A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-Mutant Melanoma Brain Metastasis

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Primary ObjectiveSafety Lead-in* Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasisPhase 2If the high-dose regimen is...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Skin neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49456

Source
ToetsingOnline

Brief title
Array 818-201

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
Mutant Melanoma Brain Metastasis, skin cancer spread to the brain

Research involving
Human

Sponsors and support

Primary sponsor: Array Biopharma Inc.
Source(s) of monetary or material Support: Array Biopharma Inc.

Intervention

Keyword: BRAFV600, Brain, Melanoma, Metastasis

Outcome measures

Primary outcome

Primary Endpoint

Safety Lead-in

* Incidence of DLTs

* Incidence and severity of AEs graded according to the NCI CTCAE version 4.03

and changes in clinical laboratory parameters, vital signs, ECGs

* Incidence of dose interruptions, dose modifications and discontinuations due

to AEs

Phase 2

* BMRR per mRECIST v1.1

Secondary outcome

Secondary Endpoints

* Extracranial response rate per RECIST v1.1

* Global response rate (brain metastasis response per mRECIST v1.1 and

extracranial response per RECIST v1.1)

* DCR

o for brain metastasis response per mRECIST v1.1

o for extracranial response per RECIST v1.1

o for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1)

* DOR

o for brain metastasis response per mRECIST v1.1

o for extracranial response per RECIST v1.1

o for global response (brain metastasis per mRECIST v1.1 and extracranial per RECIST v1.1)

* PFS

o for brain metastasis per mRECIST v1.1

o for global assessment (brain metastasis per mRECIST v1.1 and extracranial disease per RECIST v1.1)

* BMRR per mRECIST v1.1 for Safety Lead-in only

* OS

* Incidence and severity of AEs graded according to the NCI CTCAE version 4.03 and changes in clinical laboratory parameters, vital signs, ECGs

* Plasma concentration-time profiles and PK parameter estimates for encorafenib and its metabolite LHY746, and binimetinib and its metabolite AR00426032.

Exploratory Endpoints

* BMRR per RANO-BM

* Genomic analysis of ctDNA in blood samples

Study description

Background summary

Treatment options for patients with melanoma brain metastasis are evolving. The most frequent genetic alteration in melanoma is the BRAFV600 mutation, which occurs in up to 50% of cases. Local therapy modalities offer control of a limited number of melanoma brain lesions, but do not control spread of metastatic brain lesions beyond the locally controlled lesions or extracranial disease.

Recent clinical studies continue to report responses to treatment with BRAF, MEK and checkpoint inhibitors in patients with melanoma brain metastasis. Despite recent clinical improvements for patients with BRAF-mutant melanoma brain metastasis, the brain continues as a prominent organ for metastatic progression after targeted or checkpoint therapy. Current melanoma treatments show efficacy for metastatic disease to the brain, but short durations of response and suboptimal safety profiles necessitate evaluation of a new regimen for BRAFV600 melanoma brain metastasis.

The previous COLUMBUS study demonstrated favorable efficacy and safety of combination encorafenib + binimetinib for patients with BRAFV600-mutant melanoma. Moreover, the blood-brain barrier can limit concentrations of anti-cancer agents at the target for treatment of brain metastases. For this reason, a higher dose of combination therapy may potentially demonstrate greater efficacy without compromising safety for patients with BRAFV600 melanoma brain metastasis.

Study objective

Primary Objective

Safety Lead-in
* Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis
Phase 2
If the high-dose regimen is determined to be safe based on the results of the Safety Lead-in phase, then
* Evaluate the antitumor activity in brain metastases of the standard and high-dose regimens of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis

If the high-dose regimen is determined not to be safe based on the results of the Safety Lead-in phase, then
* Evaluate the antitumor activity in brain metastases of the standard dosing regimen of encorafenib + binimetinib combination in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis

Secondary Objectives
* Further evaluate the antitumor activity of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis
* Evaluate the efficacy of encorafenib + binimetinib combination therapy as measured by OS in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis
* Further evaluate the safety profile of encorafenib + binimetinib combination therapy in patients with BRAFV600-mutant melanoma who have asymptomatic brain metastasis
* Characterize the PK of encorafenib and its metabolite LHY746 and binimetinib in the 2 dosing regimens (standard dose and high dose) and its metabolite AR00426032

Exploratory Objectives
* Assess brain metastasis response
* Assess blood ctDNA mutation status

Study design

The first 9 evaluable patients in the high-dose treatment will constitute the high-dose Safety Lead-in cohort.

If the high-dose treatment is determined to be safe, approximately 100 eligible patients will be randomized 1:1 (50 in each arm) to receive either the standarddose (Arm A) or the high-dose (Arm B) encorafenib + binimetinib combination. Randomization will be stratified by baseline tumor burden in the brain (1 to 2 brain lesions vs. * 3 brain lesions at baseline assessment) and by prior local therapy [e.g., stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), (yes vs. no)].

If the high-dose treatment is determined not to be safe in the Safety Lead-in, no patients will be enrolled into Arm B and up to 100 eligible patients will be enrolled into 2 cohorts in the standard-dose Arm A. Cohort 1: Up to 50 patients with BRAFV600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, and with prior local therapy (e.g., SRS or SRT). Cohort 2: Up to 50 patients with BRAFV600 cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy (e.g., SRS or SRT). Phase 2 enrollment will close when either Cohort 1 or 2 reaches 50 patients.

The Sponsor, in consultation with the Steering Committee, will perform a

comprehensive evaluation of safety, efficacy and PK data in the Safety Lead-in, as well as periodic safety evaluations during the conduct of the study.

Intervention

Patients in the standard-dose treatment arm will receive encorafenib 450 mg orally QD and binimetinib 45 mg orally BID in 28-day cycles.

Patients in the Safety Lead-in and the high-dose treatment arm will receive encorafenib 300 mg BID and binimetinib 45 mg BID in 28-day cycles.

Study burden and risks

The combination encorafenib + binimetinib is known to cause side effects.

Among patients receiving encorafenib, the most likely side effects of encorafenib (occurring in more than 1of subjects out of 10) include the following:
* Decreased appetite
* Diarrhea
* Difficulty sleeping
* Dry skin
* Feeling tired
* Fever
* Hair loss
* Headache
* Itching
* Muscle pain or joint pain
* Nausea
* Pain including pain the arms, legs and back
* Reddening, swelling, numbness and peeling on palms and soles (hand foot skin reaction)
* Skin rash including redness, itching, hives and raised areas of skin
* Small, rough bumps on the skin
* Thickening of external part of the skin
* Tingling, numbness or abnormal sensitivity to pain or touch and nerve pain
* Vomiting
* Weakness

Among patients receiving binimetinib, the most likely side effects of binimetinib (occurring in more than 1 of subjects out of 10) include the following:
* alteration of the light sensing part of the back of the eye that may affect your vision including blurred of impaired vision

* Fatigue
* rash, acne, or skin irritation such as redness, raised bumps, dryness, or itching
* Swelling in the abdomen, arms, legs, hands, feet, or face.
* Muscle spasms, muscle pain, or inflammation

Side effects in cancer patients treated with binimetinib used in combination with encorafenib may also include :

Most likely side effects (occurring in more than 20 out of 100 subjects):
* Alteration of the light sensing part of the back of the eye that may affect your vision
* Increase in a lab test result for creatine phosphokinase (an enzyme found in the blood) that may indicate muscle inflammation or damage.

Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuation.
Also the study procedures may be accompanied by risks and discomforts. In addition the study drug, the study procedures and the combination of these may lead to risks that are as yet unknown.

Despite recent advances in the treatment of BRAFV600-mutant melanoma brain metastasis, there is a unmet need for an effective treatment with a long duration of response. The sponsor feels that the side effects and the burden associated with participation are in proportion considering the positive effects that participation in the study might have on the patient's disease progression.

Contacts

Public
Array Biopharma Inc.

Cambridge park drive 100
Cambridge, MA 02140
US
Scientific
Array Biopharma Inc.

Cambridge park drive 100
Cambridge, MA 02140
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients must meet all the following criteria to be eligible for enrollment in the study:
1. Able to provide written informed consent. Adult patients under guardianship may participate if permitted by local regulations with the consent of their legally authorized guardian. All local regulations concerning patients under guardianship must be followed.
2. Age * 18 years at the time of informed consent.
3. Histologically confirmed diagnosis of cutaneous melanoma with metastases to the brain.
4. Presence of BRAFV600 mutation in tumor tissue previously determined by a local PCR or NGS-based assay at any time prior to Screening or by a central laboratory during Screening.
5. Patients are required to submit archival or fresh tissue and a blood sample prior to enrollment. Tissue samples will be used to determine BRAFV600-mutation status by central laboratory.
6. Must have at least 1 parenchymal brain lesion * 0.5 cm and * 4 cm, defined as an MRI contrast-enhancing lesion that may be accurately measured in at least 1 dimension.
Note: Measurable intracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.
7.Patients may have received the following prior therapies:
a.Safety Lead-in, Phase 2 Randomized , Phase 2 Arm A Cohort 1: May have received prior local therapy for brain metastases including but not restricted to brain surgery, whole brain radiotherapy (WBRT), stereotactic radiotherapy or stereotactic radiosurgery (e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local (brain) therapies or combinations of local therapies are allowed. For patients

receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For patients receiving local therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.
b.Phase 2 Arm A Cohort 2: Received no prior local therapy (e.g., brain surgery, craniotomy, SRS or SRT) for brain metastases.
c.All patients (Safety Lead-In and Phase 2): May have received prior immunotherapy.
d.All patients (Safety Lead-In and Phase 2): If receiving concomitant corticosteroids must be on a stable or decreasing dose (up to a total daily dose of 4 mg of dexamethasone or equivalent) for at least 2 weeks prior to first dose of study treatment.
8.An ECOG PS of 0 or 1 and Karnofsky score * 80
9. Adequate bone marrow, organ function and laboratory parameters:
a. ANC * 1.5 × 109/L;
b. Hemoglobin * 9 g/dL with or without transfusions;
c. Platelets * 100 × 109/L;
d. AST and ALT * 2.5 × ULN; in patients with liver metastases * 5 × ULN;
e. Total bilirubin * 1.5 × ULN; NOTE: Patients with documented Gilbert syndrome or hyperbilirubinemia due to non-hepatic cause (e.g., hemolysis, hematoma) may be enrolled following discussion and agreement with the SponsorMedical Monitor.
f. Serum creatinine * 1.5 × ULN; OR calculated creatinine clearance > 50 mL/min by Cockcroft-Gault formula; OR estimated glomerular filtration rate > 50 mL/min/1.73m2.
10. Female patients of childbearing potential must have a negative serum *-HCG test result.
11. Female patients of childbearing potential must agree to protocol-approved methods of contraception and to not donate ova from Screening until 30 days after the last dose of study drug.
12. Male patients must agree to use methods of contraception that are highly effective or acceptable and to not donate sperm from Screening until 90 days after the last dose of study drug.
13. The patient is deemed by the Investigator to have the initiative and means to comply with scheduled visits, treatment plan and study procedures.

Exclusion criteria

Patients meeting any of the following criteria are not eligible for enrollment in the study.
1.Patients with symptomatic brain metastasis (e.g., have neurologic symptoms related to brain metastases).
2.Prophylactic or preventive anti-epileptic therapy. Note: Anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a

preexisting condition and not related to brain metastasis is allowed.
3.Known hypersensitivity or contraindication to any component of study treatment or their excipients.
4. Inability to swallow and retain study treatment.
5. Uveal or mucosal melanoma.
6. History of or current leptomeningeal metastases.
7.Treatment with SRS or craniotomy within 14 days prior to start of study treatment, or treatment with whole-brain radiation within 28 days prior to study treatment. Patients who received local therapy should have complete recovery with no neurological sequelae.
8. Either of the following:
a. Radiation therapy to non-brain visceral metastasis within 2 weeks prior to start of study treatment;
b. Continuous or intermittent small-molecule therapeutics or investigational agents within 5 half-lives of the agent (or within 4 weeks prior to start of study treatment, when half-life is unknown).
9. Patients treated in the adjuvant setting with BRAF or MEK inhibitor(s) < 6 months prior to enrollment. Patients treated in the adjuvant setting with BRAF or MEK inhibitors * 12 months prior to enrollment are eligible. Patients who received BRAF or MEK inhibitors in the metastatic setting are excluded.
10. Is currently participating in a study and receiving an investigational agent; has received an investigational agent or used an investigational device within 14 days prior to start of study treatment.
11. Patients who have undergone major surgery (e.g. inpatient procedure with regional or general anesthesia) * 6 weeks prior to start of study treatment. For minor surgical procedures * 6 weeks prior to start of study treatment, consult the Sponsor Medical Monitor.
12. Patient has not recovered to * Grade 1 from toxic effects of prior therapy before starting study treatment. NOTE: Stable chronic conditions (* Grade 2) that are not expected to resolve (such as neuropathy, myalgia, alopecia, prior therapy-related endocrinopathies) are exceptions and patients with these may enroll.
13. Impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, the following:
a. History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) < 6 months prior to Screening;
b. Congestive heart failure requiring treatment (New York Heart Association Grade * 2);
c. An LVEF < 50% as determined by MUGA or ECHO;
d. Uncontrolled hypertension defined as persistent systolic blood pressure * 150 mmHg or diastolic blood pressure * 100 mmHg despite current therapy;
e. History or presence of clinically significant cardiac arrhythmias (including resting bradycardia, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
f. Triplicate average baseline QTcF interval * 480 msec.
14. Impairment of gastrointestinal function or disease which may significantly

alter the absorption of study treatment (e.g., active ulcerative disease; uncontrolled nausea, vomiting or diarrhea; malabsorption syndrome; small bowel resection).
15. Concurrent neuromuscular disorder that is associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
16. Known history of acute or chronic pancreatitis.
17. History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.
18. Use of herbal supplements, medications or foods that are moderate or strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 * 1 week prior to the start of study treatment.
19. History of a thromboembolic event < 12 weeks prior to starting study treatment. Examples of thromboembolic events include transient ischemia attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism. Catheter-related venous thrombosis is not considered a thromboembolic event for this trial even if < 12 weeks prior to starting study treatment.
20. Concurrent or previous other malignancy within 2 years of study entry, except curatively adequately treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen*s disease and Gleason 6 prostate cancer. Patients with a history of other curatively treated cancers must be reviewed by the Sponsor prior to entering the study.
21. Active infection requiring systemic therapy.
22. Known history of positive test for HIV or known AIDS. Testing for HIV must be performed at sites where mandated locally.
For more details please see the Protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Braftovi
Generic name:	Encorafenib - 450 mg
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Braftovi
Generic name:	Encorafenib - 600 mg
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mektovi
Generic name:	Binimetinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-05-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-06-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2018-004555-21-NL
ClinicalTrials.gov	NCT03911869
CCMO	NL69569.028.19

Study results

Results posted: 01-11-2022

Summary results
Trial never started

First publication
05-07-2022