

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: Braftovi[®] (encorafenib)

Protocol Number: C4221010 (CLGX818X2101)

Dates of Study: 05 September 2011 to 07 November 2022

Title of this Study: A Phase 1 Study of Oral LGX818 in Adult Patients With Advanced or Metastatic BRAF Mutant Melanoma

[A Phase 1, Multicenter, Open-label, Dose-escalation Study of Oral LGX818 in Adult Patients With Locally Advanced or Metastatic BRAF Mutant Melanoma]

Date(s) of this Report: 07 October 2023



– 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 melanoma and colorectal cancer?

This study included participants with melanoma, an aggressive type of skin cancer. This study also included participants with colorectal cancer, a cancer that starts in the large intestine (colon, also known as the bowel) or the rectum (last part of the large intestine). Participants in this study had either advanced or metastatic cancer, which means that the cancer had spread to other parts of the body. Participants also had cancer cells that contained a specific change (mutation) in a gene called *BRAF*. Having the *BRAF* V600E mutation or any other *BRAF* V600 mutation may cause the cancer cells to grow and spread.

What is encorafenib?

Encorafenib (en-koe-raf-e-nib) (also known by the brand name Braftovi[®]) is a type of cancer growth blocker. It works by targeting specific proteins that can help cancer cells grow. By blocking these proteins, encorafenib may help to stop or slow down the growth of cancer cells.

Encorafenib was an investigational medicine in this study when it began in 2011. This means the medicine was still being tested and was not approved for use in patients with melanoma or colorectal cancer with a *BRAF* V600 mutation.

What was the purpose of this study?

The main purpose of this study was to identify a safe dose range of encorafenib to use in participants with melanoma or colorectal cancer. This study was the first time encorafenib was given to people.

Researchers wanted to find the highest dose of encorafenib that is well tolerated by participants without causing any serious medical problems. This will help them to decide what dose to give people in future studies.

Researchers did this by giving participants increasing doses of encorafenib. At each dose level, researchers checked if participants had any dose limiting toxicities – medical problems which usually prevent further increases in the dose of the study medication – before deciding if a higher dose could be given. They also looked at the general safety of different doses.

Researchers wanted to know:

- What was the highest tolerated dose and recommended dose of encorafenib?
- What medical problems did participants have during the study?

What happened during the study?

How was the study done?

The study had 2 parts: a dose finding part (Part 1) and a dose expansion part (Part 2).

In this study, a treatment cycle is equivalent to 28 days. All participants received encorafenib continuously in 28-day cycles until their cancer got worse, they experienced unacceptable medical problems, or they decided they wanted to stop taking the study medication. All participants in Part 1 and Part 2 were required to have a *BRAF* V600 mutation in their cancer cells.

Participants attended 2 screening visits, 6 visits during Cycle 1 (first 28-day treatment cycle), 2 visits during Cycle 2 (second 28-day treatment cycle), 2 visits during Cycle 3 (third 28-day treatment cycle), 1 visit per cycle during Cycle 4 (fourth 28-day treatment cycle) and beyond, an end of treatment visit, and a safety follow-up visit about 30 days after stopping treatment. Participants in Part 2 of the study were contacted by phone every 3 months after they stopped the treatment to monitor their health status.

This was an open-label study, which means that the participants and researchers knew which treatment the participants received. Encorafenib was given to participants once or twice daily as capsules or in liquid form by mouth.

Part 1: Dose Finding

Participants in Part 1 had advanced or metastatic melanoma with a *BRAF* V600 mutation in their cancer cells. Researchers tested single, increasing doses of encorafenib in these participants. The first group of participants was given the lowest dose of 50 milligrams (mg) of encorafenib once daily.

The safety and tolerability of encorafenib was assessed, and the dose was increased for the next group of participants. Each group of participants given a particular dose is called a dosing cohort. This process continued up to the highest dose level tested in Part 1 (700 mg once daily). A dose was considered safe if there were no dose-limiting toxicities or other medical problems of concern. In total, researchers tested 11 different dose levels of encorafenib as shown in Figure 1.

Figure 1. Study Design for Part 1



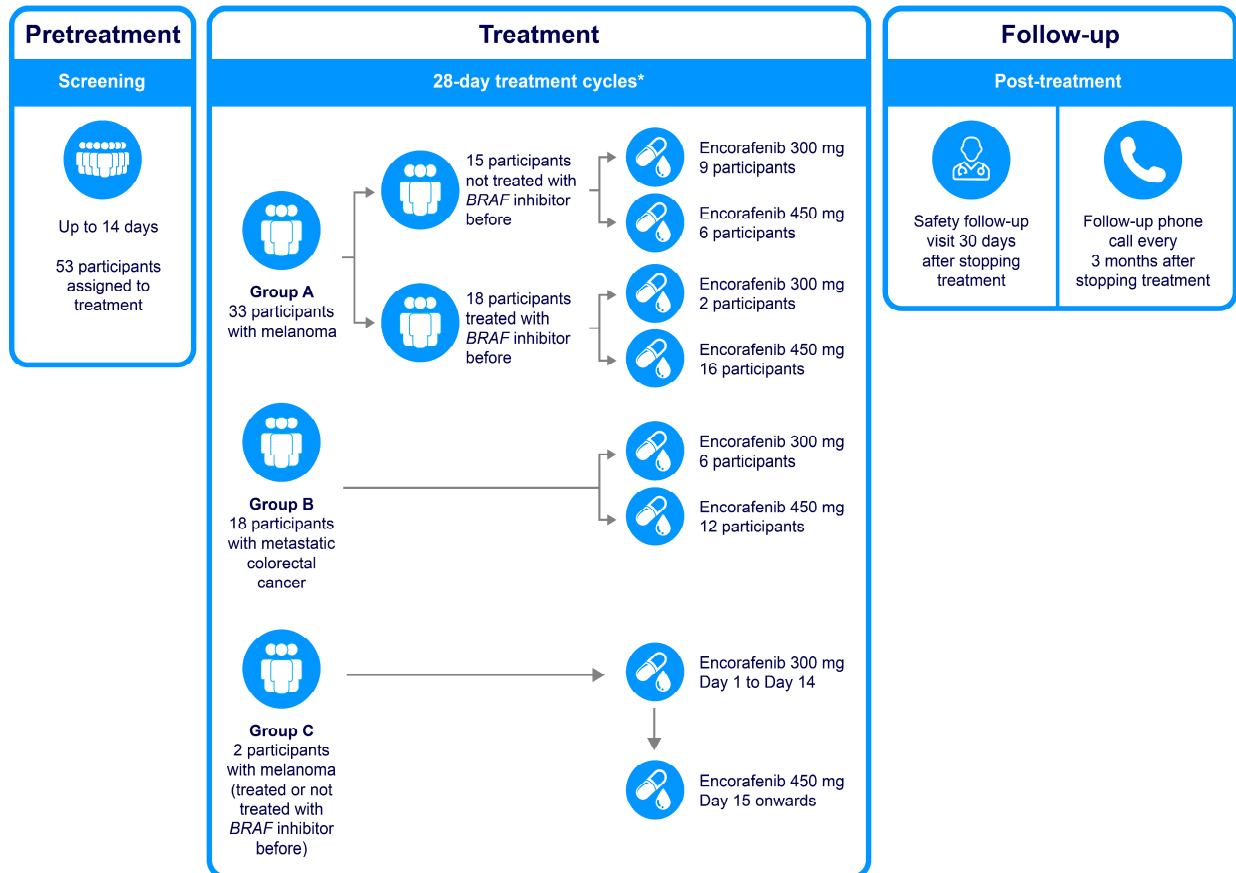
*Treatment continued until participant's cancer got worse, they experienced unacceptable medical problems, or they decided to stop treatment.

Part 2: Dose Expansion

Participants in Part 2 were divided into 3 groups: Group A, Group B, and Group C (Figure 2). Group A had a total of 33 participants with melanoma out of which 15 participants were not treated with a *BRAF* inhibitor (medicine that blocks the activity of the *BRAF* gene) before taking part in this study. Eighteen (18) participants with metastatic colorectal cancer (mCRC) took part in Group B. Two (2) participants with melanoma were treated in Group C in a stepwise dosing manner as shown in Figure 2.

All participants in Part 2 were given encorafenib once daily. Participants in Group C were given a dose of 300 mg once daily for the first 14 days followed by an increased dose of 450 mg once daily on Day 15 if they did not experience any serious medical problems. The dose was reduced if the participant experienced any unwanted medical problems.

Figure 2. Study Design for Part 2



*Treatment continued until participant's cancer got worse, they experienced unacceptable medical problems, or they decided to stop treatment.

Where did this study take place?

The Sponsor ran this study at 12 locations in 7 countries.

When did this study take place?

It began on 05 September 2011 and ended on 07 November 2022.

Who participated in this study?

Participants in Part 1 had advanced or metastatic melanoma with the *BRAF* V600E mutation or any other *BRAF* V600 mutation.

Participants in Part 2 had advanced or metastatic melanoma or mCRC.

- There were 54 participants in Part 1 (36 men and 18 women).
- There were 35 participants with advanced or metastatic melanoma in Group A and Group C of Part 2 (15 men and 20 women).
- There were 18 participants with mCRC in Group B of Part 2 (8 men and 10 women).
- All participants in Part 1 and Part 2 were between the ages of 22 and 79 years.

Part 1

Of the 54 participants who started Part 1 of the study, 54 participants (100%) stopped treatment due to the following reasons:

- Participants' cancer got worse (79.6%, 43 out of 54 participants)
- A medical problem meant that the participant or their doctor thought it was best for the participant to stop treatment (11.1%, 6 out of 54 participants)
- Participant wanted to stop treatment (3.7%, 2 out of 54 participants)
- Death of a participant (1.9%, 1 out of 54 participants)

Part 2: Participants with melanoma (Group A and Group C)

Of the 35 participants with melanoma who started the study, 35 participants (100%) stopped treatment due to the following reasons:

- Participants' cancer got worse (68.6%, 24 out of 35 participants)
- A medical problem meant that the participant or their doctor thought it was best for the participant to stop treatment (25.7%, 9 out of 35 participants)

- Participant wanted to stop treatment (5.7%, 2 out of 35 participants)

Part 2: Participants with mCRC (Group B)

Of the 18 participants with mCRC who started the study, 18 participants (100%) stopped treatment due to the following reasons:

- Participants' cancer got worse (77.8%, 14 out of 18 participants)
- A medical problem meant that the participant or their doctor thought it was best for the participant to stop treatment (22.2%, 4 out of 18 participants)

How long did the study last?

The time participants were in the study depended on the number of treatment cycles they completed and the follow-up time.

The entire study took about 11 years and 2 months to complete.

When the study ended in November 2022, the Sponsor created a report of the results. This is a summary of that report.

What were the results of the study?

How safe and well tolerated was encorafenib?

Researchers looked at the medical problems that participants had in the 28 days after their first dose of encorafenib (Cycle 1) to see if there were dose-limiting toxicities. This helped researchers to decide if each dose was safe and well tolerated and if it was safe to give the next group of participants a higher dose of encorafenib.

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

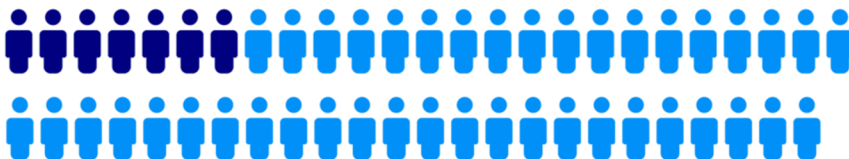
Did participants who took encorafenib have dose-limiting toxicities?

Part 1

In Part 1, 49 out of 54 participants taking encorafenib were assessed for dose-limiting toxicities during their first treatment cycle (Cycle 1). Seven (7) out of 49 (14.3%) participants had at least 1 dose-limiting toxicity. All 7 participants were in different dosing cohorts and had medical problems that were rated Grade 3 meaning that study doctors considered the events to be severe or medically significant. Nerve pain was the most common dose-limiting toxicity reported by 2 participants (Figure 3).

Figure 3. Number of Participants with Dose-limiting Toxicities (Part 1)

7 out 49 (14.3%) participants in Part 1 had at least 1 dose-limiting toxicity



- 2 out of 7 (4.1%) participants had nerve pain



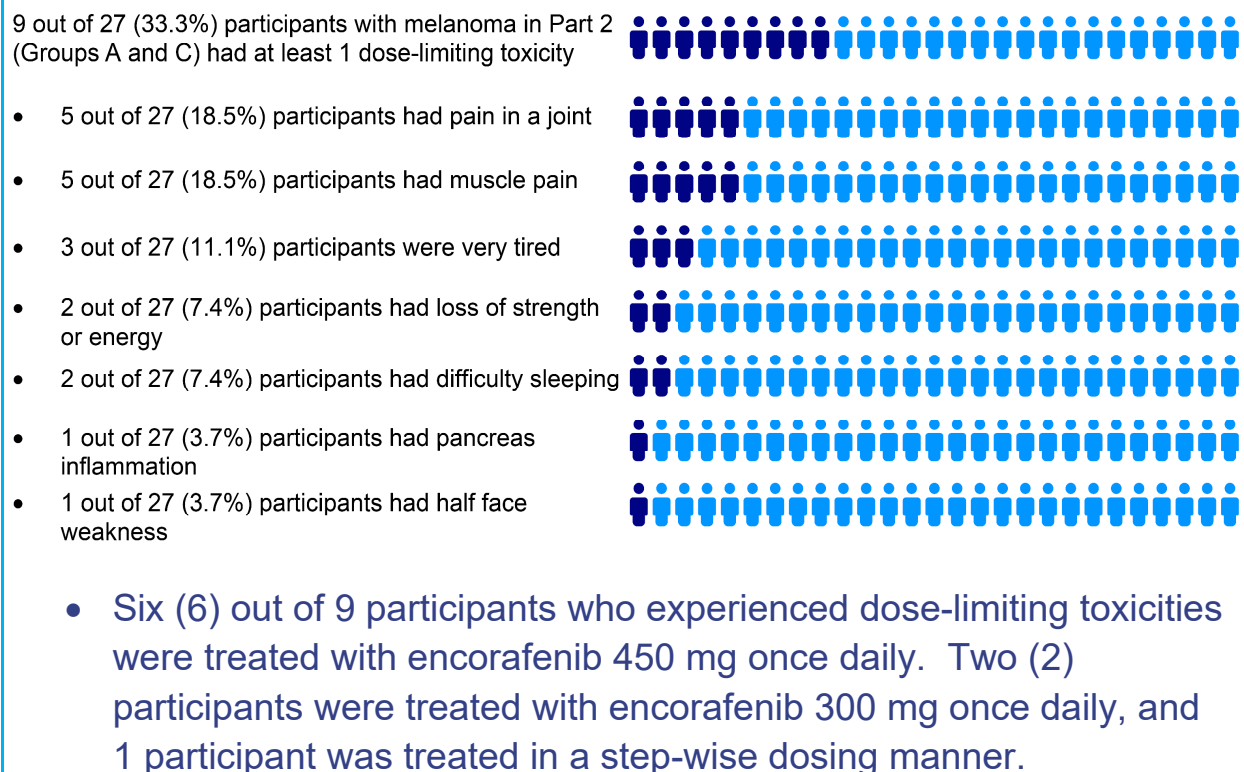
- One (1) participant who took encorafenib 150 mg twice daily experienced Grade 3 nerve pain (Study Day 4). Study treatment was interrupted for this participant.
- One (1) participant who took encorafenib 300 mg once daily experienced Grade 3 nerve pain (Study Day 26). Study treatment was permanently discontinued for this participant.

- The following Grade 3 dose-limiting toxicities were reported in 1 participant each: loss of strength, confusional state, diarrhea, facial paralysis, tiredness, headache, difficulty sleeping, muscle and bone pain, neck pain, hand-foot syndrome, and rash.

Part 2: Group A and Group C

In Part 2 (Group A and Group C), 27 out of 35 participants taking encorafenib were assessed for dose-limiting toxicities during their first treatment cycle (Cycle 1). Nine (9) out of 27 (33.3%) participants had at least 1 dose-limiting toxicity. The most common dose-limiting toxicities are shown in Figure 4.

Figure 4. Number of Participants with Dose-limiting Toxicities (Part 2: Group A and Group C)

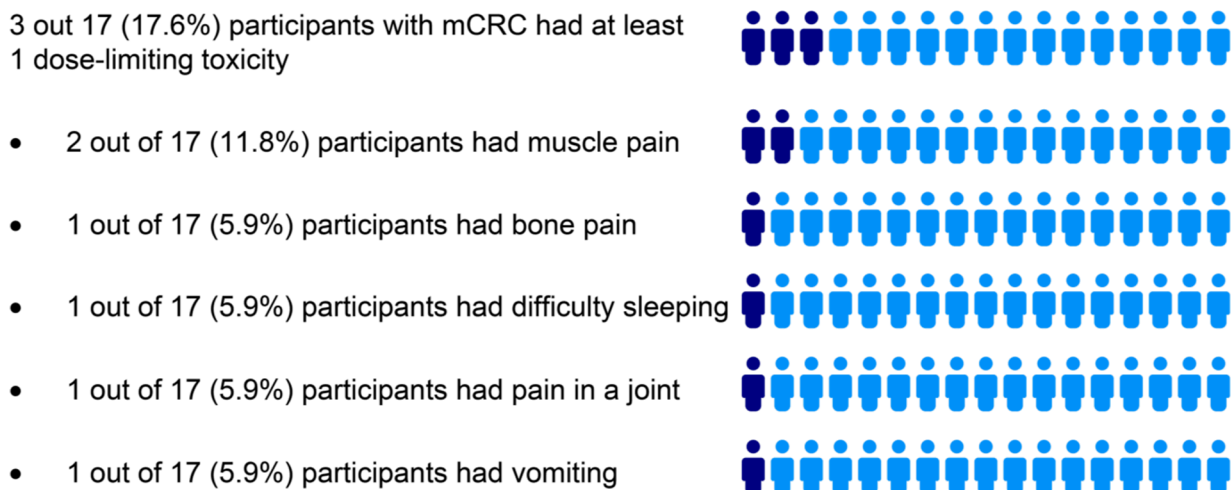


- The dose of study treatment was reduced for 4 participants, and the medical events resolved for 2 participants. Study treatment was permanently discontinued for 4 additional participants.

Part 2: Group B

In Part 2 (Group B), 17 out of 18 participants taking encorafenib were assessed for dose-limiting toxicities during their first treatment cycle (Cycle 1). Three (3) out of 17 (17.6%) participants had at least 1 dose-limiting toxicity. The most common dose-limiting toxicities are shown in Figure 5.

Figure 5. Number of Participants with Dose-limiting Toxicities (Part 2: Group B)



All 3 participants with mCRC in Part 2 (Group B) who experienced dose-limiting toxicities were treated with encorafenib 450 mg once daily.

What was the highest tolerated dose and recommended dose of encorafenib?

Researchers concluded that 450 mg once daily was the highest tolerated dose of encorafenib based on initial Part 1 study results. This dose was

determined based on the number of significant medical events reported during Part 1 of this study. However, in Part 2 participants taking this dose experienced significant medical events and dose-limiting toxicities which led to reducing the dose of encorafenib to 300 mg once daily.

As a result, researchers concluded 300 mg once daily as the recommended dose of encorafenib which was found to be well tolerated.

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. Other studies 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 54 (100%) participants in Part 1 and all 53 (100%) participants in Part 2 of this study had at least 1 medical problem. A total of 6 participants in Part 1 and 13 participants in Part 2 left the study because of medical problems. The most common medical problems – those reported by more than 30% of participants in Part 1 and Part 2 – are described below.

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 Part 1 of the study. All medical problems reported by at least 30% of participants are listed.
- The **2nd** column tells how many of the 54 participants taking the study medication reported each medical problem. Next to this number is the percentage of the 54 participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that 28 out of the 54 (51.9%) participants in Part 1 taking the study medication reported hand-foot syndrome.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists medical problems that were commonly reported during Part 2 of the study. All medical problems reported by at least 30% of participants are listed.
- The **2nd** column tells how many of the 35 participants with melanoma (Group A and Group C) taking the study medication reported each medical problem. Next to this number is the percentage of the 35 participants taking the study medication who reported the medical problem.
- The 3rd column tells how many of the 18 participants with mCRC (Group B) taking the study medication reported each medical problem. Next to this number is the percentage of the 18 participants taking the study medication who reported the medical problem.

- Using these instructions, you can see that 23 out of 35 (65.7%) participants with melanoma (Group A and Group C) and 3 out of 18 (16.7%) participants with mCRC (Group B) in Part 2 taking the study medication reported upset stomach.

Table 1. Commonly reported medical problems by at least 30% of study participants in Part 1

Medical Problem	Encorafenib (54 Participants)
Hand-foot syndrome	28 out of 54 participants (51.9%)
Thickening of outer skin	23 out of 54 participants (42.6%)
Pain in a joint	24 out of 54 participants (44.4%)
Upset stomach	24 out of 54 participants (44.4%)
Itching	21 out of 54 participants (38.9%)
Bumpy skin	21 out of 54 participants (38.9%)
Hair loss	20 out of 54 participants (37.0%)
Decreased appetite	19 out of 54 participants (35.2%)
Tiredness	19 out of 54 participants (35.2%)
Loss of strength or energy	18 out of 54 participants (33.3%)

Dry skin	17 out of 54 participants (31.5%)
Headache	17 out of 54 participants (31.5%)

Table 2. Commonly reported medical problems by at least 30% of study participants in Part 2

Medical Problem	All Melanoma (35 Participants)	All mCRC (18 Participants)
Upset stomach	23 out of 35 participants (65.7%)	3 out of 18 participants (16.7%)
Muscle pain	23 out of 35 participants (65.7%)	8 out of 18 participants (44.4%)
Hand-foot syndrome	19 out of 35 participants (54.3%)	12 out of 18 participants (66.7%)
Pain in a joint	18 out of 35 participants (51.4%)	6 out of 18 participants (33.3%)
Vomiting	17 out of 35 participants (48.6%)	8 out of 18 participants (44.4%)
Can't sleep	15 out of 35 participants (42.9%)	6 out of 18 participants (33.3%)

Table 2. Commonly reported medical problems by at least 30% of study participants in Part 2

Medical Problem	All Melanoma (35 Participants)	All mCRC (18 Participants)
Hair loss	15 out of 35 participants (42.9%)	5 out of 18 participants (27.8%)
Dry skin	15 out of 35 participants (42.9%)	7 out of 18 participants (38.9%)
Thickening of outer skin	14 out of 35 participants (40.0%)	6 out of 18 participants (33.3%)
Headache	14 out of 35 participants (40.0%)	3 out of 18 participants (16.7%)
Bumpy skin	13 out of 35 participants (37.1%)	4 out of 18 participants (22.2%)
Itching	11 out of 35 participants (31.4%)	8 out of 18 participants (44.4%)
Loss of strength or energy	12 out of 35 participants (34.3%)	6 out of 18 participants (33.3%)
Constipation	11 out of 35 participants (31.4%)	4 out of 18 participants (22.2%)

Table 2. Commonly reported medical problems by at least 30% of study participants in Part 2

Medical Problem	All Melanoma (35 Participants)	All mCRC (18 Participants)
Decreased appetite	10 out of 35 participants (28.6%)	7 out of 18 participants (38.9%)
Decreased weight	7 out of 35 participants (20.0%)	6 out of 18 participants (33.3%)
Rash	4 out of 35 participants (11.4%)	6 out of 18 participants (33.3%)

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.

Part 1

Thirty-three (33) out of 54 (61.1%) participants had serious medical problems after being treated with encorafenib. These events included:

- Overall health decline (5 participants [9.3%])
- Confusional state and headache (3 participants [5.6%] each)

Researchers thought 9 out of 54 (16.7%) participants had serious medical problems that might be related to taking encorafenib.

Eleven (11) out of 54 (20.4%) participants in Part 1 died during treatment or within 30 days after last dose of study medication due to their cancer getting worse.

Part 2: Participants with melanoma

Nineteen (19) out of 35 (54.3%) participants had serious medical problems after being treated with encorafenib. These events included:

- Upset stomach (7 participants [20.0%]) and muscle pain (4 participants [11.4%])
- Joint pain, tiredness, vomiting (3 participants [8.6%] each), back pain and intestinal obstruction (1 participant [2.9%] each)

Researchers thought 12 out of 35 (34.3%) participants had serious medical problems that might be related to taking encorafenib.

Two (2) out of 35 (5.7%) participants with melanoma in Part 2 died during treatment or within 30 days after last dose of study medication due to their cancer getting worse.

Part 2: Participants with mCRC

Nine (9) participants (50%, or 9 out of 18 participants) had serious medical problems after being treated with encorafenib. These events included:

- Vomiting, back pain, and stomach pain (2 participants [11.1%] each)

Researchers do not believe any of the serious medical problems might be related to taking encorafenib.

Three (3) out of 18 (16.7%) participants with mCRC in Part 2 died during treatment or within 30 days after last dose of study medication due to their 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.

For more details on your study protocol, please visit:

[www.pfizer.com/research/
research_clinical_trials/trial_results](http://www.pfizer.com/research/research_clinical_trials/trial_results)

Use the protocol number
C4221010

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

www.clinicaltrials.gov

Use the study identifier
NCT01436656

www.clinicaltrialsregister.eu

Use the study identifier
2011-000556-42

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!