# An Open-label Phase 1 Study to Evaluate Drug-Drug Interactions of Agents Co-Administered with Encorafenib and Binimetinib in Patients with BRAF V600-mutant Unresectable or Metastatic Melanoma or Other Advanced Solid Tumors

Published: 01-08-2019
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The main purpose of this study is to assess investigate the effect of encorafenib and binimetinib (the study drugs) on the activity of other common drugs and the effect of modafinil on the activity of encorafenib. The study will also look at the...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON55423

**Source**
ToetsingOnline

**Brief title**
Array 818-103

### Condition

- Other condition
- Malignant and unspecified neoplasms gastrointestinal NEC
- Skin neoplasms malignant and unspecified

**Synonym**
skincancer and advanced solid tumors

**Health condition**

Melanoma, Colorectal cancers, Biliary tract tumors, Non-small cell lung cancers, Glioblastoma, Papillary thyroid cancer, Multiple myeloma.

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Array BioPharma Inc. (a wholly ownd subsidairy of Pfizer Inc.)
**Source(s) of monetary or material Support:** sponsor

## Intervention

**Keyword:** BRAF V600-mutant, Drug-Drug Interactions, Melanoma, Solid Tumors

## Outcome measures

**Primary outcome**

Primary Endpoint

• Changes in plasma maximum concentration (Cmax) and area under the concentration time curve from time zero to the time of last quantifiable concentration (AUClast): midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxy omeprazole, rosuvastatin, bupropion and hydroxybupropion.

• Changes in the amount eliminated via urine over an 8-hour period (Ae0-8): losartan and its metabolite (E 3174), dextromethorphan and dextrorphan

• Changes in plasma encorafenib and LHY746 Cmax and area under the concentration time curve over the dosing interval (AUC) in Arm 3.

**Secondary outcome**

Secondary Endpoints

• Metabolite ratios (MRAUC and MRCmax) for 1-OH midazolam/midazolam,

paraxanthine/caffeine, 5-hydroxy omeprazole/omeprazole, hydroxybupropion/bupropion and LHY746/encorafenib and MRAe0-8 for E 3174/losartan and dextrorphan/dextomethorphan.

• Pharmacokinetic parameters (e.g., time to reach Cmax [Tmax], AUC from time zero extrapolated to infinity [AUCinf], percent of AUC extrapolated [AUC%extrap], apparent terminal elimination rate constant [Kel], apparent T1/2, apparent total body clearance after extravascular administration [CL/F] and apparent total volume of distribution after extravascular administration [Vz/F]) where calculable, for midazolam, 1-OH midazolam, caffeine, paraxanthine, omeprazole, 5-hydroxyomeprazole, rosuvastatin, bupropion and hydroxybupropion.

• Pharmacokinetic parameters (e.g., urine concentration [Curine], quantity of urine excreted during each collection interval [Vol], cumulative amount excreted in urine during each collection interval [CumAe], and percentage of dose recovered in urine [Fe %]) for losartan, E-3174, dextromethorphan and dextrorphan.

• Pharmacokinetic parameters (e.g., Cmax, AUClast, Tmax, AUCinf, AUC%extrap, Kel, T1/2, CL/F, and Vz/F) for encorafenib, LHY746, binimetinib and AR00426032 where calculable.

• Safety will be evaluated by monitoring AEs, physical examinations, ophthalmic examinations, vital sign measurements, 12 lead ECGs, echocardiogram (ECHO)/multigated acquisition scan (MUGA), and clinical laboratory tests.

Exploratory Endpoints

• Assessment of correlations between PK parameter estimates and genotype for

drug metabolizing enzymes such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A,

CYP2B6 and OATP1B1.

# Study description

**Background summary**

The body is built of bricks of cells and the way of how the bricks are build is decided by the information that is stored in our genes (DNA). If unwanted changes (mutations) occur in those genes there may be issues with the construction of the cells and how they work within the body. The changes in the BRAF gene that is studied in this trial cause overactivation of the BRAF gene which results in excessive cell growth. Increasing numbers of patients are identified that have a cancer type with such a mutation of the BRAF gene. Especially this mutation is found in patients with melanoma which increases the need for suitable treatments.

Previous study results suggest that a combination of the study drugs is an effective treatment.

Preclinical and clinical data suggest that the combination of a BRAF inhibitor and a MEK inhibitor may be more effective than BRAF inhibitor monotherapy in patients with BRAF mutant cancer. By simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK signaling pathway, the combination of encorafenib and binimetinib may possibly improve the duration of response and delay the emergence of resistance to single-agent treatment in patients with BRAF V600-mutant unresectable or metastatic melanoma or other advanced solid tumors.

This study is being conducted in patients with BRAF-mutant advanced solid tumors rather than in healthy volunteers due to its repeat-dose administration design and the risk of carcinogenicity (secondary neoplasm) with selective BRAF inhibitors

The study will be conducted in 3 arms to mitigate any unknown interaction between the substrates and inducer.

**Study objective**

The main purpose of this study is to assess investigate the effect of

encorafenib and binimetinib (the study drugs) on the activity of other common drugs and the effect of modafinil on the activity of encorafenib. The study will also look at the safety and how you tolerate the study drugs when administered with the other common drugs.

**Study design**

This is an open-label, 3-arm, fixed-sequence study. Enrollment to Arms 1 and 2 will occur in parallel. Patients will be assigned in an alternating fashion to Arm 1 or 2, where eligible, as assigned by the study team management. Once enrollment to Arms 1 and 2 is completed, enrollment in Arm 3 (modafinil arm) may begin.

The study will have 2 treatment phases, a DDI phase followed by a post DDI phase for each study arm.

DDI Phase:
Arm 1
Twenty patients will be enrolled into Arm 1 (CYP probe cocktail arm). Patients will receive a single oral dose of the CYP probe cocktail (losartan, dextromethorphan, caffeine, omeprazole, and midazolam) on Day -7. Encorafenib, administered once daily (QD) and binimetinib, administered twice daily (BID) will be initiated on Day 1. Patients will then receive a single oral dose of the CYP probe cocktail on Day 1 and Day 14. Blood and urine PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14.

Arm 2
Ten patients will receive a single oral dose of rosuvastatin and bupropion on Day -7. Encorafenib, administered QD and binimetinib, administered BID will be initiated on Day 1. Patients will then receive a single oral dose of rosuvastatin and bupropion on Day 1 and Day 14. Blood PK sampling will be conducted from 0 to 8 hours on Day -7, Day 1 and Day 14.

Arm 3
Six to 12 patients will inititate continuous treatment with encorafenib QD and binimetinib BID on Day 1. Patients will then receive continuous treatment of modafinil QD on Day 15 through Day 21. Blood PK sampling will be conducted from 0 to 8 hours on Day 14 and Day 21.
PK data will be analysed after the first 6 patients to look for an indication that the moderate inducer is having a significant effect on encorafenib PK. If there is a >= 20% change in geometric mean encorafenib AUC then an additional 6 patients will be enrolled to more fully characterize the effect.

All Arms
Patients who discontinue or require a dose reduction of study drug(s) prior to the final sample collection on Day 14 in Arms 1 and 2 or prior to Day 21 in Arm 3 will be considered to be unevaluable for PK analyses and replaced. If a

patient misses 3 or more consecutive doses of encorafenib and binimetinib in any arm or 3 or more doses of modafinil in Arm 3 during the DDI phase due to noncompliance, the patient may remain on treatment but may be replaced if limited data are available from the patient. In addition, patients who miss any dose of study drugs on any of the PK days, or who vomit within 4 hours after dosing on any of the PK days, may be replaced but may remain on treatment.

Safety Analysis
DDI Phase (through Day 28)
All safety data will be recorded in the patient*s source documents and electronic case report forms (eCRFs). Adverse events including serious adverse events (SAEs), laboratory profiles (hematology, biochemistry, coagulation, cardiac/muscle enzymes, urinalysis), physical examination (including vital signs, ophthalmic and dermatological examinations), Eastern Cooperative Oncology Group (ECOG) performance status (PS) assessment, and cardiac profiles (ECG and MUGA or ECHO), concomitant medications and/or therapies will be recorded.
Post DDI Phase:
If a patient chooses to not continue in the post-DDI phase, the Day 30 Safety Follow-up Visit assessments will still be performed.
During the post-DDI phase patients may continue to receive encorafenib/binimetinib combination until disease progression, unacceptable toxicity, withdrawal of consent, pregnancy, significant protocol deviation, lost to follow up, investigator decision, death, or study termination by Sponsor.
It is recommended that safety evaluations occur every 3 to 4 weeks, unless otherwise specified. Safety should be monitored by assessing physical examination, hematology and chemistry laboratory testing and any other pertinent testing required as part of the safety profile of the compound (dermatological examinations, ophthalmic exams, cardiac profiles) until discontinuation. Adverse events will be collected at every visit. Investigators will be required to record all Grade 3 or 4 AEs. All SAEs are to be reported to the Sponsor or designee using the SAE form.
Although this study does not formally assess efficacy, efficacy assessment are required every 8--12 weeks in order for the Investigator to assess continued benefit.

**Intervention**

Treatments are described as follows:

Encorafenib/binimetinib (continuous daily dosing starting on Day 1 for all arms):
450 mg (6 x 75 mg) encorafenib oral capsules QD
45 mg (3 x 15 mg) binimetinib oral tablet BID

CYP Probe Cocktail (once on Day -7, Day 1 and Day 14 for Arm 1 only) taken in

the following order:
25 mg losartan oral tablet
30 mg dextromethorphan oral capsule
100 mg caffeine 20 mg/mL oral liquid
20 mg omeprazole oral capsule
2 mg midazolam 2 mg/mL oral syrup

Rosuvastatin and bupropion (once on Day -7, Day 1 and Day 14 for Arm 2 only):
10 mg rosuvastatin oral tablet
75 mg bupropion immediate release (IR) oral tablet

Modafinil (continuous daily dosing starting on Day 15 through Day 21 for Arm 3 only):
400 mg (2 × 200 mg) modafinil tablet QD

For each arm, all drugs will be taken within 10 minutes total time.

**Study burden and risks**

Side effects in patients with cancer treated with encorafenib may include those described below.

Most likely side effects (in more than 1 out of 5 patients):
• Reddening, swelling, numbness and peeling on palms and soles (hand foot skin reaction)
• Skin rash including redness, itching and raised areas of skin
• Thickening of external part of the skin
• Dry skin
• Nausea
• Feeling tired
• Muscle pain or joint pain
• Hair loss
• Headache
• Itching

Side effects in patients with cancer treated with binimetinib may include those described below

Most likely side effects (more than 1 out of 5 patients):
• Alteration of the light sensing part of the back of the eye that may affect your vision including blurred or impaired vision
• Feeling weak, tired, or lacking in energy
• Rash, acne or skin irritation including redness, raised bumps, dryness or itching•
• Swelling due to fluid retention or a worsening of pre-existing fluid retention in specific areas of the body. This can occur throughout your body or in specific areas such as your abdomen, or arms, legs, hands, feet, face or

eyes.

More side affects on the study drugs and other treatments can be found in the study documents in this dossier (ICF, IB).

Drawing blood may be painful or cause some bruising.
The test results might have unexpected findings and/or unwanted outcomes.
Subjects are not allowed to become pregnant/father a child and will have dietary/behavioural (smoking/drugs/alcohol) restrictions.

Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or discontinuation.

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. (a wholly ownd subsidairy of Pfizer Inc.)

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New York 10017
US
**Scientific**
Array BioPharma Inc. (a wholly ownd subsidairy of Pfizer Inc.)

235 East 42nd Street -
New York 10017
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Signed written informed consent;
2. Male or female patient, age >= 18 years;
3. Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma American Joint Committee on Cancer (AJCC) Stage IIIB, IIIC or IV; or other BRAF V600-mutant advanced solid tumors;
4. Presence of BRAF V600E and/or V600K mutation in tumor tissue prior to enrollment, as determined using a local test;
5. Evidence of measurable or non-measurable lesions as detected by radiological or photographic methods according to guidelines based onResponse Evaluation Criteria in Solid Tumors (RECIST) v. 1.1;
6. Patient with unresectable locally advanced or metastatic melanoma who has progressed on standard therapy and for whom no additional standard therapies are available.
Note: Prior therapy with a BRAF inhibitor (e.g., vemurafenib, dabrafenib, encorafenib and XL281/BMS-908662) and/or a MEK inhibitor (e.g., trametinib, binimetinib, selumetinib, cobimetinib and refametinib) is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required;
7. Patient with other (non-melanoma) BRAF V600E and/or V600K -mutant advanced solid tumors who has progressed on standard therapy or for whom there are no available standard therapies
Note: Prior therapy with a BRAF inhibitor and/or a MEK inhibitor is permitted except in the regimen immediately prior to study entry. Progression during prior BRAF/MEK inhibitor treatment is not required; if it occurred, the patient*s circumstances (e.g., >= 1 year since prior BRAF and/or MEK inhibitor, equivocal progression, refractory to available therapies) must be discussed with the Sponsor prior to enrollment;
8. ECOG PS of 0 or 1;
9. Adequate bone marrow, organ function and laboratory parameters:
a. Absolute neutrophil count (ANC) >= 1.5 x 109/L,
b. Hemoglobin (Hgb) >= 9 g/dL without transfusions,
c. Platelets (PLT) >= 100 x 109/L without transfusions,
d. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) <= 2.5 × upper limit of normal (ULN); patient with liver metastases <= 5 ×ULN,
e. Total bilirubin <= 2 × ULN,
f. Creatinine <= 1.5 mg/dL, or calculated creatinine clearance (determined as

per Cockcroft-Gault) >= 50 mL/min;
10. Able to take oral medications;
11. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up);
12. Negative serum beta-human chorionic gonadotropin (β-HCG) test (female patient of childbearing potential only) performed within 72 hours prior to first dose and consent to ongoing urine pregnancy testing during the course of the study;
13. Male patients and female patients of childbearing potential must agree to use an acceptable method of contraception as defined in the study protocol;
ARM 1 ONLY:
1. Non-smoker who has not used nicotine containing products for at least 3 months prior to the first dose.

## Exclusion criteria

1. Symptomatic brain metastasis. Patients previously treated or untreated for these conditions who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. ;
2. History of reaction to any of the study medications in the arm the patient is enrolled in this trial;
3. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any herbal medications/supplements or any medications or foods that are moderate or strong inhibitors or inducers of CYP3A4/5;
4. Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting from Day -14 and through the DDI phase (Day 28), due to potential CYP3A4 interaction with the study drugs. Orange juice is allowed;
5. Symptomatic or untreated leptomeningeal disease;
6. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes);
7. Clinically significant cardiac disease including any of the following:
a. Congestive heart failure requiring treatment (New York Heart Association Grade >= 2)
b. Left ventricular ejection fraction (LVEF) < 50% as determined by MUGA or ECHO
c. Uncontrolled hypertension defined as persistent systolic blood pressure >= 150 mmHg or diastolic blood pressure >= 100 mmHg despite current therapy
d. History or presence of clinically significant ventricular arrhythmiasor atrial fibrillation
e. Clinically significant resting bradycardia
f. Unstable angina pectoris <= 3 months prior to start of study drug
g. Acute myocardial infarction <= 3 months prior to start of study drug

h. QT interval corrected for heart rate using the Fridericia formula (QTcF) > 480 msec at screening;
8. Impaired hepatic function as defined by Child-Pugh class B or C;
9. Impaired gastrointestinal function or disease which may significantly alter the absorption of study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection);
10. Known hyper-coagulability risks other than malignancy (e.g., Factor V Leiden syndrome);
11. Thromboembolic event (e.g. including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli) except catheter-related venous thrombosis <= 12 weeks prior to starting study treatment. Note: Patients with catheter-related thromboembolic events are allowed;
12. Any of the following:
a. Nitrosourea or mitomycin-C within 6 weeks prior to start of study drug
b. Other chemotherapy, radiation therapy that included > 30% of the bone marrow reserve, or biological therapy (e.g., antibodies) within 4 weeks prior to start of study drug
c. 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 drug, when half-life is unknown)
d. Residual Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 side effects of any such therapy (residual Grade 2 alopecia is permitted);
13. Discontinuation of prior BRAF and/or MEK inhibitor treatment due to left ventricular dysfunction, pneumonitis/interstitial lung disease, or retinal vein occlusion;
14. Known positive serology for human immunodeficiency virus (HIV) infection, active hepatitis B and/or active hepatitis C infection;
15. History of Gilbert*s syndrome;
16. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgement of the Investigator, would make the patient inappropriate for the study;
17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive β-hCG laboratory test (> 5 mIU/mL).
ARM 1 ONLY:
1. Positive urine cotinine test at screening;
2. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4, CYP2C9, CYP1A2, or CYP2C19 and any substrates or inhibitors CYP2D6.
ARM 2 ONLY:
1. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP2B6 or any substrates or inhibitors of BCRP, OATP1B1 or OATP1B3.

ARM 3 ONLY:
1. History of psychosis, depression or mania;
2. History of angioedema;
3. History of mitral valve prolapse;
4. History of left ventricular hypertrophy;
5. Use, within 2 weeks prior to the start of encorafenib/binimetinib treatment on Day 1 and through DDI phase (Day 28), of any substrates, inhibitors or inducers of CYP3A4.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 03-11-2020 |
| Enrollment: | 10 |
| 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: | Caffeine |
| Generic name: | Caffeine |
| Registration: | Yes - NL outside intended use |

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Losartan |
| Generic name: | Losartan |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Mektovi |
| Generic name: | Binimetinib |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | Robitussin |
| Generic name: | Dextromethorphan |
| Registration: | Yes - NL outside intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 01-08-2019 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 25-03-2020 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 19-11-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 26-01-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 24-04-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |

| | |
|---|---|
| Approved WMO Date: | 27-05-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 02-06-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 08-06-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 22-11-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 24-11-2021 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 12-08-2022 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 30-08-2022 |
| 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 | EUCTR2019-001036-66-NL |
| ClinicalTrials.gov | NCT03864042 |
| CCMO | NL69465.041.19 |

# Study results

Date completed: 05-01-2021

Results posted: 11-01-2024

**First publication**
27-03-2023