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:	Tinlorafenib (also known as PF-07284890 and ARRY-461)
Protocol Number:	C4471001
Dates of Study:	08 January 2021 to 20 March 2024
Title of this Study:	A Phase 1a/b Study of Tinlorafenib in Participants With BRAF V600-Mutant Solid Tumors With and Without Brain Involvement [A Two-Part, Phase 1a/b, Open-Label, Multicenter Trial Evaluating Pharmacokinetics, Safety and Efficacy of PF-07284890 (ARRY-461) in Participants With BRAF V600-Mutant Solid Tumors With and Without Brain Involvement]
Date(s) of this Report:	14 February 2025

– 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 are BRAF V600-mutated advanced solid tumor malignancies?

BRAF V600-mutated advanced solid tumor malignancies refer to a specific type of cancer that affects various tissues or organs in the body. It is called "advanced" because it has progressed beyond the initial stage and may have spread to other parts of the body.

In this particular type of cancer, there is a change (mutation) in a gene called BRAF, specifically at a location known as V600. This change alters the normal function of the gene and leads to uncontrolled cell growth and division, which is a hallmark of cancer.

Solid tumors are tumors that form in tissues such as the lungs, colon, skin, or thyroid, among others. Malignancies indicate that the tumors are cancerous and have the potential to invade nearby tissues or spread to distant parts of the body.

What is tinlorafenib (PF-07284890)?

Tinlorafenib (tin-loe-raf-e-nib) (PF-07284890) is an investigational medicine that researchers think may help treat people with certain cancerous solid tumors, with or without the cancer having spread to the brain. An investigational medicine is one that is not approved for use outside of research studies. Tinlorafenib is provided as a tablet and is taken by mouth.

What is binimetinib (Mektovi®)?

Binimetinib (bin-i-me-ti-nib) (Mektovi®) is a medicine that is approved in the United States, European Union, and in other countries globally for the treatment of unresectable (cannot be removed by surgery) or metastatic

(spread to other parts of the body) melanoma with BRAF V600E or V600K mutations. It is provided as a tablet and is taken by mouth.

What was the purpose of this study?

There were 2 parts to this study: Phase 1a and Phase 1b.

The purpose of Phase 1a was to determine:

- The safety and tolerability (how well participants tolerate treatment) of tinlorafenib alone or when taken with binimetinib in participants with BRAF V600-mutated advanced solid tumors with and without brain involvement.
- The maximum tolerated dose (or "MTD") of tinlorafenib when taken alone or when taken with binimetinib. This is the highest dose that does not cause unacceptable medical problems.
- The recommended dose of tinlorafenib when taken alone or when taken with binimetinib for further study.

As part of testing the safety of tinlorafenib in Phase 1a, researchers looked at whether any participants had "dose-limiting toxicities" (DLTs) during the first 21 days of the study treatment. These are medical problems that are severe and may be caused by taking study treatment at a dose that might be too high. DLTs may mean that a participant has to stop taking the study treatment, either completely or for a short time.

The purpose of Phase 1b was to see:

- If taking tinlorafenib with binimetinib reduced tumor size in participants with BRAF V600-mutated advanced solid tumors with and without brain involvement.

In Phase 1a, researchers wanted to know:

- **Did participants have any DLTs?**
- **What was the MTD and recommended dose for further study?**
- **What medical problems did participants have during the study?**
- **Were there any abnormal changes in laboratory tests?**
- **Did participants have to change their treatment dose or stop treatment (either permanently or temporarily) due to medical problems?**

In Phase 1b, researchers wanted to know:

- **How many participants had a tumor that got smaller or disappeared?**
- **How many participants with a tumor in the brain had their tumor get smaller or disappear?**
- **How many participants with a tumor outside of the brain had their tumor get smaller or disappear?**
- **How many participants with a tumor that started in the brain (called “primary brain tumors”) had their tumor get smaller or disappear?**

What happened during the study?

How was the study done?

Researchers tested different doses of tinlorafenib with or without binimetinib in participants with BRAF V600-mutated advanced solid tumors. Researchers did this to learn about how safe tinlorafenib was, determine the recommended dose for further study, and if it reduced the size of tumors, when taken with or without binimetinib.

Before joining the study, researchers checked each participant to make sure they were able to join. This is known as a screening.

In both parts of the study, both the researchers and participants knew the treatment being given. This is known as an "open-label" study.

Phase 1a

In Phase 1a of the study, participants were assigned to take different doses of tinlorafenib alone or in combination with binimetinib. Participants who took tinlorafenib alone joined one of the following dosing groups:

- Tinlorafenib 50 mg once a day (or "QD"). There were 2 participants in this group.
- Tinlorafenib 100 mg QD. There were 4 participants in this group.
- Tinlorafenib 200 mg QD. There were 3 participants in this group.
- Tinlorafenib 200 mg twice a day (or "BID"). There were 3 participants in this group.
- Tinlorafenib 300 mg BID. There were 10 participants in this group.
- Tinlorafenib 450 mg BID. There were 3 participants in this group.

Participants who took tinlorafenib with binimetinib joined one of the following dosing groups:

- Tinlorafenib 100 mg QD + binimetinib 45 mg BID. There were 4 participants in this group.
- Tinlorafenib 100 mg BID + binimetinib 45 mg BID. There were 4 participants in this group.
- Tinlorafenib 150 mg BID + binimetinib 45 mg BID. There were 2 participants in this group.
- Tinlorafenib 225 mg BID + binimetinib 45 mg BID. There were 5 participants in this group.
- Tinlorafenib 300 mg BID + binimetinib 45 mg BID. There were 8 participants in this group.

Participants received treatment until their cancer got worse, they no longer wanted to be in the study, they had unacceptable medical problems, or they had been treated in the study for 2 years.

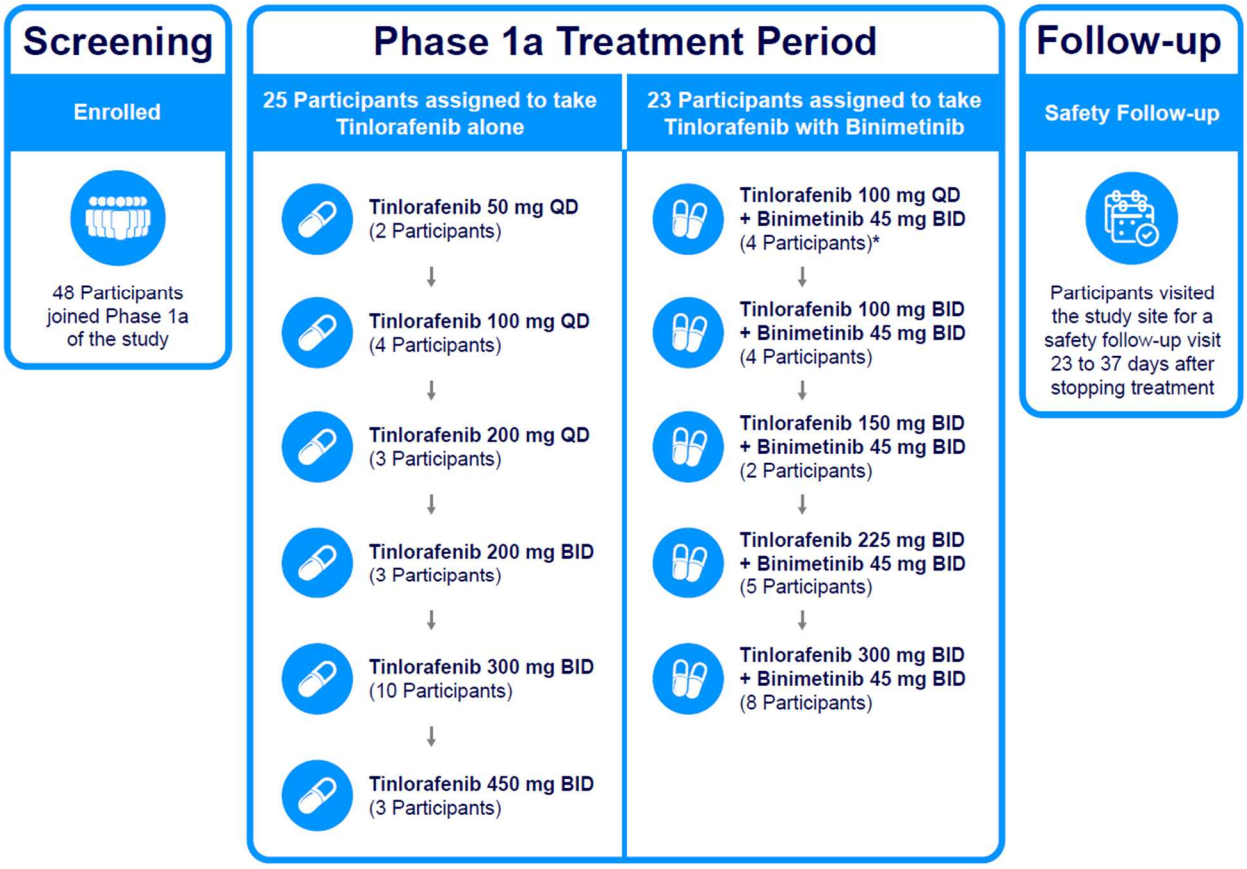
Participants in each group did not start taking treatment until the previous, lower dose was determined to be safe by researchers. Researchers started testing with tinlorafenib 50 mg QD. Participants in the tinlorafenib 100 mg QD + binimetinib 45 mg BID group did not start taking treatment until researchers determined that tinlorafenib 100 mg QD or a higher dose alone was safe.

Researchers checked the participants' health during the study by doing different medical tests. They also asked them how they were feeling.

Participants visited the study site 23 to 37 days after stopping treatment so researchers could check their health.

The study plan for Phase 1a is shown in Figure 1.

Figure 1. Phase 1a study plan



Participants received treatment until their cancer got worse, they no longer wanted to be in the study, they had unacceptable medical problems, or they had been treated in the study for 2 years.
**Participants assigned to take tinlorafenib 100 mg QD + binimetinib 45 mg BID did not start taking treatment until researchers determined that tinlorafenib 100 mg QD or a higher dose alone was safe.*

Phase 1b

Phase 1b of the study started after researchers determined the recommended dose for further study during Phase 1a. The recommended dose of tinlorafenib was determined to be 300 mg BID. After screening, participants joined 1 of 5 groups (or "Cohorts"):

- Cohort 1: Participants in this cohort had skin cancer (melanoma) and had not been treated with medicines like tinlorafenib or binimetinib. They must have also had cancer in the brain, but did not have

symptoms when joining the study. There was 1 participant in this cohort.

- Cohort 2: Participants in this cohort had melanoma and had not been treated with medicines like tinlorafenib or binimetinib. They must have also had cancer in the brain and had symptoms when joining the study. There were no participants in this cohort.
- Cohort 3: Participants in this cohort had melanoma and had been treated with medicines like tinlorafenib. They must have also had cancer in the brain, but did not have symptoms when joining the study. There were 4 participants in this cohort.
- Cohort 4: Participants in this cohort had melanoma and had been treated with medicines like tinlorafenib. They must have also had cancer in the brain and had symptoms when joining the study. There was 1 participant in this cohort.
- Cohort 5: Participants in this cohort had any solid tumor. Their cancer may have spread to the thin tissue covering the brain and spinal cord. They may or may not have had brain cancer with or without symptoms when joining the study. They may or may not have had previous treatment with medicines like tinlorafenib or binimetinib. They must not have met the requirements to be in Cohorts 1, 2, 3, or 4. There were 11 participants in this cohort.

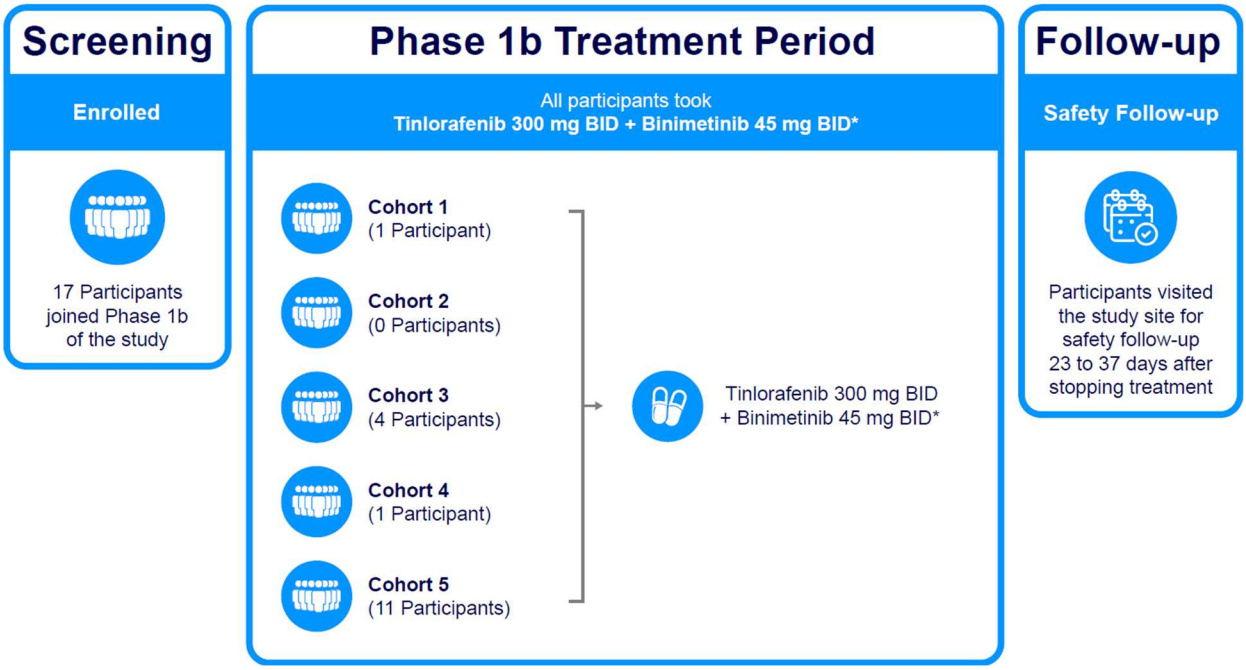
All participants in Phase 1b took tinlorafenib 300 mg BID + binimetinib 45 mg BID until their cancer got worse, they no longer wanted to be in the study, they had unacceptable medical problems, or they had been treated in the study for 2 years.

Researchers checked the participants' health during the study by doing different medical tests. They also asked them how they were feeling.

Participants visited the study site 23 to 37 days after stopping treatment so researchers could check their health.

The study plan for Phase 1b is shown in Figure 2.

Figure 2. Phase 1b study plan



**Participants received treatment until their cancer got worse, they no longer wanted to be in the study, they had unacceptable medical problems, or they had been treated in the study for 2 years.*

Where did this study take place?

The Sponsor ran this study at 21 locations in Canada, Israel, and the United States.

When did this study take place?

It began 08 January 2021 and ended 20 March 2024.

Who participated in this study?

The study included participants who had BRAF V600-mutated advanced solid tumors. Participants must have been treated for their cancer before

and had worsening of their cancer after taking their previous treatment. Participants must have had no other treatment options available.

- A total of 30 men participated
- A total of 35 women participated
- All participants were between the ages of 21 and 83 years

A total of 65 participants joined the study. The main reason that participants stopped taking treatment was due to their cancer getting worse.

How long did the study last?

Study participants could be in the study for up to 2 years. However, treatment was stopped if their cancer got worse, if they decided they did not want to be in the study anymore, or they had unacceptable medical problems. The entire study took 3 years, 2 months, and 13 days.

In December 2022, the Sponsor made a business decision to stop enrolling participants in the study. This was not due to safety of treatments.

When the study ended in March 2024, 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?

Results for Phase 1a

Did participants have any DLTs?

Of the 17 participants who took tinlorafenib alone and who had data that the researchers could check for DLTs, none had a DLT.

Of the 19 participants who took tinlorafenib with binimetinib and who had data that researchers could check for DLTs, 2 participants (10.5%) had DLTs:

- One (1) participant in the tinlorafenib 100 mg QD + binimetinib 45 mg BID group had 2 DLTs of high blood pressure and muscle protein (creatine phosphokinase) increased in the blood.
- One (1) participant in the tinlorafenib 300 mg BID + binimetinib 45 mg BID group had a DLT of decreased amount of blood pumping out of the heart in each beat.

What was the MTD and recommended dose for further study?

Researchers did not determine the MTD of tinlorafenib. Based on safety results and how tinlorafenib entered, moved through, and exited the body, the recommended dose of tinlorafenib for further study was determined to be 300 mg BID.

In Phase 1b of the study, all participants were to take tinlorafenib 300 mg BID + binimetinib 45 mg BID.

What medical problems did participants have during the study?

Medical problems are described later in this report.

Were there any abnormal changes in laboratory tests?

For participants who took tinlorafenib alone, the following abnormal changes in laboratory tests were reported:

- Blood taking longer time than normal to clot (1 participant)
- Low red blood cell count (3 participants)
- Increased blood clotting time, measured by a test called international normalized ratio (1 participant)
- Decreased white blood cells called lymphocytes (4 participants)
- Muscle protein (creatine phosphokinase) increased in the blood (1 participant)

For participants who took tinlorafenib with binimetinib, the following abnormal changes in laboratory tests were reported:

- Low red blood cell count (1 participant)
- Decreased white blood cells called lymphocytes (2 participants)
- Decreased white blood cells called neutrophils (1 participant)
- Muscle protein (creatine phosphokinase) increased in the blood (4 participants)
- Low levels of potassium in the blood (1 participant)
- Low levels of sodium in the blood (1 participant)

Did participants have to change treatment dose or stop treatment (either permanently or temporarily) due to medical problems?

Of the 48 participants in Phase 1a:

- Nine (9) participants (18.8%) had a medical problem related to treatment that led to decreasing treatment dose.
- Three (3) participants (6.3%) had a medical problem related to treatment that led to permanently stopping treatment.
- Nine (9) participants (18.8%) had a medical problem related to treatment that led to temporarily stopping treatment.

Results for Phase 1b

How many participants had a tumor that got smaller or disappeared?

Of the 17 participants in Phase 1b of the study, 12 participants (70.6%) had a tumor that researchers could measure to see if it got smaller or disappeared. Of these 12 participants, 2 participants (16.7%) had a decrease in the size of their tumor. No participant had a tumor that disappeared.

How many participants with a tumor in the brain had their tumor get smaller or disappear?

There were 7 participants who had a tumor in the brain that researchers could measure. No participant had a tumor that got smaller or disappeared.

How many participants with a tumor outside of the brain had their tumor get smaller or disappear?

There were 11 participants who had a tumor outside of the brain that researchers could measure. Of these 11 participants, 2 participants

(18.2%) had a decrease in the size of their tumor. No participant had a tumor that disappeared.

How many participants with a tumor that started in the brain (called "primary brain tumors") had their tumor get smaller or disappear?

There were 2 participants who had a primary brain tumor called "glioma" that researchers could measure. Of these 2 participants, 1 participant (50.0%) had a decrease in the size of their tumor. Neither participants' tumor disappeared.

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 unknown 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 Phase 1a, all 25 participants (100.0%) who took tinlorafenib alone had at least 1 medical problem. One (1) participant permanently stopped tinlorafenib treatment due to a medical problem.

In Phase 1a, all 23 participants (100.0%) who took tinlorafenib with binimetinib had at least 1 medical problem. One (1) participant permanently stopped tinlorafenib treatment and 3 participants permanently stopped binimetinib treatment due to a medical problem.

In Phase 1b, all 17 participants (100.0%) who took tinlorafenib with binimetinib had at least 1 medical problem. Two (2) participants permanently stopped tinlorafenib treatment due to a medical problem, and 2 participants permanently stopped binimetinib treatment due to a medical problem.

The most common medical problems – those reported by 20% or more of total participants – are described below in Table 1, Table 2, and Table 3.

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 Phase 1a of the study. All medical problems reported by 20% or more of participants are listed.
- The **2nd** column tells how many of the 2 participants taking tinlorafenib 50 mg QD reported each medical problem. Below this number is the percentage of the 2 participants taking tinlorafenib 50 mg QD who reported the medical problem.
- The **3rd** column tells how many of the 4 participants taking tinlorafenib 100 mg QD reported each medical problem. Below this number is the percentage of the 4 participants taking tinlorafenib 100 mg QD who reported the medical problem.
- The **4th** column tells how many of the 3 participants taking tinlorafenib 200 mg QD reported each medical problem. Below this number is the percentage of the 3 participants taking tinlorafenib 200 mg QD who reported the medical problem.
- The **5th** column tells how many of the 3 participants taking tinlorafenib 200 mg BID reported each medical problem. Below this number is the percentage of the 3 participants taking tinlorafenib 200 mg BID who reported the medical problem.
- The **6th** column tells how many of the 10 participants taking tinlorafenib 300 mg BID reported each medical problem. Below this number is the percentage of the 10 participants

taking tinlorafenib 300 mg BID who reported the medical problem.

- The **7th** column tells how many of the 3 participants taking tinlorafenib 450 mg BID reported each medical problem. Below this number is the percentage of the 3 participants taking tinlorafenib 450 mg BID who reported the medical problem.
- Using these instructions, you can see that 1 out of the 2 participants (50.0%) taking tinlorafenib 50 mg QD reported low red blood cell count. A total of 1 out of the 4 participants (25.0%) taking tinlorafenib 100 mg QD reported low red blood cell count. Zero (0) participants taking tinlorafenib 200 mg QD or tinlorafenib 200 mg BID reported low red blood cell count. A total of 4 out of the 10 participants (40.0%) taking tinlorafenib 300 mg BID reported low red blood cell count. Zero (0) participants taking tinlorafenib 450 mg BID reported low red blood cell count.

Table 1. Commonly reported medical problems by study participants in Phase 1a who took tinlorafenib alone

Medical Problem	Tinlorafenib 50 mg QD (2 Participants)	Tinlorafenib 100 mg QD (4 Participants)	Tinlorafenib 200 mg QD (3 Participants)	Tinlorafenib 200 mg BID (3 Participants)	Tinlorafenib 300 mg BID (10 Participants)	Tinlorafenib 450 mg BID (3 Participants)
Low red blood cell count	1 out of 2 participants (50.0%)	1 out of 4 participants (25.0%)	0	0	4 out of 10 participants (40.0%)	0

Table 1. Commonly reported medical problems by study participants in Phase 1a who took tinlorafenib alone

Medical Problem	Tinlorafenib 50 mg QD (2 Participants)	Tinlorafenib 100 mg QD (4 Participants)	Tinlorafenib 200 mg QD (3 Participants)	Tinlorafenib 200 mg BID (3 Participants)	Tinlorafenib 300 mg BID (10 Participants)	Tinlorafenib 450 mg BID (3 Participants)
Joint pain	1 out of 2 participants (50.0%)	2 out of 4 participants (50.0%)	1 out of 3 participants (33.3%)	1 out of 3 participants (33.3%)	1 out of 10 participants (10.0%)	0
Flat or raised red rash on skin	0	0	1 out of 3 participants (33.3%)	1 out of 3 participants (33.3%)	4 out of 10 participants (40.0%)	0
Difficulty passing stool	0	2 out of 4 participants (50.0%)	0	1 out of 3 participants (33.3%)	2 out of 10 participants (20.0%)	0
Feeling tired	1 out of 2 participants (50.0%)	1 out of 4 participants (25.0%)	0	1 out of 3 participants (33.3%)	0	2 out of 3 participants (66.7%)
Muscle pain	0	2 out of 4 participants (50.0%)	0	1 out of 3 participants (33.3%)	2 out of 10 participants (20.0%)	0
Nausea	0	1 out of 4 participants (25.0%)	1 out of 3 participants (33.3%)	0	2 out of 10 participants (20.0%)	1 out of 3 participants (33.3%)

Table 2. Commonly reported medical problems by study participants in Phase 1a who took tinlorafenib with binimetinib

Medical Problem	Tinlorafenib 100 mg QD + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 100 mg BID + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 150 mg BID + binimetinib 45 mg BID (2 Participants)	Tinlorafenib 225 mg BID + binimetinib 45 mg BID (5 Participants)	Tinlorafenib 300 mg BID + binimetinib 45 mg BID (8 Participants)
Loose stools	1 out of 4 participants (25.0%)	2 out of 4 participants (50.0%)	2 out of 2 participants (100.0%)	3 out 5 participants (60.0%)	3 out of 8 participants (37.5%)
Feeling tired	1 out of 4 participants (25.0%)	4 out of 4 participants (100.0%)	0	3 out 5 participants (60.0%)	2 out of 8 participants (25.0%)
Nausea	1 out of 4 participants (25.0%)	3 out of 4 participants (75.0%)	0	2 out 5 participants (40.0%)	4 out of 8 participants (50.0%)
Seizure	0	1 out of 4 participants (25.0%)	1 out of 2 participants (50.0%)	2 out 5 participants (40.0%)	4 out of 8 participants (50.0%)
Throwing up	1 out of 4 participants (25.0%)	3 out of 4 participants (75.0%)	0	1 out 5 participants (20.0%)	3 out of 8 participants (37.5%)
Muscle protein (creatine phosphokinase) increased in the blood	2 out of 4 participants (50.0%)	1 out of 4 participants (25.0%)	1 out of 2 participants (50.0%)	1 out 5 participants (20.0%)	2 out of 8 participants (25.0%)

Table 2. Commonly reported medical problems by study participants in Phase 1a who took tinlorafenib with binimetinib

Medical Problem	Tinlorafenib 100 mg QD + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 100 mg BID + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 150 mg BID + binimetinib 45 mg BID (2 Participants)	Tinlorafenib 225 mg BID + binimetinib 45 mg BID (5 Participants)	Tinlorafenib 300 mg BID + binimetinib 45 mg BID (8 Participants)
Headache	0	2 out of 4 participants (50.0%)	0	1 out 5 participants (20.0%)	3 out of 8 participants (37.5%)
Swelling of the limbs	1 out of 4 participants (25.0%)	1 out of 4 participants (25.0%)	0	1 out 5 participants (20.0%)	2 out of 8 participants (25.0%)

Table 3. Commonly reported medical problems by study participants in Phase 1b

Medical Problem	Cohort 1 (1 Participant)	Cohort 3 (4 Participants)	Cohort 4 (1 Participant)	Cohort 5 (11 Participants)
Loose stools	1 out of 1 participant (100.0%)	2 out of 4 participants (50.0%)	1 out of 1 participant (100.0%)	5 out of 11 participants (45.5%)
Nausea	1 out of 1 participant (100.0%)	2 out of 4 participants (50.0%)	0	6 out of 11 participants (54.5%)

Table 3. Commonly reported medical problems by study participants in Phase 1b

Medical Problem	Cohort 1 (1 Participant)	Cohort 3 (4 Participants)	Cohort 4 (1 Participant)	Cohort 5 (11 Participants)
Muscle protein (creatine phosphokinase) increased in the blood	0	0	0	6 out of 11 participants (54.5%)
Feeling tired	0	1 out of 4 participants (25.0%)	0	5 out of 11 participants (45.5%)
Throwing up	1 out of 1 participant (100.0%)	2 out of 4 participants (50.0%)	0	3 out of 11 participants (27.3%)
Feeling dizzy	1 out of 1 participant (100.0%)	1 out of 4 participants (25.0%)	0	2 out of 11 participants (18.2%)
Headache	0	1 out of 4 participants (25.0%)	1 out of 1 participant (100.0%)	2 out of 11 participants (18.2%)
Swelling of the limbs	0	1 out of 4 participants (25.0%)	0	3 out of 11 participants (27.3%)

Note: there were no participants in Cohort 2.

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 Phase 1a, 10 out of 25 participants (40.0%) who took tinlorafenib alone had serious medical problems. Of the 23 participants who took tinlorafenib with binimetinib in Phase 1a, 8 participants (34.8%) had serious medical problems.

In Phase 1b, 6 out of 17 participants (35.3%) who took tinlorafenib with binimetinib had serious medical problems.

Serious medical problems reported during the study may or may not have been related to the study treatments.

The most common serious medical problems – those reported by more than 5% of total participants – are shown below in the Table 4, Table 5, and Table 6.

Table 4. Common serious medical problems reported by study participants in Phase 1a who took tinlorafenib alone

Serious Medical Problem	Tinlorafenib 50 mg QD (2 Participants)	Tinlorafenib 100 mg QD (4 Participants)	Tinlorafenib 200 mg QD (3 Participants)	Tinlorafenib 200 mg BID (3 Participants)	Tinlorafenib 300 mg BID (10 Participants)	Tinlorafenib 450 mg BID (3 Participants)
Cancer got worse	0	1 out of 4 participants (25.0%)	0	0	1 out of 10 participants (10.0%)	2 out of 3 participants (66.7%)
Bleeding inside the skull	0	0	0	2 out of 3 participants (66.7%)	0	0
Headache	0	0	0	0	1 out of 10 participants (10.0%)	1 out of 3 participants (33.3%)

Table 5. Common serious medical problems reported by study participants in Phase 1a who took tinlorafenib with binimetinib

Serious Medical Problem	Tinlorafenib 100 mg QD + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 100 mg BID + binimetinib 45 mg BID (4 Participants)	Tinlorafenib 150 mg BID + binimetinib 45 mg BID (2 Participants)	Tinlorafenib 225 mg BID + binimetinib 45 mg BID (5 Participants)	Tinlorafenib 300 mg BID + binimetinib 45 mg BID (8 Participants)
Muscle protein (creatine phosphokinase) increased in the blood	1 out of 4 participants (25.0%)	0	1 out of 2 participants (50.0%)	0	0
Cancer got worse	0	0	0	0	2 out of 8 participants (25.0%)
Tumor got bigger	0	0	0	2 out of 5 participants (40.0%)	0
Seizure	0	1 out of 4 participants (25.0%)	0	1 out of 5 participants (20.0%)	0

Table 6. Common serious medical problems reported by study participants in Phase 1b

Serious Medical Problem	Cohort 1 (1 Participant)	Cohort 3 (4 Participants)	Cohort 4 (1 Participant)	Cohort 5 (11 Participants)
Blockage in blood vessel	0	1 out of 4 participants (25.0%)	0	0
Blockage in gallbladder	0	0	0	1 out of 11 participants (9.1%)
Bleeding in the abdomen, around the organs	0	0	0	1 out of 11 participants (9.1%)
Hole in small bowel	0	0	0	1 out of 11 participants (9.1%)
Uncontrolled spread and growth of cancer cells	0	1 out of 4 participants (25.0%)	0	0
Small bowel blockage	0	0	0	1 out of 11 participants (9.1%)
Infection of the kidneys, bladder, or urine tube	0	1 out of 4 participants (25.0%)	0	0

Note: there were no participants in Cohort 2.

In Phase 1a, 13 out of the 25 participants (52.0%) who took tinlorafenib alone died. Twelve (12) participants (48.0%) died due to their cancer and 1 participant (4.0%) died due to an unknown reason.

In Phase 1a, 14 out of the 23 participants (60.9%) who took tinlorafenib with binimetinib died. Thirteen (13) participants (56.5%) died due to their cancer and 1 participant (4.3%) died due to an unknown reason.

In Phase 1b, 7 out of the 17 participants (41.2%) who took tinlorafenib with binimetinib died. Five (5) participants (29.4%) died due to their cancer and 2 participants (11.8%) died due to unknown reasons.

Researchers determined that the deaths in the study were not related to the study treatment.

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 C4471001

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

www.clinicaltrials.gov	Use the study identifier **NCT04543188**

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!