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 (PF-07263896/LGX818) + Binimetinib (MEK162)

Encorafenib (PF-07263896/LGX818) + Binimetinib (MEK162) + Ribociclib (LEE011)

Protocol Number: C4221005 (CMEK162X2110)

Dates of Study: 28 May 2012 to 09 March 2023

Title of this Study: A Phase Ib/II Study of LGX818 in Combination With MEK162 in Adult Patients With *BRAF* Dependent Advanced Solid Tumors

[A Phase Ib/II, Multicenter, Open-Label, Dose Escalation Study of LGX818 in Combination With MEK162 in Adult Patients With *BRAF* V600 - Dependent Advanced Solid Tumors]

Date(s) of this Report: 09 January 2024

– 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 locally advanced metastatic melanoma, metastatic colorectal cancer, and solid tumor?

Cancer is a disease in which some of the body's cells grow without control and may spread to other parts of the body. Metastatic means a cancer has spread from where it started to a distant part of the body. Cancer that is unlikely to be cured or controlled with treatment is known as advanced cancer. Melanoma is a skin cancer from melanocytes (cells that colour the skin). Colorectal cancer is cancer that starts in the large intestine (colon, also known as the bowel) or the rectum (last part of the large intestine). Solid tumor is the most common type of cancer which forms abnormal mass that usually does not contain any liquid.

Participants in this study had cancer cells which contained a specific change (mutation) in a gene called V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*). Having the *BRAF* V600 mutation may cause the cancer cells to grow and spread.

What are encorafenib, binimetinib, and ribociclib?

Encorafenib (en-koe-raf-e-nib) (also known by the brand name Braftovi®), binimetinib (bin-i-me-ti-nib) (also known as Mektovi®), and ribociclib (ri-bo-ci-clib) (also known as Kisqali) are different types of cancer growth blockers. They work by targeting certain proteins that can help cancer cells grow. By blocking these proteins, encorafenib and binimetinib may help to stop or slow down the growth of cancer cells.

Encorafenib and ribociclib were given as capsules and binimetinib was given as tablets; all three medicines were taken by mouth. Two different combinations of study drugs were tested in this study:

- Dual combination of encorafenib and binimetinib
- Triple combination of encorafenib, ribociclib, and binimetinib

In 2018, the United States Food and Drug Administration and the European Medicines Agency approved encorafenib, in combination with binimetinib for the treatment of participants with unresectable (unable to be surgically removed) or metastatic (cancer which have spread to different body parts) *BRAF* V600-mutant melanoma.

What was the purpose of this study?

There were 2 parts to this study.

- The main purpose of Part 1 was to learn about the safety of the study drugs when combined to identify the highest dose of dual combination of encorafenib and binimetinib and triple combination of encorafenib, binimetinib, and ribociclib that is well tolerated by participants with advanced solid tumors with *BRAF* V600 mutation without causing any serious medical problems. This is known as the maximum tolerated dose (MTD). Researchers also wanted to find a recommended safe dose of the study drugs to be used in Part 2 of the study.
- The main purpose of Part 2 was to learn how well the drug combination can reduce the tumor and/or stop the tumor from growing (also called clinical efficacy), and to study the safety of the study drug combination in participants with metastatic melanoma or colorectal (cancer in the rectum) cancer.

Researchers wanted to know:

- **What was the highest tolerated dose and recommended safe dose of encorafenib and binimetinib dual combination, and encorafenib, binimetinib, and ribociclib triple combination?**
- **Did participants have any "dose-limiting toxicities"?**
- **Did participants taking the dual combination of encorafenib and binimetinib, and triple combination of encorafenib, binimetinib, and ribociclib have positive effects on their tumors?**
- **What medical problems did participants have during the study?**

What happened during the study?

How was the study done?

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

In Phase 1b of the study, researchers tested the safety and tolerability of dual combination of encorafenib and binimetinib, and triple combination of encorafenib, binimetinib, and ribociclib on a group of study participants with advanced solid tumors with *BRAF* V600 mutation. "Tolerability" refers to how well participants can tolerate taking the study treatment.

The main purpose of Part 2 of the study was to learn whether dual combination of encorafenib and binimetinib, and triple combination of

encorafenib, binimetinib, and ribociclib had positive effects for Phase 2 study participants with advanced solid tumors with *BRAF* V600 mutation.

The Phase 2 study population was divided into three arms:

Arm 1 (Dual combination): Metastatic *BRAF* V600-mutant metastatic colorectal cancer (mCRC) participants.

Arm 2 (Dual combination): metastatic *BRAF* V600-mutant melanoma participants who have progressed after prior selective *BRAF* inhibitor treatment.

Arm 3 of the dual combination / Arm A of the triple combination: metastatic *BRAF* V600-mutant melanoma participants who are naive to prior selective *BRAF* inhibitor treatment.

Participants received continuous treatment in cycles for 28 days in each cycle. Researchers did this by giving participants increasing doses (dose escalation) of dual combination of encorafenib and binimetinib, and triple combination of encorafenib, binimetinib, and ribociclib for once daily on a continuous schedule (encorafenib), twice daily on a continuous schedule (binimetinib), and once daily (ribociclib) 21 consecutive days followed by a 7-day planned break (three week on, one week off schedule) until, their cancer got worse, they experienced unacceptable medical problems, they left the study, the participant died, they started new anticancer treatment, they stopped study treatment for other reasons, or the Sponsor closed the study.

Participants entering Phase 1b received the following dual combination:

- Encorafenib 50 mg/100 mg/200 mg/400 mg/450 mg/600 mg/800 mg once daily + binimetinib 45 mg twice daily

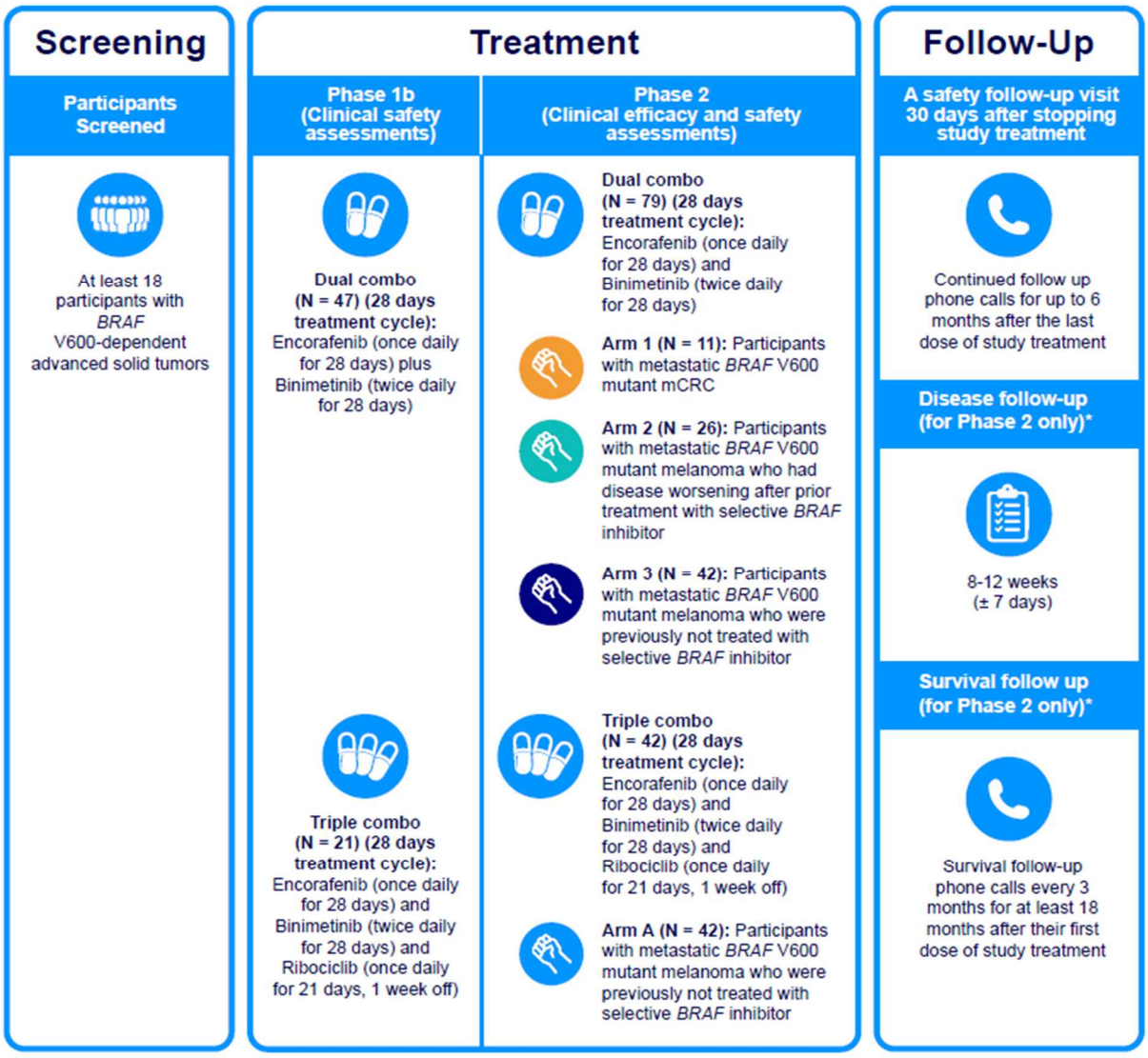
Participants entering Phase 2 received the following dual combination:

- Encorafenib 600 mg/450 mg once daily + binimetinib 45 mg twice daily

Participants entering Phase 1b/2 received the following triple combination:

- Arm A: Encorafenib 200 mg once daily + binimetinib 45 mg twice daily + ribociclib 100 mg/ 200 mg/ 400 mg/ 600 mg once daily

Figure 1: Study Design



NOTE: Participants treated until their cancer got worse, they experienced unacceptable medical problems, they left the study.
** Survival follow-up & disease follow-up was no longer performed for participants who discontinued study treatment in the Phase II part of the study.*

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. "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 find the recommended dose of a study treatment. They also looked at the general safety of different doses.

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

Where did this study take place?

The Sponsor ran this study at 17 locations in 9 countries in Australia, Asia, Europe, and North America.

When did this study take place?

It began 28 May 2012 and ended 09 March 2023. For results of dual combination assessments, 31 August 2015 was considered as the end date.

Who participated in this study?

The study included participants who were at least 18 years old. They must have been diagnosed with advanced solid tumors 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

Phase 1b (Dual Combination) - A total of 47 participants treated with dual combination therapy were enrolled in the Phase 1b of the study:

- A total of 25 men participated
- A total of 22 women participated
- All participants were between the ages of 24 and 89

All 47 participants discontinued study Phase 1b treatment (stopped taking the study medication) because their cancer got worse (32 [68.1%]), they experienced unacceptable medical problems (6 [12.8%]), they left before the study was over by their choice or a doctor decided it was best for a participant to stop being in the study (3 [6.4%]) or they died (2 [4.3%]).

Two (2 [4.3%]) participants left before the study was over due to other issues and two participants left the study due to change from the study design (2 [4.3%]).

Phase 2 (Dual Combination) - A total of 79 participants (Arm 1 [mCRC] 11 participants; Arm 2 [prior *BRAF* inhibitor {*BRAF*i} melanoma] 26 participants; Arm 3 [*BRAF*i-naïve melanoma] 42 participants) treated with dual combination therapy were enrolled in the Phase 2 of the study:

- A total of 53 men participated
- A total of 26 women participated
- All participants were between the ages of 23 and 86

All 79 participants discontinued the study Phase 2 treatment (stopped taking the study medication) because their cancer got worse (61 [77.2%]), they experienced unacceptable medical problems (9 [11.4%]), they left before the study was over by their choice or a doctor decided it was best for a participant to stop being in the study (3 [3.8%]), or they died (2 [2.5%]).

Three (3 [3.8%]) participants left before the study was over due to other issues and (1 [1.3%]) participant left the study due to change from the study design.

Phase 1b/2 (Triple Combination) - A total of 63 participants were treated with triple combination therapy:

- 21 participants were enrolled in the Phase 1b of the study
- 42 participants were enrolled in Arm A of Phase 2 study

All the 63 participants who started the study did not finish the study (stopped taking the study medication) because their cancer got worse (38 [60.3%]), they experienced unacceptable medical problems (18 [28.6%]), or they died (2 [3.2%]).

Among the remaining 5 participants, (1 [1.6%]) participant left before the study was over by their choice or a doctor decided it was best for a participant to stop being in the study and (4 [6.3%]) participants left before the study was over due to other issues.

How long did the study last?

Study participants were in the study for varied amount of time. The entire study took approximately 11 years to complete.

The study completed as planned. When the study ended in March 2023, the Sponsor began reviewing 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?

How safe and well tolerated was encorafenib, binimetinib, and ribociclib?

Researchers looked at the medical problems that participants had in the 28 days after their first dose of dual combination of encorafenib and binimetinib and triple combination of encorafenib, binimetinib, and ribociclib to see if there were DLTs. Researchers also looked at results of laboratory tests to see if there were any abnormal results of concern. This helped researchers decide if each dose was safe and well tolerated, and if it was safe to give a higher dose of the drug.

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

Did participants who took dual combination of encorafenib and binimetinib and triple combination of encorafenib, binimetinib, and ribociclib have any "dose-limiting toxicities"?

Phase 1b (Dual combination)

All 47 (100%) participants were dosed with 45 mg binimetinib twice daily. Seven dose levels of encorafenib were evaluated in the Phase 1b part of the study: 50 mg, 100 mg, 200 mg, 400 mg, 450 mg, 600 mg, and 800 mg. Only 1 participant (2.3%) (in the encorafenib 800 mg once daily + binimetinib 45 mg twice daily cohort) experienced a DLT that was rated as Grade 3, which means that study doctors considered the events to be severe or medically significant.

At the dose level of encorafenib 600 mg once daily + binimetinib 45 mg twice daily, 3 participants experienced Grade 3 creatinine increases. Hence, dose of encorafenib 450 mg once daily + binimetinib 45 mg twice daily was selected as the dose combination for all future enrolment.

Phase 1b (Triple Combination)

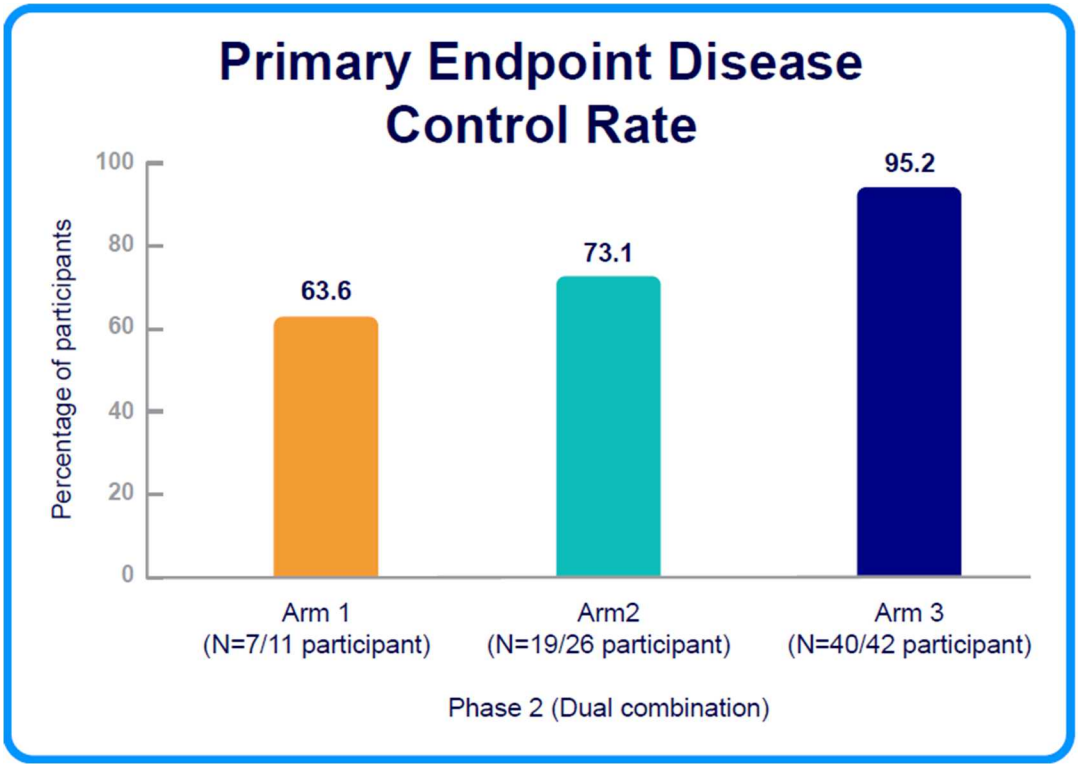
All 47 (100%) participants were dosed with encorafenib 200 mg once daily + binimetinib 45 mg twice daily. Four ribociclib doses levels 100 mg, 200 mg, 400 mg, and 600 mg once daily were evaluated in the Phase 1b. On average, all participants who took the study medication had no DLTs. Encorafenib 200 mg once daily + binimetinib 45 mg twice daily + ribociclib 600 mg once daily was declared as the recommended Phase 2 dose (R2PD) and was applied as the starting dose for participants with locally advanced or metastatic *BRAF* V600 mutant melanoma who are naïve to previous treatment with a selective *BRAF* inhibitor in Phase 2.

Did the study medications have positive effects on the participants tumors as measured by Disease Control Rate (DCR)?

Phase 2 (Dual combination)

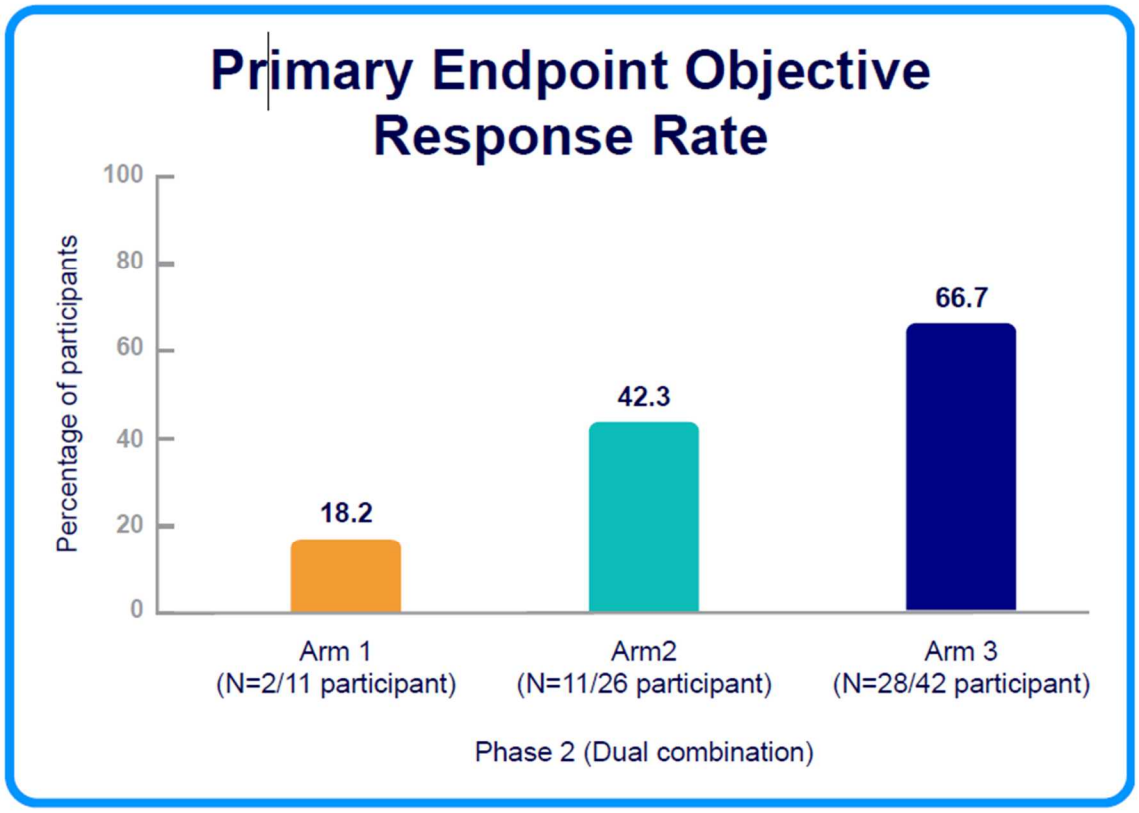
Seven (7) out of 11 participants (63.6%) had met the criteria of disease control which is the percentage of participants whose disease shrank or remained stable over a certain time period in the mCRC population (Arm 1). 19 out of 26 participants (73.1%) had met the criteria of DC in the prior *BRAF*i melanoma population (Arm 2) and 40 out of 42 participants (95.2%) had met the criteria for the *BRAF*i-naive melanoma population (Arm 3).

Figure 2: Disease Control Rate (Dual combination)



Two (2) out of 11 participants (18.2%), 11 out of 26 participants (42.3%) and 28 out of 42 participants (66.7%) met the criteria of objective response which is the percentage of participants whose cancer got better (their tumor shrank or disappeared) during Phase 2 of the study, in Arm 1, Arm 2, and Arm 3, respectively.

Figure 3: Objective Response Rate (Dual combination)



Phase 2 (Triple Combination)

Twenty-five (25) out of 42 (59.5%) *BRAF*i-naïve melanoma participants met the criteria of objective response during Phase 2 of the study (triple combination).

Based on these results, the researchers have decided that treatment with the combination of encorafenib, binimetinib, and ribociclib may offer a new standard of care for participants with *BRAF V600* mutant melanoma.

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.

Forty-six (46) out of 47 (97.9%) participants in Phase 1b (dual combination) of this study had at least 1 medical problem, 74 out of 79 (93.7%) participants in Phase 2 of this study (dual combination) had at least 1 medical problem, and 58 out of 63 (92.1%) participants in Phase 1b/2 of the study (triple combination had at least 1 medical problem. A total of 6 (12.8%) participants in Phase 1b (dual combination), 9 (11.4%) participants in Phase 2 (dual combination), and 18 (28.6%) participants in Phase1b/2 (triple combination) left the study treatment because of medical problems. The most common medical problems – those reported by more than 25% of participants – 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 the study (Phase 1b, Phase 2, and Phase 1b/2). All medical problems reported by more than 25% of participants are listed.
- The **2nd – 4th** column tells how many of the participants in each treatment group reported each medical problem. Next to this number is the percentage of the participants taking the study medication who reported the medical problem.
- Using these instructions, you can see that:
    - A total of 26 out of the 47 (55.3%) participants taking the dual combination study medication in Phase 1b of the study reported diarrhea.
    - A total of 42 out of the 79 (53.2%) participants taking the dual combination study medication in Phase 2 of the study reported diarrhea.
    - A total of 27 out of the 63 (42.9%) participants taking the triple combination study medication in Phase 1b/2 of the study reported diarrhea.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Phase 1b Dual Combination (47 Participants)	Phase 2 Dual Combination (79 Participants)	Phase 1b/2 Triple Combination (63 Participants)
Nausea	28 out of 47 participants (59.6%)	39 out of 79 participants (49.4%)	24 out of 63 participants (38.1%)
Diarrhea	26 out of 47 participants (55.3%)	42 out of 79 participants (53.2%)	27 out of 63 participants (42.9%)
Vomiting	22 out of 47 participants (46.8%)	32 out of 79 participants (40.5%)	21 out of 63 participants (33.3%)
Constipation	21 out of 47 participants (44.7%)	22 out of 79 participants (27.8%)	16 out of 63 participants (25.4%)
Feeling tired (Fatigue)	21 out of 47 participants (44.7%)	24 out of 79 participants (30.4%)	20 out of 63 participants (31.7%)
Abdominal pain	18 out of 47 participants (38.3%)	-	-
Fever (Pyrexia)	12 out of 47 participants (25.5%)	28 out of 79 participants (35.4%)	19 out of 63 participants (30.2%)
Headache	16 out of 47 participants (34.0%)	-	-

Table 1. Commonly reported medical problems by study participants

Medical Problem	Phase 1b Dual Combination (47 Participants)	Phase 2 Dual Combination (79 Participants)	Phase 1b/2 Triple Combination (63 Participants)
Abnormally low levels of white blood cells called neutrophils (Neutropenia)	-	-	21 out of 63 participants (33.3%)
Joint pain (Arthralgia)	-	26 out of 79 participants (32.9%)	-
Increased muscle protein (Blood creatine phosphokinase increased)	-	21 out of 79 participants (26.6%)	20 out of 63 participants (31.7%)
Cough	13 out of 47 participants (27.7%)	20 out of 79 participants (25.3%)	-
Low levels of red blood	-	-	17 out of 63 participants (27.0%)

Table 1. Commonly reported medical problems by study participants

Medical Problem	Phase 1b Dual Combination (47 Participants)	Phase 2 Dual Combination (79 Participants)	Phase 1b/2 Triple Combination (63 Participants)
cells (Anemia)			
Pain in extremity	12 out of 47 participants (25.5%)	-	-
Vision blurred	12 out of 47 participants (25.5%)	-	-
Aspartate aminotransferase increased (sign of liver damage)	-	20 out of 79 participants (25.3%)	-

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.

Overall, 19 participants (40.4%) who received dual combination therapy in Phase 1b of the study reported at least 1 serious medical problem during Phase 1b of the study.

- The most common serious medical problems were cancer pain in 3 participants (6.4%), followed by abdominal pain, nausea, vomiting, fever (pyrexia), dizziness, seizure, and acute kidney injury (2 participants [4.3%] each).
- All, except 2 serious medical problems (blood vessel blockage through your retinal vein and eye problems caused by high blood pressure) in 2 participants were not related to at least 1 of the study treatments.

Overall, 31 participants (39.2%) who received dual combination therapy in Phase 2 of the study had serious medical problems.

- The most common serious medical problems reported was vomiting in 6 participants (7.6%); followed by nausea and pyrexia (5 participants [6.3%] each); high creatinine levels causing kidney disease (hypercreatininemia) (4 participants [5.1%]); abnormally low levels of sodium in the blood (hyponatremia) (3 participants [3.8%]); and anemia, diarrhea, intestinal obstruction, and headache (2 participants [2.5%] each).
- All, except serious medical problems of diarrhea (2 events), high creatinine levels causing kidney disease (hypercreatininemia), tumor lysis syndrome, fever (pyrexia), eye problems (visual impairment), diarrhea, vomiting, eye inflammation (iritis), kidney disorder (renal failure), ALT (alanine aminotransferase) and AST (aspartate aminotransferase) liver test increased in 10 participants were not related to at least 1 of the study treatments.

Overall, 49.2% participants who received triple combination therapy in Phase 1/2b of the study had serious medical problems.

- The most common serious medical problems reported by participants in the triple combination therapy in Phase 2 of the study was intestinal obstruction, fever (pyrexia), and vomiting (3 out of 63 [4.8%] each). No other serious medical problems were reported in more than 2 participants.

A total of 7 participants (14.9%) died in Phase 1b and 8 participants (10.1%) died in Phase 2 of the study treatment. These deaths mainly occurred due to the participant's 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	Use the protocol number **C4221005**

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

www.clinicaltrials.gov	Use the study identifier **NCT01543698**
www.clinicaltrialsregister.eu	Use the study identifier **2011-005875-17**

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!