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), binimetinib (PF-06811462)
Protocol Number:	C4221009 (ARRAY-818-302, BEACON CRC)
Dates of Study:	13 October 2016 to 10 November 2022
Title of this Study:	Binimetinib, Encorafenib, And Cetuximab Combined to Treat *BRAF*-mutant ColoRectal Cancer [A Multicenter, Randomized, Open-Label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab with a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With *BRAF* V600E-mutant Metastatic Colorectal Cancer]
Date(s) of this Report:	14 June 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 colorectal cancer?

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). Participants in this study had metastatic colorectal cancer, which means that the cancer had spread outside of the colon or rectum. In addition, the participants in this study had cancer cells which contained a specific change (mutation) in a gene called *BRAF*. Having the *BRAF* V600E mutation may cause the cancer cells to grow and spread.

What are encorafenib, binimetinib, cetuximab, irinotecan, and FOLFIRI?

Encorafenib (en-koe-raf-e-nib) (also known by the brand name Braftovi®) and binimetinib (bin i me-ti-nib) (also known as Mektovi®) are both 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 binimetinib were both investigational medicines in this study when it began in 2016. This means these medicines were still being tested and were not approved for use in patients with metastatic colorectal cancer with a *BRAF* V600E mutation.

Cetuximab (se-tux-i-mab), irinotecan (ir-in-oh-TEE-kan), and FOLFIRI are the other treatments used in this study. These medicines are all approved for treating patients with metastatic colorectal cancer, either as single agents on their own, or together with other medicines as part of a combined treatment regimen. FOLFIRI itself is a combined treatment of 3 separate medicines: irinotecan, 5-fluorouracil, and folinic acid.

Different combinations of these investigational and approved medicines were tested during this study. These were as follows:

- Triplet combination treatment: encorafenib + binimetinib + cetuximab
- Doublet combination treatment: encorafenib + cetuximab
- Control treatment: either irinotecan/cetuximab or FOLFIRI/cetuximab

Encorafenib was given as capsules and binimetinib was given as tablets; both medicines were taken by mouth. Cetuximab, irinotecan, and FOLFIRI were all given by injection through a needle into the vein; this is known as "intravenous" (IV).

During this study, the United States Food and Drug Administration approved the doublet combination of encorafenib + cetuximab for treating patients with metastatic colorectal cancer with a *BRAF* V600E mutation after prior therapy. This was in April 2020. The European Medicines Agency gave their approval in June 2020. In November 2020, the triplet combination of binimetinib + encorafenib + cetuximab and the doublet combination of encorafenib + cetuximab were approved in Japan for treating patients with unresectable (unable to be surgically removed) late-stage or recurrent (cancer has come back after treatment) colorectal cancer, which has a *BRAF* mutation.

What was the purpose of this study?

There were 2 parts to this study. Only the triplet combination was tested in Part 1. In Part 2, participants could receive the triplet combination, the doublet combination, or the control treatment.

- The main purpose of Part 1 was to learn about the safety and tolerability of the triplet combination treatment. "Tolerability" refers to how well participants can tolerate taking the study treatment.

- The main purpose of Part 2 was to learn whether the triplet combination had positive effects for participants with metastatic colorectal cancer with a *BRAF* V600E mutation, compared to the control treatment. In addition, one of the key secondary purposes of Part 2 was to learn whether the doublet combination had positive effects on participants, compared to the control treatment.
- Irinotecan/cetuximab and FOLFIRI/cetuximab were chosen as the control (or otherwise considered standard) treatments in this study because both therapies are approved for treating patients with metastatic colorectal cancer.

Researchers wanted to know:

1. **Part 1: did participants have any "dose-limiting toxicities"?**
2. **Part 1: did participants have any abnormal laboratory tests, blood pressure and body measurements, electrocardiogram tests, imaging tests of the heart, and vision tests?**
3. **Part 1: did participants have medical problems leading to dose changes or stopping study treatment?**
4. **Part 2: how many participants had their cancer get better when receiving triplet (encorafenib + binimetinib + cetuximab) or doublet combinations (encorafenib + cetuximab) compared to the control treatment?**
5. **Part 2: did participants receiving the triplet (encorafenib + binimetinib + cetuximab) or doublet**

combinations (encorafenib + cetuximab) live longer compared to participants receiving the control treatment?

6. What medical problems did participants have during the study?

"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.

What happened during the study?

How was the study done?

Participants joined either Part 1 or Part 2 of this study. Part 2 was started after the researchers had reviewed some of the results from Part 1; this happened before Part 1 was fully completed.

This study was an "open-label" study, which means that participants and researchers knew which medicines the participants received.

Part 1

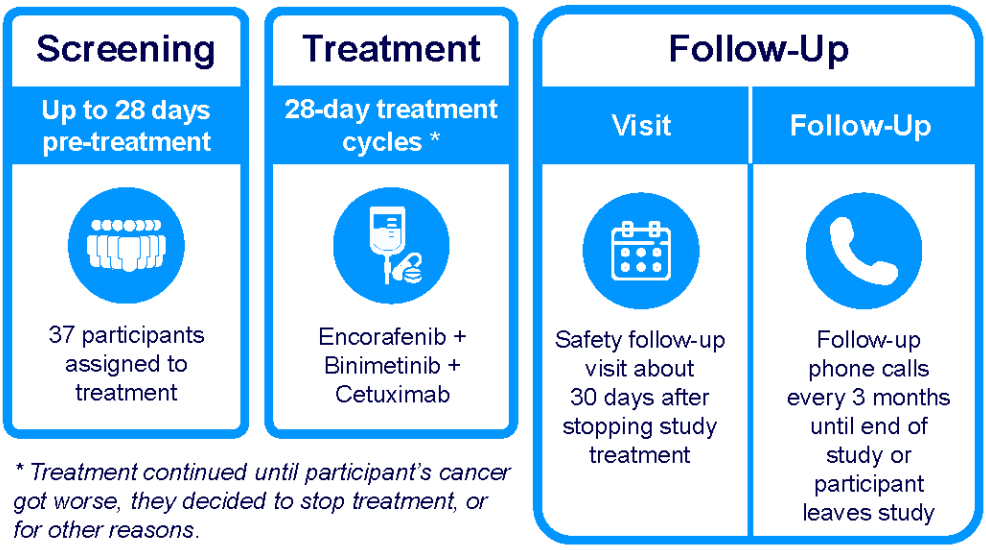
All participants entering Part 1 of the study received the triplet combination:

- Encorafenib 300 mg once daily by mouth +
- Binimetinib 45 mg twice daily by mouth +
- Cetuximab once weekly (or every 2 weeks) at standard approved dose by IV infusion.

Note: During this study, the recommended dosing frequency of cetuximab was changed from once weekly to every 2 weeks.

The study treatments were given in 28-day "treatment cycles". Participants were to attend a screening visit, 4 visits during their first 28-day treatment cycle, 2 visits during each subsequent cycle, an end of treatment visit, and a safety follow-up visit about 30 days after stopping treatment. Participants were then contacted by phone every 3 months until they left the study, or the study ended. Figure 1 shows what happened during Part 1.

Figure 1. Study Design for Part 1



Part 2

Participants entering Part 2 of the study were put into 1 of 3 treatment groups. They were assigned to each group by chance alone; this is known as "randomized". This helps to make the groups more even to compare.

The triplet combination group received the following treatments:

- Encorafenib 300 mg once daily by mouth +

- Binimetinib 45 mg twice daily by mouth +
- Cetuximab once weekly (or every 2 weeks) at standard approved dose by IV infusion.

The doublet combination group received the following treatments:

- Encorafenib 300 mg once daily by mouth +
- Cetuximab once weekly (or every 2 weeks) at standard approved dose by IV infusion.

The control group received either of the following:

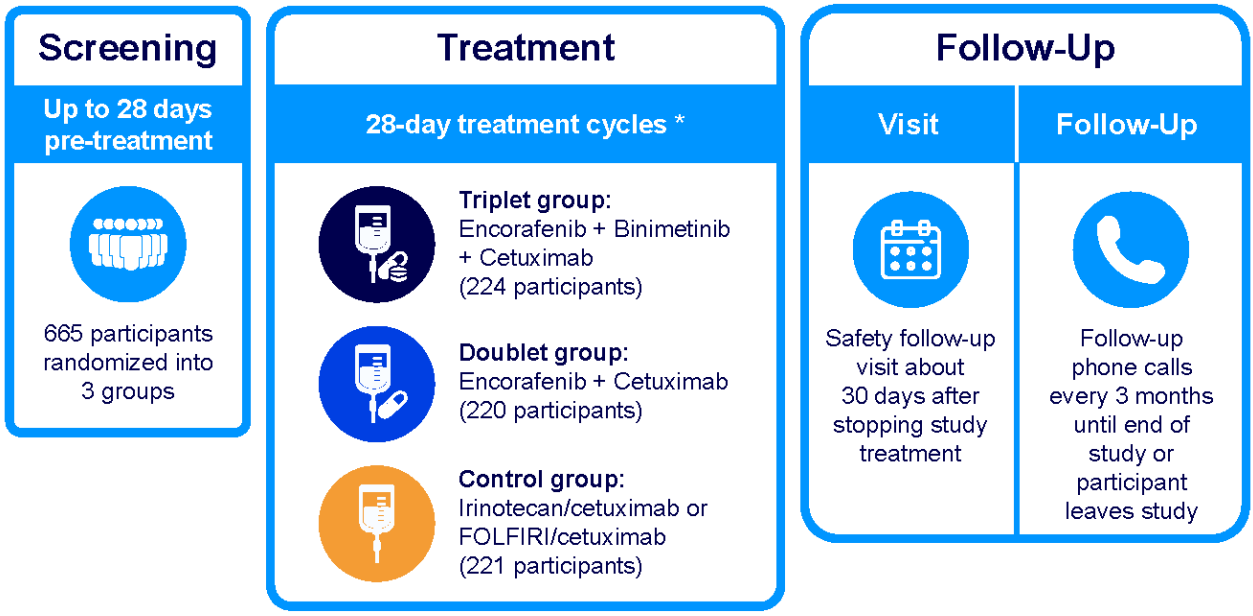
- Irinotecan every 2 weeks at standard approved dose by IV infusion +
- Cetuximab once weekly (or every 2 weeks) at standard approved dose by IV infusion.

Or

- FOLFIRI every 2 weeks at standard approved dose by IV infusion +
- Cetuximab once weekly (or every 2 weeks) at standard approved dose by IV infusion.

It was the study doctor's choice about which of the control treatments a participant would receive if assigned to that group. The study treatments were given in 28-day "treatment cycles" and participants attended study center visits as described previously for Part 1 of the study. Figure 2 shows what happened during Part 2.

Figure 2. Study Design for Part 2



** Treatment continued until participant's cancer got worse, they decided to stop treatment, or for other reasons.*

In Part 1 and Part 2, participants were treated 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.

During Part 1 and Part 2, the researchers took samples of blood and urine from the participants. Researchers also checked the participants' health and asked them how they were feeling. Researchers also looked at the results of laboratory tests, blood pressure and body measurements, electrocardiogram (ECG) tests, imaging tests to see how the heart pumps blood, and vision tests. An ECG is a machine that looks at how well the heart is working when it pumps blood around the body.

In Part 2, researchers also measured the effect of the study treatment on the participants' cancer by looking at images of their tumors before, during and after treatment.

Where did this study take place?

The Sponsor ran this study at 221 locations in 28 countries in North America, South America, Europe, Asia, and Australia.

When did this study take place?

It began 13 October 2016 and ended 10 November 2022.

Who participated in this study?

The study included adult participants who had a confirmed diagnosis of metastatic colorectal cancer, with a *BRAF* V600E mutation. Participants must have received at least 1 but no more than 2 previous treatments for their metastatic colorectal cancer, but the treatment was not effective or had stopped working.

A total of 702 participants joined this study: 37 participants in Part 1, and 665 participants in Part 2.

In Part 1,

- A total of 15 men and 22 women participated
- All participants were between the ages of 36 and 77

In Part 2,

- A total of 313 men and 352 women participated
- All participants were between the ages of 26 and 91

Of the 37 participants who started Part 1 and received treatment, all 37 participants (100%) stopped taking the study treatment. The most common reason for participants stopping study treatment was because their cancer got worse (26 participants [70.3%]). All 37 participants in Part 1 left before the study was over because of death, the Sponsor closed

the study, the participants were unavailable for follow-up, or due to other reasons. Most participants in Part 1 left the study because they died (30 participants [81.1%]).

Of the 665 participants who started Part 2, 631 participants (94.9%) received treatment. There were 34 participants (5.1%) who were assigned to treatment in Part 2 but were not treated. For the 631 participants who received treatment in Part 2, the most common reason for stopping study treatment was because their cancer got worse (460 participants [69.2%]). All 665 participants in Part 2 left before the study was over by their choice, or because of death, the Sponsor closed the study, the participants were unavailable for follow-up, or due to other reasons. Most participants in Part 2 left the study because they died (600 participants [90.2]).

How long did the study last?

The amount of time that participants were in the study varied. The entire study took about 6 years and 1 month to complete.

The study ended in November 2022. The Sponsor reviewed all information collected and created a report of the results. This is a summary of that report.

What were the results of the study?

Part 1: Did participants have any "dose-limiting toxicities"?

- In Part 1, 34 out of 37 participants who received the triplet combination of encorafenib + binimetinib + cetuximab were assessed for DLTs during their first treatment cycle (Cycle 1).
- Three (3) participants were excluded from this assessment as they did not receive a sufficient dose of the planned study treatments.

- There were 6 out of 34 participants who had medical problems considered as DLTs during their first treatment cycle.
- These DLTs included immune reactions (2 participants), eye problems (2 participants), signs of heart failure (1 participant), and increased creatinine levels (sign of kidney problems; 1 participant).

Based on these results, the triplet combination of encorafenib 300 mg once daily + binimetinib 45 mg twice daily + standard approved dose of cetuximab once weekly (or every 2 weeks) was determined by the researchers to be safe and tolerated by study participants.

This allowed Part 2 of the study to be started, using the same doses of encorafenib and binimetinib as were given during Part 1.

Part 1: Did participants have any abnormal laboratory tests, blood pressure and body measurements, ECG tests, imaging tests of the heart, and vision tests?

What were the results of laboratory tests after participants had taken Encorafenib, Binimetinib, and Cetuximab in Part 1?

- In Part 1 of the study, abnormal laboratory values reported in at least 10% of participants were low hemoglobin (an iron-rich protein in red blood cells that carries oxygen to tissues) (29.7%), low lymphocytes (type of white blood cells) (21.6%), increased liver enzyme - ALT (10.8%), increased liver enzyme - AST (10.8%), low protein, albumin (35.1%), low calcium (13.5%), increased muscle enzyme – creatinine kinase (21.6%), increased chemical found in kidneys – creatinine (32.4%), increased blood sugar, glucose (15.8%), and low levels of minerals magnesium (10.8%), potassium (10.8%), and sodium (10.8%).

What were the results of the blood pressure and body measurement tests after participants had taken Encorafenib, Binimetinib, and Cetuximab in Part 1?

- There were 37 participants assessed for blood pressure and body measurement abnormalities during Part 1 of the study. Two numbers are recorded while measuring blood pressure. Abnormal increase in the top number was reported in 16.2% of subjects, and abnormal increase in the bottom number was reported in 13.5% of subjects.
- Abnormal decrease in the top number was reported in 13.9% of subjects, and abnormal decrease in the bottom number was reported in 13.5% of subjects.
- Body measurement changes observed in at least 10% of participants were high temperature (34.4%), low temperature (57.6%), and weight gain of 10% or more (13.5%).

What were the results of the ECG tests after participants had taken Encorafenib, Binimetinib, and Cetuximab in Part 1?

- One (1) out of the 37 participants reported abnormal ECG during Part 1 of the study. Abnormal ECG results were not considered a medical problem or related to the study treatment by the researchers.

What were the results of the imaging tests of the heart after participants had taken Encorafenib, Binimetinib, and Cetuximab in Part 1?

- During the study, researchers took images of the heart to measure how well participants' heart was pumping and how much blood the

bottom left chamber of their heart pumped out with each heartbeat. There were 37 participants whose heart pumping was measured during Part 1 of the study. Of these, 9 participants had less blood pumped during each heartbeat. Less blood pumped during each heartbeat considered a medical problem was reported in 5 of the 9 participants. Researchers thought that this may be related to the study treatment.

How many participants had vision problems after they had taken Encorafenib, Binimetinib, and Cetuximab in Part 1?

- Vision tests were done in 37 participants in Part 1 of the study. Of these, 1 participant reported reduced visual acuity, that is, they did not have a normal 20/20 vision. This was not considered a medical problem by the researchers.

Part 1: Did participants have medical problems leading to dose changes or stopping study treatment?

- In Part 1, 16 out of 37 participants (43.2%) had medical problems leading to a lowering of the dose for any study drug.
- Thirty (30) out of 37 participants (81.1%) in Part 1 had medical problems leading to stopping of any study drug temporarily.
- Eight (8) out of 37 participants (21.6%) in Part 1 had medical problems leading to stopping of any study drug permanently.
- Two (2) out of 37 participants (5.4%) in Part 1 had medical problems leading to stopping of all study drug permanently.

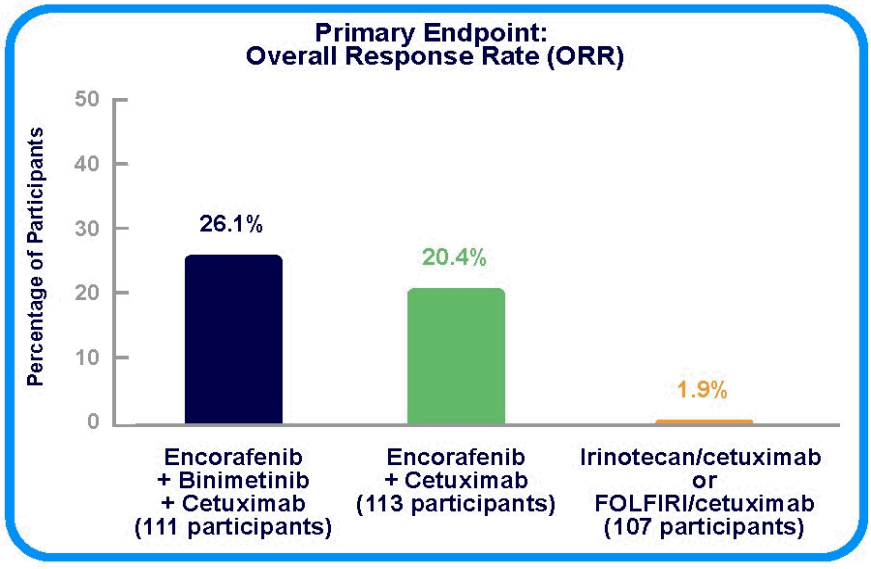
Medical problems are discussed in full in the next section of this document.

In Part 2, how many participants had their cancer get better when receiving triplet (encorafenib + binimetinib + cetuximab) or doublet combinations (encorafenib + cetuximab) compared to the control treatment?

To answer this question, the researchers measured the “overall response rate”, which is the percentage of participants whose cancer got better (their tumor shrank or disappeared) during Part 2 of the study.

In Part 2 of the study, based on the data collected through 11 February 2019, a total of 26.1% of participants in the triplet combination group and 20.4% of participants in the doublet combination group had their cancer get better, compared to 1.9% of participants in the control group. These results are shown in Figure 3.

Figure 3. Percentage of Participants Whose Cancer Got Better

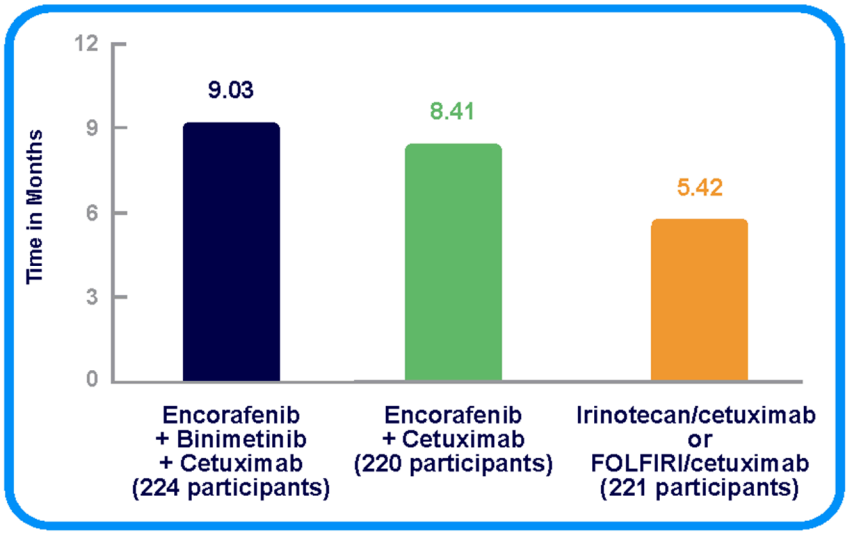


In Part 2, did participants receiving the triplet (encorafenib + binimetinib + cetuximab) or doublet combinations (encorafenib + cetuximab) live longer compared to participants receiving the control treatment?

To answer this question, the researchers looked at "overall survival" during Part 2 of the study. Overall survival measures how long a participant lives. The researchers looked at the time from the start of the study treatment until the time half of the participants were still alive. This is known as the "median" overall survival time.

In Part 2 of the study, based on the data collected through 11 February 2019, the median overall survival time was 9.03 months in the triplet combination group and 8.41 months in the doublet combination group, compared to 5.42 months in the control group. These results are shown in Figure 4.

Figure 4. Median Overall Survival Time



Based on the results shown in Figure 3 (percentage of participants whose cancer got better) and Figure 4 (median overall survival time), the researchers have decided that the differences between the triplet and the control groups, and the doublet and control groups were not likely the result by chance. The triplet combination of encorafenib + binimetinib + cetuximab and the doublet combination of encorafenib + cetuximab may be a better treatment than the control treatment to have positive effects for participants with metastatic colorectal cancer with a *BRAF* V600E mutation.

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 this study, all 37 participants (100%) had at least 1 medical problem. A total of 8 participants (21.6%) in Part 1 permanently stopped taking at least 1 of the study treatments because of medical problems.

In Part 2 of this study, 220 participants (99.1%) in the triplet combination group, 212 participants (98.1%) in the doublet combination group, and

190 participants (98.4%) in the control group had at least 1 medical problem. A total of 39 participants (17.6%) in the triplet combination group, 27 participants (12.5%) in the doublet combination group, and 33 participants (17.1%) in the control group in Part 2 permanently stopped taking at least 1 of the study treatments because of medical problems.

Table 1 shows the most common medical problems – those reported by at least 20% of participants in any of the treatment groups in Part 1 or Part 2 of the study.

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 20% of participants in any treatment group are listed.
- The **2nd – 5th** 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 treatment who reported the medical problem.
- Using these instructions, you can see that:
  - In Part 1, 29 out of the 37 participants (78.4%) taking the triplet combination treatment reported diarrhoea.
  - In Part 2, 150 out of 222 participants (67.6%) taking the triplet combination treatment, 85 out of 216 participants (39.4%) taking the doublet combination treatment, and 96 out of 193 participants (49.7%) taking the control treatment reported diarrhoea.

Table 1. Commonly reported medical problems by at least 20% of study participants in Part 1 or Part 2 of the study

Medical Problem	Part 1 Triplet combination (37 Participants)	Part 2 Triplet: combination (222 Participants)	Part 2 Doublet: combination (216 Participants)	Part 2 Control treatment (193 Participants)
Diarrhoea	29 out of 37 participants (78.4%)	150 out of 222 participants (67.6%)	85 out of 216 participants (39.4%)	96 out of 193 participants (49.7%)
Acne-like skin condition	25 out of 37 participants (67.6%)	113 out of 222 participants (50.9%)	65 out of 216 participants (30.1%)	77 out of 193 participants (39.9%)
Nausea	22 out of 37 participants (59.5%)	108 out of 222 participants (48.6%)	82 out of 216 participants (38.0%)	84 out of 193 participants (43.5%)
Low levels of red blood cells	16 out of 37 participants (43.2%)	106 out of 222 participants (47.7%)	44 out of 216 participants (20.4%)	37 out of 193 participants (19.2%)
Vomiting	19 out of 37 participants (51.4%)	100 out of 222 participants (45.0%)	60 out of 216 participants (27.8%)	61 out of 193 participants (31.6%)
Stomach pain	14 out of 37 participants (37.8%)	78 out of 222 participants (35.1%)	62 out of 216 participants (28.7%)	55 out of 193 participants (28.5%)
Feeling tired	20 out of 37 participants (54.1%)	74 out of 222 participants (33.3%)	75 out of 216 participants (34.7%)	54 out of 193 participants (28.0%)
Decreased appetite	15 out of 37 participants (40.5%)	67 out of 222 participants (30.2%)	68 out of 216 participants (31.5%)	56 out of 193 participants (29.0%)

Table 1. Commonly reported medical problems by at least 20% of study participants in Part 1 or Part 2 of the study

Medical Problem	Part 1 Triplet combination (37 Participants)	Part 2 Triplet: combination (222 Participants)	Part 2 Doublet: combination (216 Participants)	Part 2 Control treatment (193 Participants)
Constipation	14 out of 37 participants (37.8%)	64 out of 222 participants (28.8%)	40 out of 216 participants (18.5%)	39 out of 193 participants (20.2%)
Loss of strength or energy	6 out of 37 participants (16.2%)	63 out of 222 participants (28.4%)	52 out of 216 participants (24.1%)	53 out of 193 participants (27.5%)
Fever	16 out of 37 participants (43.2%)	54 out of 222 participants (24.3%)	44 out of 216 participants (20.4%)	30 out of 193 participants (15.5%)
Dry skin	19 out of 37 participants (51.4%)	49 out of 222 participants (22.1%)	28 out of 216 participants (13.0%)	17 out of 193 participants (8.8%)
Rash	3 out of 37 participants (8.1%)	49 out of 222 participants (22.1%)	35 out of 216 participants (16.2%)	28 out of 193 participants (14.5%)
Back pain	8 out of 37 participants (21.6%)	36 out of 222 participants (16.2%)	32 out of 216 participants (14.8%)	27 out of 193 participants (14.0%)
Mouth pain and sores	6 out of 37 participants (16.2%)	32 out of 222 participants (14.4%)	13 out of 216 participants (6.0%)	45 out of 193 participants (23.3%)
Blurred vision	12 out of 37 participants (32.4%)	27 out of 222 participants (12.2%)	10 out of 216 participants (4.6%)	1 out of 193 participants (0.5%)

Table 1. Commonly reported medical problems by at least 20% of study participants in Part 1 or Part 2 of the study

Medical Problem	Part 1 Triplet combination (37 Participants)	Part 2 Triplet: combination (222 Participants)	Part 2 Doublet: combination (216 Participants)	Part 2 Control treatment (193 Participants)
Joint pain	9 out of 37 participants (24.3%)	26 out of 222 participants (11.7%)	52 out of 216 participants (24.1%)	3 out of 193 participants (1.6%)
Increased muscle protein (creatinine phosphokinase) in blood	13 out of 37 participants (35.1%)	26 out of 222 participants (11.7%)	3 out of 216 participants (1.4%)	4 out of 193 participants (2.1%)
Increased creatinine levels (sign of kidney problems)	11 out of 37 participants (29.7%)	25 out of 222 participants (11.3%)	6 out of 216 participants (2.8%)	1 out of 193 participants (0.5%)
Shortness of breath	13 out of 37 participants (35.1%)	24 out of 222 participants (10.8%)	30 out of 216 participants (13.9%)	20 out of 193 participants (10.4%)
Muscle pain	9 out of 37 participants (24.3%)	23 out of 222 participants (10.4%)	35 out of 216 participants (16.2%)	4 out of 193 participants (2.1%)
Cracked skin	9 out of 37 participants (24.3%)	21 out of 222 participants (9.5%)	9 out of 216 participants (4.2%)	13 out of 193 participants (6.7%)
Dizziness	8 out of 37 participants (21.6%)	16 out of 222 participants (7.2%)	16 out of 216 participants (7.4%)	16 out of 193 participants (8.3%)

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 this study, 22 participants (59.5%) had serious medical problems. Of these, researchers believed 10 participants (27.0%) had serious medical problems that were related to at least 1 of the study treatments. The most common serious medical problem reported by participants in Part 1 was infection of the kidneys, bladder, or urethra (4 participants [10.8%]).

In Part 2 of this study, serious medical problems were reported in:

- 118 participants (53.2%) in the triplet combination group. Of these, researchers believed 43 participants (19.4%) had serious medical problems that were related to at least 1 of the study treatments. The most common serious medical problem reported by participants in the triplet group was blockage in intestine (11 participants [5.0%]).
- 91 participants (42.1%) in the doublet combination group. Of these, researchers believed 23 participants (10.6%) had serious medical problems that were related to at least 1 of the study treatments. The most common serious medical problem reported by participants in the doublet group was blockage in intestine (12 participants [5.6%]).
- 78 participants (40.4%) in the control group. Of these, researchers believed 25 participants (13.0%) had serious medical problems that were related to at least 1 of the study treatments. The most common serious medical problem reported by participants in the control group was diarrhoea (10 participants [5.2%]).

A total of 27 participants died during study treatment or within 30 days of stopping study treatment. These “on-treatment” deaths did not include deaths occurring due to the participant’s cancer getting worse. All the on-treatment deaths happened in Part 2 of the study and included:

- 11 participants (5.0%) in the triplet combination group.
- 8 participants (3.7%) in the doublet combination group.
- 8 participants (4.1%) in the control group.

Deaths in 3 participants were considered by the researchers as related to at least 1 of the study treatments: 1 case of hole in the large bowel (Part 2 triplet combination group), 1 case of severe allergic reaction (control group), and 1 case of lung failure (control group).

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 **C4221009**

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

www.clinicaltrials.gov	Use the study identifier **NCT02928224**
www.clinicaltrialsregister.eu	Use the study identifier **2015-005805-35**

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!