

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 study participants. The results of this study might be different than the results of other studies that the researchers review.

Sponsor: Pfizer Inc.

Medicine(s) Studied: Binimetinib, nivolumab, ipilimumab

Protocol Number: C4211004 (ARRAY-162-202)

Dates of Study: 18 October 2017 to 25 February 2021

Title of this Study: Study of Binimetinib + Nivolumab Plus or Minus Ipilimumab in Patients With Previously Treated Microsatellite-stable (MSS) Metastatic Colorectal Cancer With RAS Mutation

[An Open-Label Phase 1b/2 Study of Binimetinib Administered in Combination With Nivolumab or Nivolumab Plus Ipilimumab in Patients With Previously Treated Microsatellite-Stable (MSS) Metastatic Colorectal Cancer With RAS Mutation]

Date(s) of this Report: 20 December 2021; amended 30 May 2022



— Thank You —

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

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

Why was this study done?

What is colorectal cancer?

Colorectal cancer is cancer that starts in the large intestine (colon) 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. Additionally, the participants in this study had tumors that were considered to be "microsatellite stable" (MSS), and which contained a specific mutated gene called RAS that can cause cancer cells to grow and to spread.

What are binimetinib, nivolumab, and ipilimumab?

There were 3 treatments tested in this study: binimetinib, nivolumab, and ipilimumab.

Binimetinib is a treatment that may block the growth and spread of cancer. Binimetinib is taken as a tablet by mouth. In this study, binimetinib was an investigational treatment, which means that it is still being tested and has not been approved for use in patients with colorectal cancer.

Nivolumab and ipilimumab are 2 types of antibody treatments that may help the immune system to fight cancer. Nivolumab and ipilimumab are given through a needle into the vein (IV). In this study, nivolumab and ipilimumab were investigational treatments.

What was the purpose of this study?

The main purposes of this study were to learn more about the safety of binimetinib, nivolumab, and ipilimumab and to determine the recommended dose for further testing, and to learn whether binimetinib, nivolumab, and ipilimumab had positive effects for patients with metastatic colorectal cancer with RAS mutations and that are MSS.

Researchers wanted to know:

Part 1: did participants have dose-limiting toxicities?

Part 2: did participants have a reduction in tumor size?

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

What happened during the study?

How was the study done?

This study was an open-label study, which means that participants and doctors knew what medicines were given to participants. This study was done in 2 parts.

Part 1

The purpose of Part 1 was to find the recommended dose of binimetinib to study in Part 2. During Part 1, participants were assigned to 1 of 2 treatment groups, Group 1A and Group 1B. Group 1A participants received the following treatments:

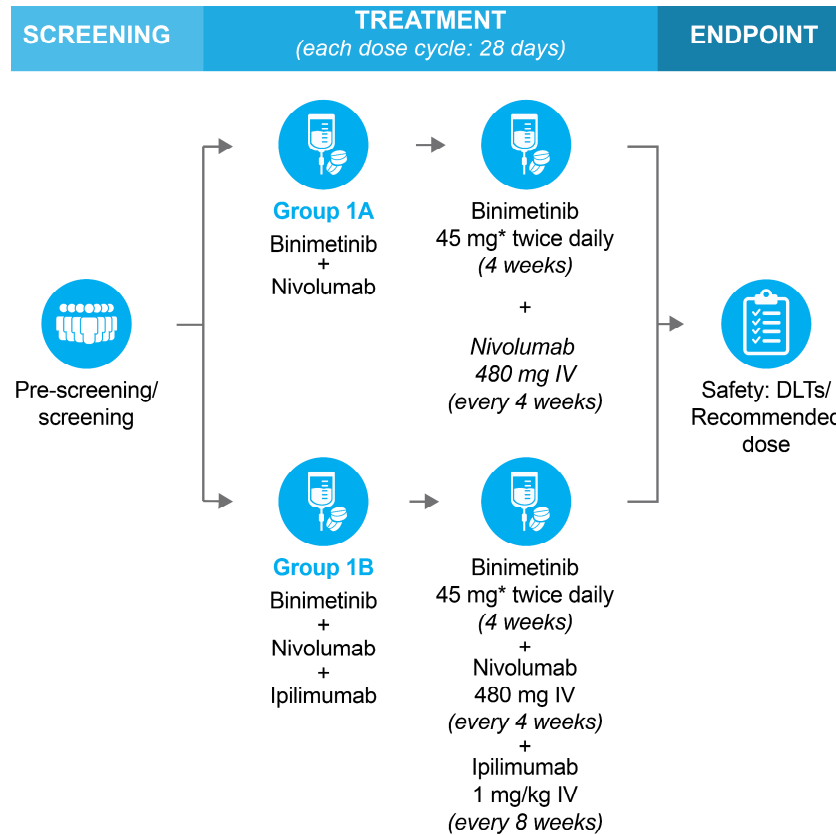
- Binimetinib 45 milligrams (mg) twice daily by mouth for 4 weeks; if this dose level of binimetinib had DLTs, the following lower dose levels of binimetinib were tested in order as follows:
 - 45 mg twice daily for 3 weeks then 1 week off
 - 30 mg twice daily for 4 weeks
 - 30 mg twice daily for 3 weeks then 1 week off
- Nivolumab 480 mg IV over 30 minutes every 4 weeks

Researchers used the results from Group 1A to determine the recommended dose to test in Group 1B. After Group 1A completed study treatment, other participants started Group 1B. Group 1B participants received the following treatments:

- Binimetinib 45 milligram (mg) twice daily by mouth for 4 weeks; if this dose level of binimetinib had DLTs, the following lower dose levels of binimetinib were tested in order as follows:
 - 45 mg twice daily for 3 weeks then 1 week off
 - 30 mg twice daily for 4 weeks
 - 30 mg twice daily for 3 weeks then 1 week off
- Nivolumab 480 mg IV over 30 minutes every 4 weeks
- Ipilimumab 1 mg per kilogram (kg) (1 mg/kg) IV over 30 minutes about every 8 weeks

Participants received study treatments in cycles that lasted 28 days. Participants were to attend visits at the study center on Days 1, 15, and 22 of the first cycle, and on Days 1 and 15 of the following cycles. They were also asked to attend an end of treatment visit within 2 weeks of stopping study treatment, and attend follow-up visits 30 days and 100 days after stopping treatment. They were then contacted by phone 150 days after stopping study treatment, and every 12 weeks until the study ended.

The figure below shows what happened during Part 1.



***There were plans to reduce dose level of binimetinib if needed, but this wasn't necessary*

Abbreviations: mg=milligram; kg=kilogram; IV= intravenous; through a small tube in a vein

Part 2

During Part 2 of the study, participants were randomly assigned to 1 of 2 treatment groups, Group 2A and Group 2B. Randomly means that participants were assigned to the treatment groups by chance, like a flip of a coin. Participants had an equal chance of being in Group 2A or Group 2B.

Group 2A participants received the following treatments:

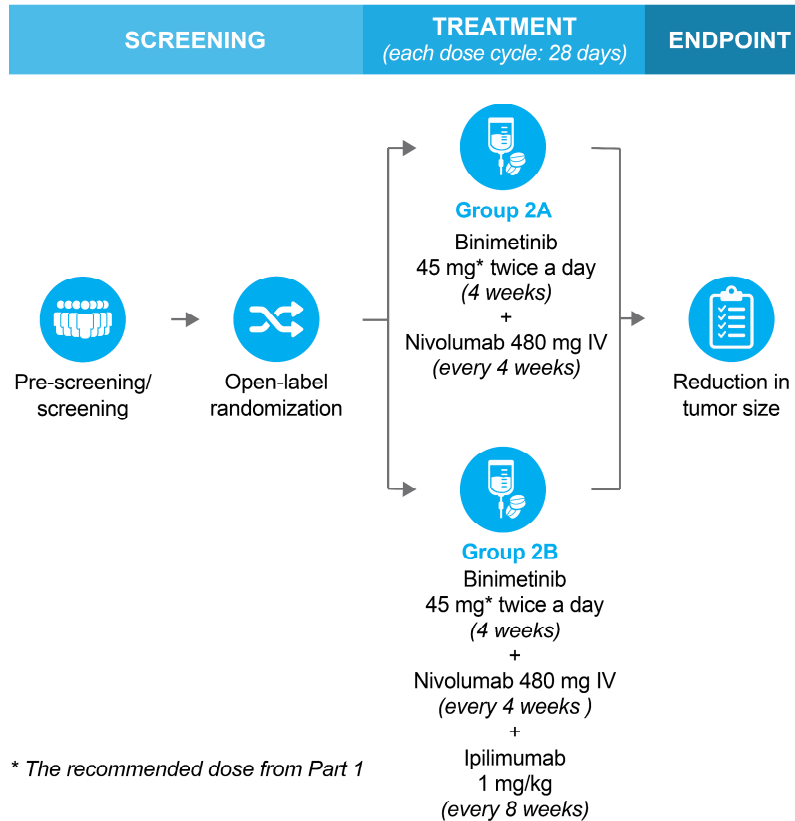
- Binimetinib at the recommended dose from Part 1, given twice a day by mouth for 4 weeks
- Nivolumab 480 mg IV over 30 minutes every 4 weeks

Group 2B participants received the following treatments:

- Binimetinib at the recommended dose from Part 1, twice a day by mouth for 4 weeks
- Nivolumab 480 mg every 4 weeks IV over 30 minutes on Day 1 of each treatment cycle
- Ipilimumab 1 mg/kg IV over 30 minutes about every 8 weeks

Participants received study treatments in cycles that lasted 28 days. Participants were to attend visits at the study center on Days 1, 15, and 22 of the first cycle, and on Days 1 and 15 of the following cycles. They were also asked to attend an end of treatment visit within 2 weeks of stopping study treatment, and attend follow-up visits 30 days and 100 days after stopping treatment. They were then contacted by phone 150 days after stopping study treatment, and every 12 weeks until the study ended.

The figure below shows what happened during Part 2.



Where did this study take place?

The Sponsor ran this study at 22 locations in 5 countries (Belgium, the Netherlands, Spain, the United Kingdom, and the United States).

When did this study take place?

It began 18 October 2017 and ended 25 February 2021.

Who participated in this study?

The study included participants who:

- Were at least 18 years of age
- Had metastatic colorectal cancer that was microsatellite stable
- Had RAS mutation

- Had received at least 1 but no more than 2 prior systemic treatments (treatments that travel through the blood cells to all over the body) for colorectal cancer, and were either unable to tolerate the treatment or had unsatisfactory results
- Had never received certain other treatments for colorectal cancer

A total of 75 participants enrolled in the study and received study treatment. During Part 1, there were 10 participants in Group 1A and 11 participants in Group 1B. During Part 2, there were 27 participants in Group 2A and 27 participants in Group 2B.

The participants included:

- A total of 48 men participated
- A total of 27 women participated
- 53 participants were less than age 65 years old
- 22 participants were age 65 years old or older

Participants could continue receiving study treatment until their colorectal cancer got worse (up to a maximum of 2 years for nivolumab and ipilimumab). Of the 75 participants who started the study:

- 1 (3%) participant who received binimetinib + nivolumab completed the study through the follow-up part of the study
- 5 (13%) participants who received binimetinib + nivolumab + ipilimumab completed the study through the follow-up part of the study

36 (97%) participants who took binimetinib + nivolumab did not finish the study because they:

- Passed away: 28 (76%) participants
- Withdrew consent: 5 (14%) participants
- Were lost to follow-up: 3 (8%) participants

33 (87%) participants who took binimetinib + nivolumab + ipilimumab did not finish the study because they:

- Passed away: 29 (76%) participants
- Withdrew consent: 2 (5%) participants
- Were lost to follow-up: 1 (3%) participant
- Other reason: 1 (3%) participant

How long did the study last?

The entire study took about 3 years and 4 months to complete.

When the study ended in February 2021, 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?

Part 1: did participants have dose-limiting toxicities?

- In Group 1A, 1 out of 9 participants (11%) who received binimetinib + nivolumab had a DLT (severe acne-like rash) during the first treatment cycle.
- In Group 1B, 2 out of 11 participants (18%) who received binimetinib + nivolumab + ipilimumab had DLTs during the first treatment cycle (1 participant had colitis and 1 participant had blurry vision, rash, and inflammation in lungs).

Using this information, the researchers determined that 45 mg twice per day was the recommended dose of binimetinib for further testing.

Part 2: did participants have a reduction in tumor size?

- To answer this question, the researchers looked at the percentage of participants with either a complete response to study treatment (all tumors disappeared), or a partial response to study treatment (at least a 30% decrease in tumors).
- Out of 27 participants in Group 2A, no participants (0%) had a complete response or a partial response to study treatment.
- Out of 27 participants in Group 2B, no participants (0%) had a complete response, and 2 participants (7%) had a partial response to study treatment

This means that the study results did not show that the study treatments had positive effects for participants with RAS mutant, MSS colorectal cancer.

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.

Below are instructions for understanding 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 15% of participants are listed.
- The **2nd** column tells how many of the 37 participants taking binimetinib + nivolumab reported each medical problem. Next to this number is the percentage of the 37 participants taking binimetinib + nivolumab who reported the medical problem.
- The **3rd** column tells how many of the 38 participants taking binimetinib + nivolumab+ ipilimumab reported each medical problem. Next to this number is the percentage of the 38 participants taking binimetinib + nivolumab+ ipilimumab who reported the medical problem.
- Using these instructions, you can see that 20 out of the 37 participants (54%) taking binimetinib + nivolumab reported diarrhea. A total of 19 out of the 38 participants (50%) taking binimetinib + nivolumab+ ipilimumab reported diarrhea.

All 75 participants (100%) treated in this study had at least 1 medical problem. A total of 16 (21%) participants stopped taking study treatment because of medical problems. The most common medical problems – those reported by at least 15% of participants in any group – are described below.

Table 1. Commonly reported medical problems by study participants

Medical Problem	Binimetinib + Nivolumab (37 Treated)	Binimetinib + Nivolumab + Ipilimumab (38 Treated)
Diarrhea	20 out of 37 treated (54%)	19 out of 38 treated (50%)
Acne-like rash	20 out of 37 treated (54%)	18 out of 38 treated (47%)
Increase in enzyme, which could indicate heart damage	20 out of 37 treated (54%)	16 out of 38 treated (42%)
Feeling tired	15 out of 37 treated (41%)	17 out of 38 treated (45%)
Nausea	17 out of 37 treated (46%)	13 out of 38 treated (34%)
Swelling in arms and legs	13 out of 37 treated (35%)	16 out of 38 treated (42%)
Fever	11 out of 37 treated (30%)	17 out of 38 treated (45%)
Vomiting	9 out of 37 treated (24%)	18 out of 38 treated (47%)
Rash	11 out of 37 treated (30%)	15 out of 38 treated (40%)
Poor appetite	15 out of 37 treated (41%)	9 out of 38 treated (24%)

Feeling weak	10 out of 37 treated (27%)	10 out of 38 treated (26%)
Constipation	11 out of 37 treated (30%)	9 out of 38 treated (24%)
Cough	8 out of 37 treated (22%)	9 out of 38 treated (24%)
Increased liver enzyme (AST)	3 out of 37 treated (8%)	12 out of 38 treated (32%)
Itching	5 out of 37 treated (14%)	10 out of 38 treated (26%)
Stomach pain	6 out of 37 treated (16%)	6 out of 38 treated (16%)
Increased liver enzyme (ALT)	2 out of 37 treated (5%)	10 out of 38 treated (26%)
Low number of red blood cells	7 out of 37 treated (19%)	5 out of 38 treated (13%)
Trouble breathing	4 out of 37 treated (11%)	8 out of 38 treated (21%)
Heart pumping decreased amount of blood	5 out of 37 treated (14%)	7 out of 38 treated (18%)
Dry skin	3 out of 37 treated (8%)	7 out of 38 treated (18%)
Dry mouth	3 out of 37 treated (8%)	6 out of 38 treated (16%)

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.

34 out of 75 (45%) participants had serious medical problems, including 17 participants (46%) who received binimetinib + nivolumab, and 17 participants (45%) who received binimetinib + nivolumab + ipilimumab. The most common serious medical problems were:

- Fever: 2 participants (5%) who received binimetinib + nivolumab
- Fluid build-up around the heart: 2 participants (5%) who received binimetinib + nivolumab
- Lung infection: 2 participants (5%) who received binimetinib + nivolumab+ ipilimumab
- Inflammation in lungs: 2 participants (5%) who received binimetinib + nivolumab+ ipilimumab
- Fluid build-up around the lungs: 2 participants (5%) who received binimetinib + nivolumab+ ipilimumab

57 participants (76%) died during this study. 7 of these participants (9%) died during study treatment or within 30 days of stopping study treatment. Most of the deaths were due to colorectal cancer. The study doctors did not consider any of the deaths to be related to taking study treatments.

Where can I learn more about this study?

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

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

www.clinicaltrials.gov

Use the study identifier **NCT03271047**

www.clinicaltrialsregister.eu

Use the study identifier **2017-003464-12**

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

Again, if you participated in this study,
thank you for volunteering.

We do research to try to find the
best ways to help study participants, and you
helped us to do that!