus, participation into this trial might increase the burden for participants in terms of the amount of visits and imaging compared to the local / national guidelines for stage II melanoma. Moreover, participants will also need to have more blood drawn than in an active surveillance protocol. Of course, the largest burden and risk for participants is the chance to develop adverse events due to the encorafenib & binimetinib treatment in this trial. However, it is known from BRAF/MEK inhibition therapy

in advanced / metastatic melanoma and also from adjuvant therapy trials with BRAF or BRAF/MEK inhibition that, although the frequency of adverse events (including grade 3/4 adverse events) is relatively high, they usually resolve quickly if the treatment is withheld for a short period of time. The rate of treatment discontinuation that were suspected to be related to adverse events on the combination treatment was only 6%. Although one cannot simply extrapolate this rate to the adjuvant situation, where there is less incentive to persist through adverse events and continue treatment, we expect less treatment discontinuation on this specific BRAF/MEK inhibitor combination due to a better safety profile compared to others such as dabrafenib & trametinib (in the COMBI-AD trial, 26% of the participants discontinued the treatment due to AEs). Potential benefit for participants is the chance that, for those participants receiving encorafenib and binimetinib, the adjuvant therapy might improve relapse-free survival (RFS), but also the distant-metastasis-free survival (DMFS) and overall survival (OS). Considering the lack of other treatment options and the high risk of relapse for these participants with a pT3b-pT4bN0M0 melanoma, we believe the additional burden requested from participants who participate in this trial, in terms of extra assessments (blood, scans, visits) and potential adverse events is justified by the potential benefits of their participation as described above.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Molecular Pre-screening
1.Before any related study activity, written informed consent must be given according to ICH/GCP, and national/local regulations;
2.Male or female >= 18 years of age;
3.Surgically resected, with tumor free margins, and histologically/pathologically confirmed new diagnosis of stage II (pT3bpT4bN0) cutaneous melanoma per AJCC 8th edition;
4.Sentinel node (SN) staged node negative (pN0);
5.Sentinel node (SN) biopsy within 14 weeks from initial diagnosis of melanoma;
6.Available tumor sample for central determination of the BRAFV600E/K mutation. FFPE tumor tissue block or a minimum of 10 slides, optimally up to 20 slides.

Screening
1.Before any related study activity, written informed consent must be given according to ICH/GCP, and national/local regulations;
2.Presence of BRAF V600E/K mutation in tumor tissue as determined by a local assay any time prior to screening (if done routinely in clinical practice) and/or the central laboratory
i.If the participant is screened based on local assay result, the BRAF V600E/K mutation status must be confirmed by the central laboratory prior to randomization.
3.Participant still free of disease as evidenced by the required baseline imaging and physical/dermatological assessments performed respectively within 6 weeks and 2 weeks before the randomization (Day 1);
4.Randomization within 12 weeks from full surgical resection including sentinel lymph node biopsy (SLNB);
5.Recovered from definitive surgery (e.g. complete wound healing, no uncontrolled wound infections or indwelling drains);
6.ECOG performance status of 0 or 1;
7.Adequate haematological function:
i.Absolute neutrophil count (ANC) >= 1.5 x 1000000000/L
ii.Platelets >= 100 x 1000000000/L
iii.Hemoglobin >= 9.0 g/dL
8.Adequate renal function:
Serum creatinine <= 1.5 × ULN; or calculated creatinine clearance >= 50

mL/min by Cockcroft Gault formula;
9.Adequate electrolytes, defined as serum potassium and magnesium levels within institutional normal limits;
10.Adequate hepatic function:
i.Serum total bilirubin <= 1.5 x ULN and < 2 mg/dL
ii.Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) <= 2.5 x ULN
11.Adequate cardiac function:
i.Left ventricular ejection fraction (LVEF) >= 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram
ii.Mean triplicate QT interval corrected for heart rate according to Fridericia's formula (QTcF) value <= 480 msec and no history of QT syndrome
12.Adequate coagulation function, defined as INR <=1.5× ULN unless the patient is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range;
13.Negative serum β-HCG test (female patient of childbearing potential only) performed within 3 days prior to Day 1;
14.Participants of childbearing / reproductive potential should use adequate birth control measures (see Appendix 4, section 10.4.2):
Female participants are either postmenopausal for at least 1 year, surgically sterile for at least 6 weeks or must agree to take appropriate precautions to avoid pregnancy.
Male participants must agree to take appropriate precautions to avoid fathering a child.

Exclusion criteria

Molecular pre-screening
1.Unknown ulceration status;
2.Uveal and mucosal melanoma;
3.Clinically apparent metastases (N+/M1);
4.Microsatellites, satellites and/or in-transit metastases;
5.Local (scar) recurrences.
Screening
1.Breast feeding women;
2.Pregnancy;
3.History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO.
4.History of thromboembolic or cerebrovascular events <= 12 weeks prior to randomization;
i.Note 1: Thromboembolic or cerebrovascular events include stroke, transient ischemic attacks, cerebrovascular accidents, hemodynamically significant deep vein thrombosis, pulmonary emboli, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis;

ii.Note 2: Participants with thromboembolic events related to indwelling catheters or other procedures may be enrolled;
5.Previous or concurrent malignancy for the past 3 years. Except for non-melanoma skin cancer and any in situ cancer;
6.Any condition with a life expectancy of less than 5 years;
7.Participants with a prior cancer associated with RAS mutation;
8.Previous treatment for melanoma beyond complete surgical resection (any prior systemic anticancer therapy; prior radiotherapy);
9.Hypersensitivity to the study drugs or to any of the excipients;
10.Participants with severe lactose intolerance;
11.Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
i.History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) <= 6 months prior to randomization;
ii.Congestive heart failure requiring treatment (New York Heart Association Grade >= 2);
iii.Uncontrolled hypertension defined as persistent systolic blood pressure >= 150 mmHg or diastolic blood pressure >= 100 mmHg despite optimal therapy;
iv.Presence of clinically significant cardiac arrhythmias including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia (stable controlled atrial fibrillation or paroxysmal supraventricular tachycardia is accepted);
12.Neuromuscular disorders that are associated with CK > ULN;
13.Non-infectious pneumonitis and Interstitial Lung Disease;
14.Positive SARs-CoV-2 or variants of SARs-CoV2 RT-PCR test at screening or suspected to be infected with SARs-CoV2 or variants of SARsCoV2 with confirmation pending;
15.Participants with active bacterial, fungal, or viral infection, including, but not limited to: HBV, HCV, and known HIV or AIDS-related illness, or an infection requiring systemic therapeutic treatment within 2 weeks prior to randomization.
Note: Participants receiving prophylactic antibiotics are exceptions and may participate.
Note: Participants with a positive HBsAg (i.e., either acute or chronic active hepatitis) are excluded. Those with positive anti-HBcAb but negative HBsAg and anti-HBsAb profile may be eligible upon review and approval by the sponsor or designee.
Note: Participants with positive HCV antibody but undetectable HCV viral load may be eligible upon review and approval by the sponsor or designee.
Note: Participants with confirmed stable HIV disease may be eligible if they have viral load < 50 copies/mL and CD4 count > 200 cells/mm3, and on stable antiretroviral therapy for at least 6 months, provided that they meet all other study eligibility criteria. Testing for HIV is not mandated for study entry; however, testing must be performed at sites

where mandated locally following local clinical practice.;
16.Unable to ingest or digest tablets and capsules. This can be caused by any impaired gastrointestinal function or disease, such as for example: ulcerative diseases, malabsorption syndrome, small bowel resection, ileus, etc. Or any condition causing uncontrolled nausea, vomiting or diarrhea;
17.Presence of any psychological, familial, sociological or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule according to Investigators's judgement; those conditions should be assessed with the patient before randomization in the trial;
18.Participant is a family member of the investigator or any associate, colleague and employee assisting in the study conduct (secretary, nurse, technician) or is otherwise in a position likely to represent a conflict of interest, the participant is only eligible if the informed consent has been sought by an appropriately qualified individual who is completely independent of this relationship;
19.Participation in a clinical study with administration of an investigational product within 4 weeks or five times the half-life of the investigational product, whichever is longer, before the first dose of study treatment;
20.Participants who has forfeited his / her freedom by administrative or legal award or is under guardianship.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-11-2022

Enrollment:	31
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Braftovi
Generic name:	Encorafenib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mektovi
Generic name:	Binimetinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	21-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-02-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-004310-19-NL
ClinicalTrials.gov	NCT05270044
CCMO	NL77403.031.21

Study results

Date completed: 30-05-2024

Summary results
Trial ended prematurely