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 + Binimetinib

Protocol Number: C4221013 (CLGX818X2109)

Dates of Study: 23 July 2014 to 13 January 2023

Title of this Study: Encorafenib and Binimetinib in Combination With Targeted Third Agents in Advanced BRAF Melanoma (LOGIC-2)

[The LOGIC 2 Trial a Phase II, Multi-Center, Open-Label Study of Sequential LGX818/MEK162 Combination Followed by a Rational Combination With Targeted Agents After Progression, to Overcome Resistance in Adult Patients With Locally Advanced or Metastatic BRAF V600 Melanoma.]

Date of this Report: 06 December 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 unresectable or metastatic advanced melanoma?

Cancer is a disease in which some of the body's cells grow without control and may spread to other parts of the body. Unresectable means a cancer cannot be completely removed by surgery. Metastatic means a cancer has spread from where it started to a distant part of the body. Both unresectable and metastatic cancers are considered as advanced cancers. Melanoma is a skin cancer from melanocytes (cells that color the skin).

Participants in this study had cancer cells which contained a specific change (mutation) in a gene called BRAF. Having the BRAF V600 mutation may cause the cancer cells to grow and spread.

What is encorafenib and binimetinib?

Encorafenib (en-koe-raf-e-nib) (also known by the brand name Braftovi®) and binimetinib (bin-i-me-ti-nib) (also known by the brand name Mektovi®) are 2 different types of cancer growth blockers. Encorafenib is called as a "BRAF inhibitor" and binimetinib (MEK162) as a "MEK inhibitor". They work by targeting certain proteins that help cancer cells to grow. By blocking these proteins, encorafenib and binimetinib may help to stop or slow down the growth of cancer cells.

Encorafenib and binimetinib are both taken by mouth. In this study, these treatments were given together so the study medication is referred to as "encorafenib + binimetinib combination treatment".

A combination treatment of encorafenib + binimetinib have been approved in several countries including the United States, Japan, Canada, and European Union for the treatment of patients with unresectable or metastatic melanoma having the BRAF V600E or BRAF V600K mutations.

What was the purpose of this study?

The study was conducted in two parts: Part 1 and Part 2. The purpose of Part 1 was to learn whether encorafenib + binimetinib combination treatment had positive effects on participants with specific type of melanoma who had BRAF V600 mutation. In Part 2 researchers wanted to know if the addition of one of the third medication known as ribociclib (LEE011), infigratinib (BGJ398), capmatinib (INC280), or buparlisib (BKM120) could overcome the development of resistance to the previous combination treatment of encorafenib + binimetinib.

Researchers measured the effect of the medications by comparing images of the tumors before, during and after treatment. Using this information, researchers determined how many participants benefited by the treatment. Investigators looked at a type of measure called the "Objective Response Rate" (ORR). ORR is the percentage of participants in whom all signs of cancer disappeared, called complete response (CR), or got smaller or shrank during treatment (decrease of 30% in size or extent of cancer compared to before treatment), called partial response (PR). The extent of response is determined by the study doctor.

Researchers wanted to know:

- **Did the participants taking encorafenib in combination with binimetinib have positive effects on their tumors?**
- **What medical problems did the participants have during the study?**

What happened during the study?

How was the study done?

This was an “open-label” study. This means researchers and participants knew what study medication each participant was receiving.

The study was divided into two treatment parts: Part 1 and Part 2.

In Part 1, researchers assigned two groups of participants to receive 450 mg of encorafenib once daily (QD) and 45 mg of binimetinib twice daily (BID) for 21 days in each cycle, as shown below:

- **Group A**: Participants who were not previously treated with BRAF and MEK inhibitor.
- **Group B**: Participants whose cancer got worse after they were treated with either single agent BRAF or MEK inhibitors or the combination of BRAF/MEK inhibitors before the study start received encorafenib and binimetinib combination treatment for at least 3 weeks. This is called ‘run-in’ phase. Based on the tumor assessments performed, participants either received Part 2 treatment or continued Part 1 treatment.
- Participants whose cancer did not get worse after prior treatment with BRAF/MEK inhibitor entered run-in phase and received Part 1 treatment until their cancer got worse. Based on the tumor assessment performed, participants were assigned Part 2 treatment.

A complete treatment cycle for Part 1 of the study was defined as 21 days of continuous dosing, with the first dose of study medication on Day 1. Participants received treatment until their cancer got worse, they experienced unacceptable medical problems, they left the study, the participant died, or they were assigned Part 2 study treatment.

In Part 2, participants were assigned to triple combination treatment based on the genetic assessments performed during Part 1 of the study. For participants whose tumor grew back during Part 1 treatment, a sample of the tumor was collected and analysed for genetic alterations in the tumor after treatment with encorafenib and binimetinib combination. Participants received treatments best matched to their genetic alteration as shown below:

- **Group 1:** Ribociclib up to 600 mg once daily was administered along with encorafenib up to 200 mg QD plus binimetinib up to 45 mg BID treatment combination.
- **Group 2:** Infigratinib 75 mg once daily was administered along with encorafenib 450 mg QD plus binimetinib 45 mg BID treatment combination.
- **Group 3:** Capmatinib 200 mg BID (tablets when available), 300 mg or 400 mg BID capsules were administered along with encorafenib 200 mg QD plus binimetinib 45 mg BID treatment combination in a 21-day treatment cycle.
- **Group 4**: Buparlisib 60 mg or 90 mg QD was administered along with encorafenib 450 mg QD plus binimetinib 45 mg BID treatment combination in a 21-day treatment cycle.

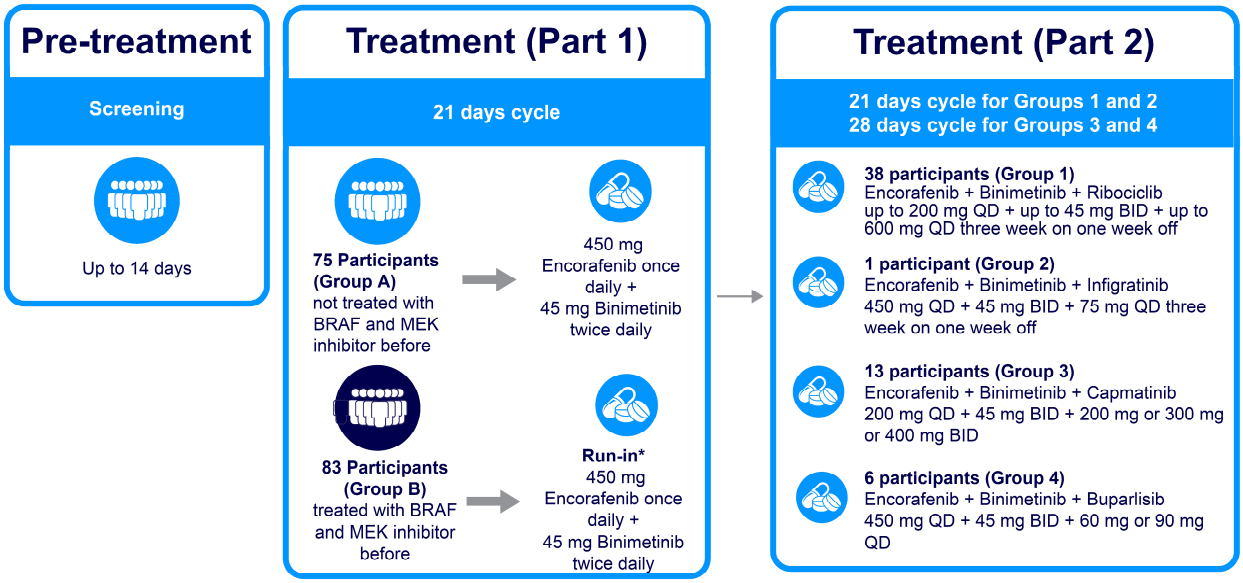
Participants in Groups 1 and 2 received continuous treatment in cycles for 28 days in each cycle, with ribociclib and infigartinib taken for 21 consecutive days followed by a 7-day planned break (three week on, one week off schedule). Encorafenib plus binimetinib treatment combination were administered continuously.

All participants were followed up for safety assessments 30 days after receiving last dose of the study medication. Participants in Part 2 were

followed up for long-term safety assessments every 3 months via phone calls or registered letters.

The detailed Part 1 and Part 2 study design is shown below in Figure 1.

Figure 1: Study Flow Diagram



**Participants received the combination treatment based on their prior treatment for initial 3 weeks followed by early tumor assessment*
QD: once daily; BID: twice daily

Where did this study take place?

The Sponsor ran this study at 16 locations in 9 countries (Australia, Canada, Germany, Italy, the Netherlands, Spain, Switzerland, the United Kingdom, and the United States).

When did this study take place?

It began 23 July 2014 and ended 13 January 2023.

Who participated in this study?

The study included participants who were at least 18 years old. They must have been diagnosed with advanced or metastatic melanoma with BRAF V600 mutation.

Participants were treated until one of the following occurred:

- The participant's cancer got worse
- The participant left before the study was over by their own choice
- A doctor decided it was best for a participant to stop being in the study
- The participant experienced unacceptable medical problems

Part 1

- A total of 91 men participated
- A total of 67 women participated
- All participants were between the ages of 23 and 83 years

Of the 158 participants who started Part 1 of the study, all participants reached the end of treatment (date of discontinuation or study end). Treatment for one participant was reported ongoing due to missing information. The most common reason for end of treatment was disease getting worse (56.3%, or 89 out of 158 participants). Remaining participants discontinued the study treatment due to the following reasons:

- Death (10.1%, or 16 out of 158 participants)
- Study doctor decided it was best for the participants to stop being in the study (9.5%, 15 out of 158 participants)
- Unacceptable medical problems (8.9%, or 14 out of 158 participants)

- Participants wanted to stop study treatment by their own choice (8.2%, 13 out of 158 participants)
- Study terminated by sponsor (3.2%, 5 out of 158 participants)

Part 2

- A total of 29 men participated
- A total of 29 women participated
- All participants were between the ages of 24 and 82 years

Of the 58 participants who started Part 2 of the study, all participants reached the end of treatment. The most common reason for end of treatment was disease getting worse (82.8%, or 48 out of 58 participants). Remaining participants stopped the study treatment due to the following reasons:

- Death (6.9%, or 4 out of 58 participants)
- Unacceptable medical problems (5.2%, or 3 out of 58 participants)
- Participants wanted to stop study treatment by their own choice (3.4%, 2 out of 58 participants)
- Study doctor decided it was best for the participants to stop being in the study (1.7%, 1 out of 58 participants)

How long did the study last?

The entire study took around 8 years and 6 months to complete. The amount of time each participant was involved in the study varied.

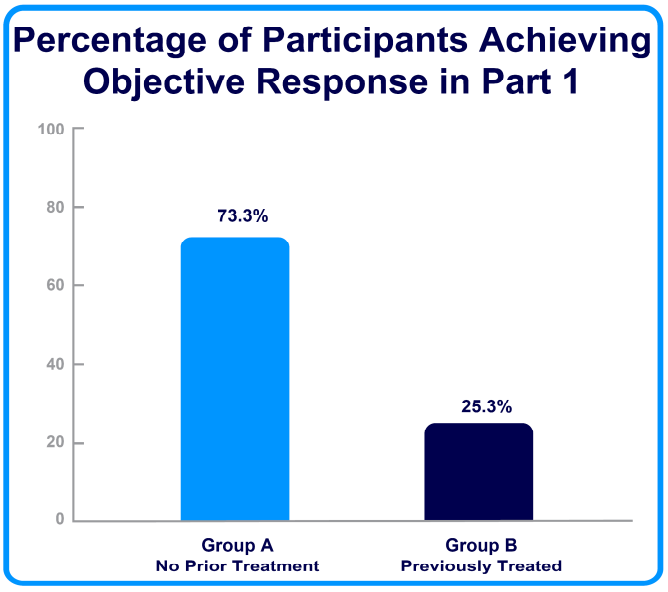
When the study ended in January 2023, the sponsor reviewed the information collected and created a report of the results. This is a summary of that report.

What were the results of the study?

Did the participants taking encorafenib in combination with binimetinib have positive effects on their tumors as measured by ORR?

In Part 1, the ORR, which is the percentage of participants whose tumors decreased/shrank under therapy (PR) and/or disappeared (CR) after treatment was 73.3% (55 out of 75 participants) in Group A and 25.3% (21 out of 83 participants) in Group B (as shown in Figure 2). Ten (10) out of 75 participants (13.3%) in Group A and 3 out of 83 participants (3.6%) in Group B had best response recorded with no signs of cancer (CR). Forty-five (45) out of 75 participants (60.0%) in Group A and 18 out of 83 participants (21.7%) in Group B had their tumor shrinking enough up to an extent (to a certain size) under therapy that qualified for PR.

Figure 2: Objective Response Rate for Part 1 of Study Treatment



The percentage of participants whose tumor either stayed the same or had small variations of increase or decrease in size was 18.7% (14 out of 75 participants) in Group A, and 16.9% (14 out of 83 participants) in Group B.

In Part 2, 1 out of 38 participants (2.6%) in Group 1 had his/her tumor shrinking enough up to an extent (to a certain size) under therapy that qualified for PR. No participant had best response recorded with no signs of cancer in Part 2 of the study treatment.

The percentage of participants whose tumor either stayed the same or had small variations of increase or decrease in size was 23.7% (9 out of 38 participants) in Group 1, 15.4% (2 out of 13 participants) in Group 3, and 16.7% (1 out of 6 participants) in Group 4.

Based on the results from Part 1, researchers found that treatment with combination of encorafenib and binimetinib may offer a new standard of care for participants with advanced unresectable metastatic melanoma with BRAF V600 mutation. However, researchers observed a lower effect of the triplet combination on participants' tumors during Part 2 of the study.

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.

- In Part 1 of the study a total of 147 participants had at least 1 medical problem, all participants in Group A and 72 out of 83 participants in Group B. A total of 14 participants left Part 1 of the study due to medical problems, 9 participants in Group A and 5 participants in Group B. The most common medical problems – those reported by 20% or more participants in any Group during Part 1 of the study – are described in Table 1.
- In Part 2 of the study 32 out of 38 participants in Group 1, 11 out of 13 participants in Group 3 and 5 out of 6 participants in Group 4 had at least 1 medical problem. No participant in Group 2 had any medical problems. A total of 3 participants left Part 2 of the study due to medical problems, 1 participant each in Groups 1, 3, and 4 respectively. The most common medical problems – those reported by more than 20% participants in any Group during Part 2 of the study - are described in Table 2.

Below are instructions on how to read Table 1 and Table 2.

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 more than 20% of participants are listed.

- The **2nd** column tells how many of the 75 participants in Group A taking the study medication reported each medical problem. Next to this number is the percentage of the 75 participants in Group A taking the study medication who reported the medical problem.
- The **3rd** column tells how many of the 83 participants in Group B taking study medication reported each medical problem. Next to this number is the percentage of the 83 participants in Group B taking the study medication who reported the medical problem.
- Using these instructions, you can see that 28 out of the 75 (37.3%) participants in Group A taking the study medication reported low red blood cell count during Part 1 of the study. A total of 17 out of the 83 (20.5%) participants in Group B taking the study medication reported low red blood cell count during Part 1 of the study.

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 more than 20% of participants are listed.
- The **2nd** column tells how many of the 38 participants in Group 1 taking the study medication reported each medical problem. Next to this number is the percentage of the 38 participants in Group 1 taking the study medication who reported the medical problem.
- The **3rd** column tells if 1 participant in Group 2 taking study medication reported each medical problem. Next to this

number is the percentage of that participant in Group 2 taking the study medication who reported the medical problem.

- The **4th** column tells how many of the 13 participants in Group 3 taking the study medication reported each medical problem. Next to this number is the percentage of the 13 participants in Group 3 taking the study medication who reported the medical problem.
- The **5th** column tells how many of the 6 participants in Group 4 taking the study medication reported each medical problem. Next to this number is the percentage of the 6 participants in Group 4 taking the study medication who reported the medical problem.
- Using these instructions, you can see that:
    - In Group 1, 10 out of the 38 (26.3%) participants taking the study medication reported low red blood cell count during Part 2 of the study.
    - In Group 2, no participants taking the study medication reported low red blood cell count during Part 2 of the study.
    - In Group 3, 3 out of the 13 (23.1%) participants taking the study medication reported low red blood cell count during Part 2 of the study.
    - In Group 4, 3 out of the 6 (50.0%) participants taking the study medication reported low red blood cell count during Part 2 of the study.

Table 1. Commonly reported medical problems by study participants during Part 1 of the study

Medical Problem	Encorafenib 450 mg + Binimetinib 45 mg (75 Participants)	Encorafenib 450 mg + Binimetinib 45 mg (83 Participants)
Low red blood cell count	28 out of 75 participants (37.3%)	17 out of 83 participants (20.5%)
Damage to the retina	22 out of 75 participants (29.3%)	10 out of 83 participants (12.0%)
Nausea	30 out of 75 participants (40.0%)	35 out of 83 participants (42.2%)
Loose stools	33 out of 75 participants (44.0%)	26 out of 83 participants (31.3%)
Vomiting	17 out of 75 participants (22.7%)	25 out of 83 participants (30.1%)
Constipation	22 out of 75 participants (29.3%)	14 out of 83 participants (16.9%)
Feeling tired	31 out of 75 participants (41.3%)	27 out of 83 participants (32.5%)
Fever	13 out of 75 participants (17.3%)	17 out of 83 participants (20.5%)

Table 1. Commonly reported medical problems by study participants during Part 1 of the study

Medical Problem	Encorafenib 450 mg + Binimetinib 45 mg (75 Participants)	Encorafenib 450 mg + Binimetinib 45 mg (83 Participants)
Increased muscle protein (creatinine phosphokinase) in blood	38 out of 75 participants (50.7%)	11 out of 83 participants (13.3%)
Joint pain	26 out of 75 participants (34.7%)	15 out of 83 participants (18.1%)
Muscle spasms	16 out of 75 participants (21.3%)	7 out of 83 participants (8.4%)
Back pain	16 out of 75 participants (21.3%)	6 out of 83 participants (7.2%)

Table 2. Commonly reported medical problems by study participants during Part 2 of the study				
Medical Problem	(Group 1) Encorafenib + Binimetinib + Ribociclib (38 Participants)	(Group 2) Encorafenib + Binimetinib + Infigratinib (1 Participant)	(Group 3) Encorafenib + Binimetinib + Capmatinib (13 Participants)	(Group 4) Encorafenib + Binimetinib + Buparlisib (6 Participants)
Low red blood cell count	10 out of 38 participants (26.3%)	0 out of 1 participant (0%)	3 out of 13 participants (23.1%)	3 out of 6 participants (50.0%)
Nausea	15 out of 38 participants (39.5%)	0 out of 1 participant (0%)	3 out of 13 participants (23.1%)	2 out of 6 participants (33.3%)
Vomiting	10 out of 38 participants (26.3%)	0 out of 1 participant (0%)	1 out of 13 participants (7.7%)	1 out of 6 participants (16.7%)
Loose stools	9 out of 38 participants (23.7%)	0 out of 1 participant (0%)	2 out of 13 participants (15.4%)	1 out of 6 participants (16.7%)
Fever	8 out of 38 participants (21.1%)	0 out of 1 participant (0%)	1 out of 13 participants (7.7%)	2 out of 6 participants (33.3%)

Table 2. Commonly reported medical problems by study participants during Part 2 of the study

Medical Problem	(Group 1) Encorafenib + Binimetinib + Ribociclib (38 Participants)	(Group 2) Encorafenib + Binimetinib + Infigratinib (1 Participant)	(Group 3) Encorafenib + Binimetinib + Capmatinib (13 Participants)	(Group 4) Encorafenib + Binimetinib + Buparlisib (6 Participants)
Swelling of the ankles and feet (due to fluid retention)	4 out of 38 participants (10.5%)	0 out of 1 participant (0%)	3 out of 13 participants (23.1%)	1 out of 6 participants (16.7%)
Liver test enzyme increased	4 out of 38 participants (10.5%)	0 out of 1 participant (0%)	0 out of 13 participants (0%)	2 out of 6 participants (33.3%)
Back pain	5 out of 38 participants (13.2%)	0 out of 1 participant (0%)	0 out of 13 participants (0%)	2 out of 6 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.

In Part 1 of the study, a total of 84 participants had serious medical problems. Forty-seven (47) participants (62.7% or 47 out of 75 participants) in Group A and 37 participants (44.6%, or 37 out of 83 participants) in Group B reported serious medical problems. The most common serious medical problems reported during Part 1 of the study were nausea and vomiting. Researchers believed that serious medical problems related to study treatment that were reported in more than 1 participant were vomiting, nausea, increased muscle protein (creatinine phosphokinase) in blood, and fever.

In Part 2 of the study, 19 participants (50.0%, or 19 out of 38 participants) in Group 1, 6 participants (46.2%, or 6 out of 13 participants) in Group 3, 4 participants (66.7%, or 4 out of 6 participants) in Group 4 reported serious medical problems. No participants in Group 2 had serious medical problems. Serious medical problems related to study treatment were increase in the liver enzymes such as alanine aminotransferase and aspartate aminotransferase, stroke, nausea, inflammation in the large intestine, and bleeding in esophagus, stomach, or small intestines.

A total of 49 out of 158 participants died during Part 1 of the study. Of these 49 participants, 24 participants died while on treatment or within 30 days after the last dose of the study medication.

A total of 41 out of 58 participants died during Part 2 of the study. Of these 41 participants, 12 participants died while on treatment or within 30 days after the last dose of the study medication. The most common reason for deaths in both Parts 1 and 2 of study was cancerous melanoma. One participant in Part 1 died due to intestinal mass (sores in the intestine) also called as ulcerative mass ileocecal. Researchers believed that the death due to intestinal mass was considered to be related to the study medication.

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	Use the protocol number C4221013

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

www.clinicaltrials.gov	Use the study identifier **NCT02159066**
www.clinicaltrialsregister.eu	Use the study identifier **2013-004552-38**

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!