Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Encorafenib and binimetinib in combination

Protocol Number: C4221006 (ARRAY-818-201)

Dates of Study: 07 May 2019 to 27 January 2022

Title of this Study: A Study Comparing Combination of Encorafenib + Binimetinib as a Standard-dose and a High-dose Regimen in Patients with BRAFV600-Mutant Melanoma Brain Metastasis

[A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With *BRAF*V600-Mutant Melanoma Brain Metastasis]

Date(s) of this Report: 24 October 2022

– Thank You –

If you participated in this study, Pfizer, the Sponsor, would like to thank you for your participation.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is Metastatic melanoma?

Metastatic melanoma is a form of cancer that starts in the skin and spreads to other areas of the body. Metastatic melanoma has a high risk of spreading to the central nervous system (the brain and spinal cord). Participants in this study had *BRAF*V600-mutant melanoma with asymptomatic brain metastasis. This means that the melanoma had spread to the participant's brain but they were not showing any brain-related symptoms. The participant's cancer had also been found by their doctor to have a change (mutation) in a gene called *BRAF*V600.

What are encorafenib and binimetinib?

This study tested 2 treatments: encorafenib (en-koe-raf-e-nib) and binimetinib (bin-i-me-ti-nib). These treatments were given together so the study medication is referred to as "encorafenib + binimetinib combination treatment".

Encorafenib and binimetinib are both cancer growth blockers. They work by targeting certain proteins that help cancer cells grow. By blocking these proteins, this combination treatment may help to stop or slow down the growth of cancer cells.

Encorafenib and binimetinib are both taken by mouth. Two different dose combinations were tested in this study:

- High dose treatment: Encorafenib 300 milligrams (mg) twice a day in combination with binimetinib 45 mg twice a day.
- Standard dose treatment: Encorafenib 450 mg once a day in combination with binimetinib 45 mg twice a day.
    - After 4 weeks of treatment, participants who tolerated the standard dose (did not have unacceptable medical problems) could have the dose increased to encorafenib 600 mg once a day in combination with binimetinib 45 mg twice a day.

In this study, encorafenib + binimetinib combination treatment is an investigational treatment which means that it has not been approved for use in patients with *BRAF*V600-mutant melanoma with brain metastasis.

The standard dose combination treatment (encorafenib 450 mg once a day + binimetinib 45 mg twice a day) has already been approved by the United States Food and Drug Administration, the European Medicines Agency, and several other regions for the treatment of patients with unresectable (cannot be removed with surgery) or metastatic melanoma that has a *BRAF*V600 mutation, but not for the treatment of *BRAF*V600-mutant melanoma with brain metastases. The approved standard dose combination treatment does not include the dose increase option (encorafenib 600 mg once a day in combination with binimetinib 45 mg twice a day) which is being tested in this study.

What was the purpose of this study?

This study was divided into 2 parts, or "phases". The main purpose of the Safety Lead-in phase ("Part 1") was to learn about the safety of the high dose encorafenib + binimetinib combination treatment. The main purpose of Phase 2 ("Part 2") was to learn whether encorafenib + binimetinib combination treatment had positive effects in shrinking tumors for participants with mutant melanoma brain metastasis.

Researchers wanted to know:

What medical problems did participants have?

In Part 1, did participants have any "dose-limiting toxicities"?

In Part 1, did participants have medical problems leading to dose changes or stopping study treatment?

In Part 2, how many participants had a reduction in tumor size for brain metastasis?

"Dose-limiting toxicities" (DLTs) are certain medical problems caused by taking study treatment which require the participant to lower the dose or stop taking the treatment (permanently or temporarily). Researchers collect information on DLTs to help determine the recommended dose of a study treatment.

What happened during the study?

How was the study done?

Part 1

During Part 1, all participants received the high dose combination treatment as follows:

- Encorafenib 300 mg twice a day by mouth and binimetinib 45 mg twice a day by mouth, given in 28-day treatment cycles.

Part 2

Two treatment options were possible for Part 2. The researchers planned to choose the best option after reviewing the results of Part 1.

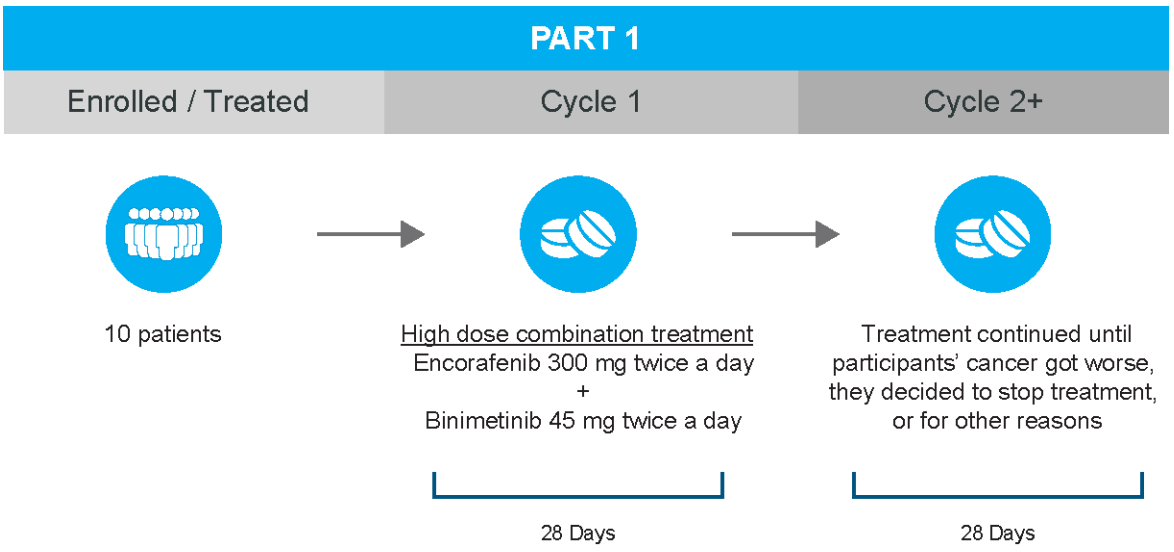
The first option had 2 treatment groups for the encorafenib + binimetinib combination treatment: (1) a high dose group and (2) a standard dose group. The second option had only 1 treatment group, with all participants assigned to receive the standard dose encorafenib + binimetinib combination treatment (with a dose increase option after 4 weeks of treatment). Based on the results of Part 1, the researchers chose the second option for Part 2.

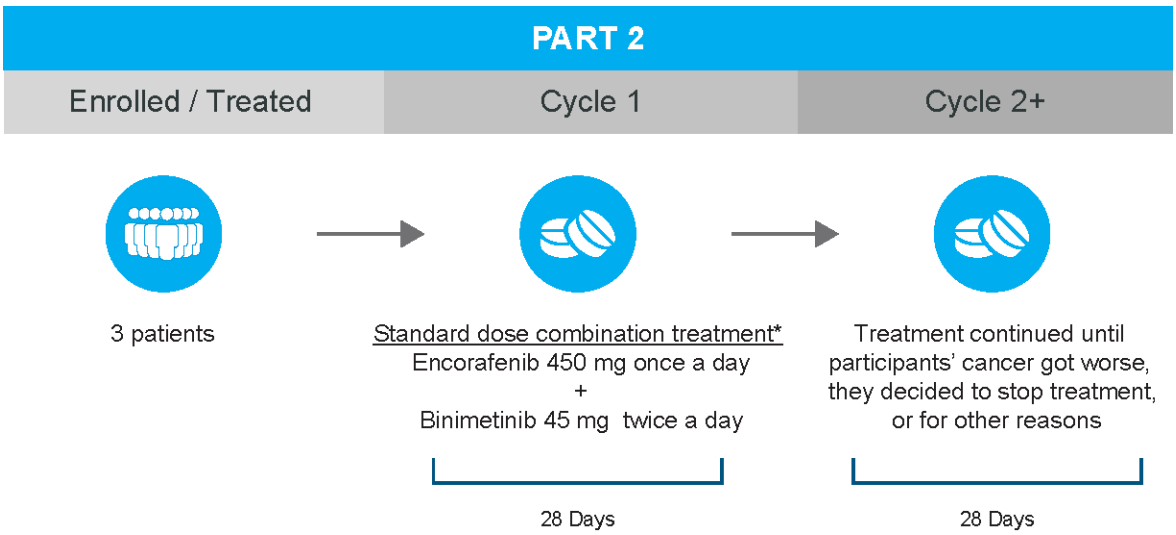
During Part 2, all participants received the standard dose combination treatment as follows:

- Encorafenib 450 mg once a day by mouth and binimetinib 45 mg twice a day by mouth, given in 28-day treatment cycles.

- Participants who tolerated the standard dose during the first 4 weeks of treatment (Cycle 1) could have the dose increased to encorafenib 600 mg once a day and binimetinib 45 mg twice a day.

This study was an open-label study, which means that participants and doctors knew what treatments were given to participants. The figures below show what happened during Part 1 and Part 2 of the study.





* Patients who tolerated the standard dose combination during the first 4 weeks of treatment (Cycle 1) could have the dose increased to encorafenib 600 mg once a day + binimetinib 45 mg twice a day.

In both Part 1 and Part 2 of the study, participants received study treatment in cycles that lasted 28 days. Participants were to attend visits at the study center on Days 1 and 15 of Cycle 1, on Day 1 of Cycle 2, and on Days 1 and 15 of the following cycles. They were also asked to attend an end of treatment visit within 1 week of stopping study treatment. A follow-up visit was done 30 days after stopping treatment. Participants were then contacted by phone every 12 weeks until the study ended.

Where did this study take place?

The Sponsor ran this study at 10 locations in 5 countries (Argentina, Australia, Belgium, Italy, and the United States).

When did this study take place?

It began 07 May 2019 and ended 27 January 2022.

Who participated in this study?

The study included participants who were at least 18 years old. They must have been diagnosed with metastatic melanoma with a *BRAF*V600 mutation and with asymptomatic brain metastases.

- A total of 10 men participated
- A total of 3 women participated
- All participants were between the ages of 39 and 83

In Part 1 of the study, 10 participants received the high dose combination treatment. In Part 2 of the study, 3 participants received the standard dose combination treatment. During Part 2 of the study, 2 out of 3 participants tolerated the standard dose combination treatment and had their dose increased from encorafenib 450 mg once a day to encorafenib 600 mg once a day (both treatments in combination with binimetinib 45 mg twice a day).

Participants were to be treated until their cancer got worse, they experienced unacceptable medical problems, they left the study, they started new anticancer treatment, the participant died, or the study ended.

Of the 13 participants who started the study, all 13 participants stopped taking the study treatment. The most common reason for participants stopping study treatment was because their cancer got worse. All 13 participants stopped being in the study because they:

- Passed away: 10 (77%) participants
- The Sponsor stopped the study: 2 (15%) participants
- Started a new treatment: 1 (8%) participant

How long did the study last?

The entire study took about 2 years and 9 months to complete.

The study was stopped early during Part 2. About 110 participants were planned to be enrolled but due to the lack of new participants joining the study, enrollment in Part 2 was closed in June 2021. Participants that were actively receiving treatment at that time were allowed to continue in the study until they met one of the factors for stopping treatment.

When the study ended in January 2022, the Sponsor reviewed the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

In Part 1, did participants have any "dose-limiting toxicities"?

- In Part 1, 9 out of 10 participants taking high dose encorafenib + binimetinib combination treatment were assessed for DLTs during their first treatment cycle (Cycle 1). One (1) participant was excluded from the assessment because they did not take the study treatment as instructed by the study doctor.
- 3 out of 9 participants (33%) had DLTs:
    - 1 participant had diarrhea
    - 1 participant had nausea (feeling like about to vomit), stomach pain, decreased appetite, and feeling very tired
    - 1 participant had fever and increased liver enzyme levels (ALT and AST)

Using this information, the researchers decided the correct dose to use during Part 2 of the study was the standard dose encorafenib + binimetinib combination treatment (with the dose increase option after 4 weeks of treatment).

In Part 1, did participants have medical problems leading to dose changes or stopping the study treatment?

- 4 out of 10 participants (40%) in Part 1 had medical problems leading to a lowering of the dose for both encorafenib and binimetinib.
- 6 out of 10 participants (60%) in Part 1 had medical problems leading to stopping study treatment temporarily for both encorafenib and binimetinib.
- 1 out of 10 participants (10%) in Part 1 had medical problems leading to stopping study treatment permanently for both encorafenib and binimetinib.

Medical problems are discussed in full in the next section of this document.

In Part 2, how many participants had a reduction in tumor size for brain metastasis?

To answer this question, the researchers looked at the percentage of participants with either a complete response to study treatment (all brain tumors disappeared), or a partial response to study treatment (at least a 30% decrease in brain tumor size).

Only Part 2 participants were planned for this assessment but due to the small number of participants joining Part 2 of the study, the researchers also assessed reduction of tumor size in the Part 1 participants.

- Out of 10 participants in Part 1, 1 participant (10%) had a complete response, and 5 participants (50%) had a partial response to study treatment.
- Out of 3 participants in Part 2, no participants (0%) had a complete response, and 2 participants (67%) had a partial response to study treatment.

This does not mean that everyone in this study had these results.

This is a summary of just some of the main results of this study.

There are many other ongoing and completed studies for encorafenib and binimetinib. Other studies with encorafenib + binimetinib combination treatment may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was

taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

All 13 participants (100%) in this study had at least 1 medical problem. This included all 10 participants in Part 1 and all 3 participants in Part 2. One (1) participant (8%) left the study because of medical problems (decreased appetite, dehydration, and feeling very tired); this happened during Part 1. The most common medical problems – those reported by at least 10% of participants in either Part 1 or Part 2 of the study – are described in the table on the next page.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by at least 10% of participants in either Part 1 or Part 2 are listed.
- The **2nd** column tells how many of the 10 participants taking the high dose encorafenib + binimetinib combination treatment during Part 1 reported each medical problem. Next to this number is the percentage of the 10 participants taking the high dose combination treatment who reported the medical problem.
- The **3rd** column tells how many of the 3 participants taking the standard dose encorafenib + binimetinib combination treatment during Part 2 reported each medical problem. Next to this number is the percentage of the 3 participants taking the standard dose combination treatment who reported the medical problem.
- Using these instructions, you can see that 6 out of the 10 participants (60%) taking the high dose combination treatment in Part 1 reported feeling very tired. One (1) out of the 3 participants (33%) taking the

standard dose combination treatment in Part 2 reported feeling very tired.

Table 1. Commonly reported medical problems by at least 10% of study participants in Part 1 or Part 2 of the study

Medical problem	Part 1: High dose encorafenib + binimetinib combination treatment (10 Participants)	Part 2: Standard dose encorafenib + binimetinib combination treatment (3 Participants)
Feeling very tired	6 out of 10 participants (60%)	1 out of 3 participants (33%)
Increased liver enzyme (ALT)	5 out of 10 participants (50%)	2 out of 3 participants (67%)
Diarrhea	5 out of 10 participants (50%)	2 out of 3 participants (67%)
Nausea (feeling like about to vomit)	5 out of 10 participants (50%)	2 out of 3 participants (67%)
Stomach pain	5 out of 10 participants (50%)	1 out of 3 participants (33%)
Increased liver enzyme (AST)	3 out of 10 participants (30%)	2 out of 3 participants (67%)
Being sick (vomiting)	4 out of 10 participants (40%)	1 out of 3 participants (33%)
Headache	3 out of 10 participants (30%)	1 out of 3 participants (33%)
Infection affecting the larger airways into lungs (bronchitis)	1 out of 10 participants (10%)	1 out of 3 participants (33%)
Memory loss	1 out of 10 participants (10%)	1 out of 3 participants (33%)

Did study participants have any serious medical problems?

A medical problem is considered "serious" when it is life-threatening, needs hospital care, or causes lasting problems.

Five (5) participants (38%, or 5 out of 13 participants) had serious medical problems.

- In Part 1, 4 participants (40%, or 4 out of 10 participants) who took the high dose encorafenib + binimetinib combination treatment had serious medical problems.
- In Part 2, 1 participant (33%, or 1 out of 3 participants) who took the standard dose encorafenib + binimetinib combination treatment had a serious medical problem.

All serious medical problems were reported in only 1 participant each. Researchers believe that 2 out of 13 participants (15%) had serious medical problems related to at least 1 of the study treatments; these 2 participants were both in Part 1 of the study:

- 1 participant had fever
- 1 participant had dehydration (body doesn't have enough water to keep it working right)

In total, 10 participants (77%, or 10 out of 13 participants) died during the study: 7 participants during Part 1 and 3 participants during Part 2. Of these, 2 participants (15%) died during study treatment or within 30 days of stopping study treatment, and 8 participants (62%) died more than 30 days after stopping the study treatment. Most of the deaths (8 out of 10 participants) were due to the participants' cancer getting worse.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT03911869**
www.clinicaltrialsregister.eu	Use the study identifier **2018-004555-21**
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **C4221006**

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study,
thank you for volunteering.
We do research to try to find the
best ways to help patients, and you helped
us to do that!