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: Xalkori® (crizotinib [PF-02341066])

Protocol Number: A8081001 PROFILE 1001

Dates of Study: 19 April 2006 to 30 July 2020

Title of this Study: Study Investigating the Safety and Tolerability of Different Doses of Crizotinib in Participants with Advanced Cancers.

[Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, a MET/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer.]

Date(s) of this Report: 08 July 2021

– 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 advanced non-small cell lung cancer?

Lung cancer is the name for cancer that starts in the lungs. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Some patients have NSCLC that is referred to as "anaplastic lymphoma kinase (ALK)-positive" or "c-ros oncogene 1 (ROS1)-positive". These patients have changes in their genes that can cause cancer cells to grow. As they grow, the cancer cells can form into a tumor and spread to other parts of the body. When the cancer has spread to other parts of the body it is called advanced cancer.

What is crizotinib?

When this study began in 2006, Pfizer was developing the anti-cancer medication Xalkori® or crizotinib. This treatment has been approved in the United States (US), Europe, and in some other countries for the treatment of certain types of NSCLC that has spread to other parts of the body and is caused by a defect in the ALK or ROS1 genes. Crizotinib is known as an ALK-inhibitor and ROS1-inhibitor (and is also a MET/HGFR inhibitor) medication. Potentially, crizotinib may be able to reduce tumor size and stop ALK-positive and ROS1-positive lung cancers from being able to grow and spread.

What was the purpose of this study?

The purpose of the study was to assess the safety and tolerability of different doses of crizotinib in participants with advanced cancer, and if appropriate, to identify the dose that could be used in larger studies.

Researchers wanted to know:

How many medical problems, including toxicities, were seen in participants during the first 28 days of treatment with different doses of crizotinib?

What happened during the study?

How was the study done?

Researchers tested crizotinib on groups of study participants to find out about medical problems in study participants. Researchers then compared the results between study participants who took crizotinib at different doses. The study participants and researchers knew who took what dose of crizotinib. This is known as an "open-label" study. Participants with a range of cancer types were included in this study so that the researcher could see if the type of cancer made a difference.

The dose that the first small group of participants was given was 50 milligrams (mg) of crizotinib once a day for 28 days. The next small group of participants were given a slightly higher dose of crizotinib and the researchers watched for medical problems. This was then repeated for 5 small groups of participants in the low dose group and 5 small groups of participants in the high dose group:

- In the low dose group, the dose of crizotinib was increased from 50 mg once a day to 100 mg once a day to 200 mg once a day and then to 200 mg twice a day to 250 mg twice a day, and finally to 300 mg twice a day.

- In the high dose group, the dose of crizotinib was increased from 300 mg once a day to 400 mg once a day to 500 mg once a day to 650 mg once a day, and finally to 800 mg once a day.

For each participant in this part of the study, the 28 days after the first dose were called Cycle 1, and the next 28 days were called Cycle 2, etc. Treatment with crizotinib was to be continued in 28-day cycles for all participants unless the participant developed any severe medical problems.

The way that the doses of crizotinib were gradually increased is called "dose escalation". The researchers did this to find out what was the highest or maximum amount of crizotinib that could be given before the participants had too many medical problems. This dose is known as the "maximum tolerated dose" or MTD.

The researchers used the information they collected on medical problems to work out the MTD for crizotinib.

Taking more than one drug at the same time as another, may mean that one or more of these medicines does not work as well as they should or could cause additional medical problems, or there may be no change in the way that the drugs behave in the body. As people with cancer often take many different drugs, the researchers wanted to see if taking crizotinib with other drugs would cause any new medical problems or increase the number of medical problems seen in the study. This type of study is known as a "drug-drug interaction" study.

To investigate drug-drug interactions, the researchers gave the next small group of new participants a dose of crizotinib that was slightly lower than the MTD, crizotinib at the MTD, or at a dose of crizotinib that was slightly higher than the MTD. These participants were also given midazolam on Day 1 of Cycle 2. Midazolam is a medicine that helps with sleep or anxiety and may be given to people with cancer. It is also a medicine that potentially could interact with crizotinib.

The researchers also wanted to see what would happen when other medicines were given with crizotinib. In a second small group of new participants, the participants were given crizotinib at the MTD as well as rifampin for part of Cycle 1. A third small group of new participants were given crizotinib at the MTD as well as itraconazole for part Cycle 1. Rifampin and itraconazole are medicines used to treat infections and may be given to people with cancer. It is also a medicine that potentially could interact with crizotinib.

Treatment with crizotinib was to be continued in 28-day cycles for all participants in the drug-drug interaction groups unless the participant developed any severe medical problems.

The researchers also gave the MTD of crizotinib to participants with different types of cancer. This included participants with ALK-negative NSCLC as well as other types of NSCLC (MET-amplified NSCLC, ROS1-positive NSCLC, ALK-positive NSCLC, MET Exon-14 positive NSCLC, and other cancers). Participants with

ALK-negative NSCLC were given the MTD twice a day in a 21-day cycle instead of the usual 28-day cycle. All other participants in this part of the study were given the MTD twice a day in a 28-day cycle. Treatment with crizotinib was continued in either 21- or 28-day cycles unless the participant developed any severe medical problems.

Where did this study take place?

The Sponsor ran this study at 16 locations in 4 countries (the US, Japan, South Korea, and Australia).

When did this study take place?

It began on 19 April 2006 and was ongoing on 30 July 2020.

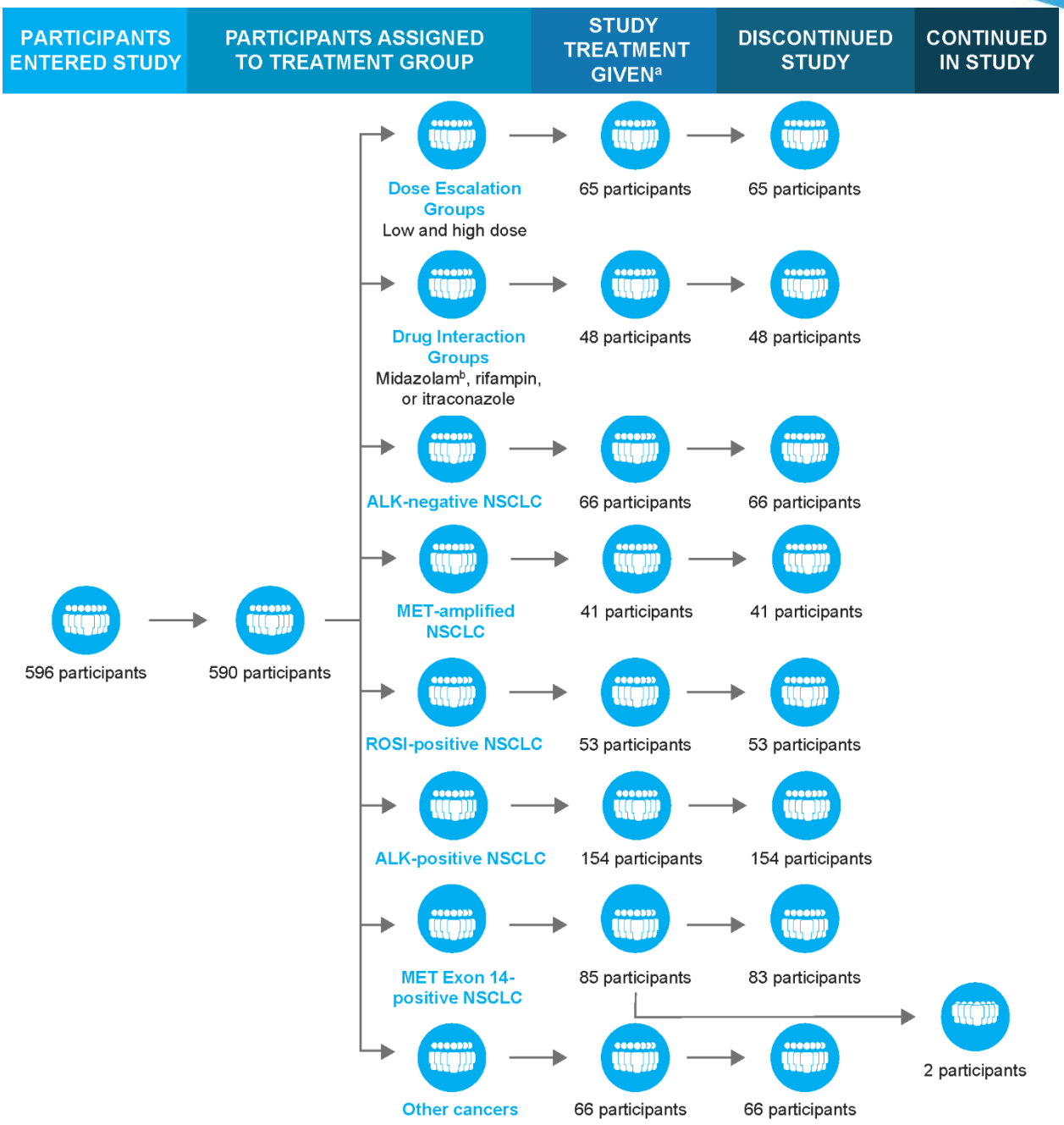
Who participated in this study?

The study included adult participants who had advanced cancer that was not responding to their current treatment.

- A total of 285 men participated[a]
- A total of 281 women participated[a]
- All participants were between the ages of 18 and 91 years[a], and most were white
- The majority of participants had either previously smoked or had never smoked and there were very few who were current smokers.

[a] There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interaction group. These data were reported in 2011 and are not discussed in this summary.

Of the 578 participants who started the study and were treated, 576 stopped treatment with crizotinib and left the study. These participants left before the study was over by choice or the doctor discussed the options with the participant, and they decided it was best for a participant to stop being in the study, or the participant passed away. There were 2 participants who were still in the study on 30 July 2020 when data were collected for the final report.



[a] Participants were treated until their cancer got worse, they developed unacceptable medical problems, until they chose to stop treatment, or the doctor discussed the options with the participant, and they decided it was best for the participant to stop being in the study, or the participant passed away.

[b] There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interactions group. These data were reported in 2011 and are not discussed in this summary. Data for the 18 participants treated with crizotinib and rifampin and the 18 participants treated with crizotinib and itraconazole are included in this summary.

How long did the study last?

Study participants were in the study until they were no longer able to continue in the study or were unwilling to participate. The entire study over 14 years to complete and 2 participants were still in the study as of 30 July 2020.

In July 2020, the Sponsor began reviewing the information collected up to 30 July 2020. The Sponsor then created a report of the final results of this study. This is a summary of that report.

What were the results of the study?

How many participants had medical problems, including toxicities, that were severe or life-threatening, or disabling during the first 28 days of treatment with different doses of crizotinib?

In this study, the researchers looked at the medical problems that participants had during Cycle 1 to see if there were any dose limiting toxicities. A dose limiting toxicity is a medical problem that may mean that dose of drug is unsafe or unacceptable. This can also include severe or life-threatening, or disabling medical problems. Other medical problems that were seen in this study are discussed in full in the next 2 sections of this document.

The number of participants who had a dose limiting toxicity during Cycle 1 in the dose escalation groups are shown in Table 1. The researchers used this information to identify the MTD for crizotinib as 250 mg when taken twice a day or 650 mg when taken once a day.

Below are instructions on how to read Table 1.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists the group of participants who were treated with crizotinib in the study.
- The **2nd** column in tells how many of the participants in each group reported a dose limiting toxicity. Next to this number is the percentage of the participants in that group who reported a dose limiting toxicity.
- Using these instructions, you can see that 3 out of the 36 participants (8%) in the Dose escalation – Low dose group had a dose limiting toxicity.

Table 1. Participants with dose limiting toxicities in Cycle 1

Study group	Dose limiting toxicities
Dose escalation – Low dose	3 out of 36 participants (8%)
Dose escalation – High dose	3 out of 29 participants (10%)

The researchers also looked at the number of participants who had a severe, life-threatening, or disabling medical problems within 28 days of their last dose of crizotinib. This information is shown in Table 2.

Below are instructions on how to read Table 2.

Instructions for Understanding Table 2.

- The **1st** column of Table 2 lists the group of participants who were treated with crizotinib in the study.
- The **2nd** column in tells how many of the participants in each group reported a severe, life-threatening, or disabling medical problem. Next to this number is the percentage of the participants in that group who reported the severe, life-threatening, or disabling medical problem.
- Using these instructions, you can see that 14 out of the 36 participants (39%) in the Dose escalation – Low dose group had severe, life-threatening, or disabling medical problems.

Table 2. Severe, life-threatening, or disabling medical problems within 28 days of the last dose of crizotinib

Study group	Severe, life-threatening, or disabling medical problems
Dose escalation – Low dose	14 out of 36 participants (39%)
Dose escalation – High dose	17 out of 29 participants (59%)
Drug-drug interaction with Rifampin	9 out of 18 participants (50%)
Drug-drug interaction with Itraconazole	12 out of 18 participants (67%)
ALK-negative NSCLC – Group 1	31 out of 48 participants (65%)
ALK-negative NSCLC - Group 2	14 out of 18 participants (78%)
MET amplified NSCLC	33 out of 41 participants (81%)
ROS1-positive NSCLC	36 out of 53 participants (68%)
ALK-positive NSCLC	104 out of 154 participants (68%)
MET Exon 14-positive NSCLC	65 out of 85 participants (77%)

Table 2. Severe, life-threatening, or disabling medical problems within 28 days of the last dose of crizotinib	
Study group	**Severe, life-threatening, or disabling medical problems**
Other cancers	40 out of 66 participants (61%)

Note: There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interactions group. These data were reported in 2011 and are not discussed in this summary.

As well as the severe, life-threatening, or disabling medical problems shown in the table above, participants could also have other medical problems, serious medical problems or may have passed away during the study. These medical problems are discussed in the rest of this document.

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.

There were 564 out of 566 (almost 100%) participants that were treated in this study and for whom data were available who had at least 1 medical problem. The most common medical problems – those reported by 30% or more participants – are described in Table 3.

For 54 participants, (10%, or 54 out of 566 participants treated in this study and for whom data were available), the main reason they left the study was because of medical problems. A total of 94 participants (17%, or 94 out of 566 participants treated in this

study and for whom data were available) had medical problems associated with leaving the study.

Below are instructions on how to read Table 3.

Instructions for Understanding Table 3.

- The **1st** column of Table 3 lists medical problems that were commonly reported during the study within each group of participants who were treated with crizotinib in the study. All medical problems reported by 30% or more of the participants are listed.
- The **2nd** column tells how many of the participants in each group reported each medical problem. Next to this number is the percentage of the participants who reported the medical problem.
- Using these instructions, you can see that 20 out of the 36 participants (56%) in the Dose escalation – Low dose group who were taking the study medication reported feeling sick.

Table 3. Commonly reported medical problems by study participants

Study group	Participants with the medical problem
Dose escalation – Low dose (36 participants)	
Feeling sick (nausea)	20 out of 36 participants (56%)
Being sick (vomiting)	19 out of 36 participants (53%)
Feeling tired (fatigue)	17 out of 36 participants (47%)
Not feeling hungry	15 out of 36 participants (42%)
Dose escalation – High dose (29 participants)	
Constipation	16 out of 29 participants (55%)

Table 3. Commonly reported medical problems by study participants

Study group	Participants with the medical problem
Feeling sick (nausea)	14 out of 29 participants (48%)
Problem with eyesight	14 out of 29 participants (48%)
Being sick (vomiting)	13 out of 29 participants (45%)
Feeling tired (fatigue)	11 out of 29 participants (38%)
Drug-drug interaction with Rifampin (18 participants)	
Problem with eyesight	13 out of 18 participants (72%)
Feeling sick (nausea)	12 out of 18 participants (67%)
Being sick (vomiting)	10 out of 18 participants (56%)
Constipation	7 out of 18 participants (39%)
Diarrhea	7 out of 18 participants (39%)
Not feeling hungry	6 out of 18 participants (33%)
Feeling tired (fatigue)	6 out of 18 participants (33%)
Drug-drug interaction with Itraconazole (18 participants)	
Constipation	11 out of 18 participants (61%)
Feeling sick (nausea)	10 out of 18 participants (56%)
Problem with eyesight	10 out of 18 participants (56%)
Breathlessness (dyspnea)	9 out of 18 participants (50%)
Feeling tired (fatigue)	8 out of 18 participants (44%)
Being sick (vomiting)	8 out of 18 participants (44%)

Table 3. Commonly reported medical problems by study participants

Study group	Participants with the medical problem
Diarrhea	7 out of 18 participants (39%)
Swelling/fluid retention (edema)	7 out of 18 participants (39%)
ALK-negative NSCLC – Group 1 (48 participants)	
Problem with eyesight	29 out of 48 participants (60%)
Being sick (vomiting)	26 out of 48 participants (54%)
Feeling tired (fatigue)	23 out of 48 participants (48%)
Constipation	21 out of 48 participants (44%)
Feeling sick (nausea)	20 out of 48 participants (42%)
Diarrhea	17 out of 48 participants (35%)
Swelling/fluid retention (edema)	16 out of 48 participants (33%)
Breathlessness (dyspnea)	15 out of 48 participants (31%)
ALK-negative NSCLC – Group 2 (18 participants)	
Problem with eyesight	12 out of 18 participants (67%)
Constipation	11 out of 18 participants (61%)
Feeling sick (nausea)	10 out of 18 participants (56%)
Being sick (vomiting)	9 out of 18 participants (50%)
Feeling tired (fatigue)	8 out of 18 participants (44%)
MET amplified NSCLC (41 participants)	
Swelling/fluid retention (edema)	18 out of 41 participants (44%)

Table 3. Commonly reported medical problems by study participants

Study group	Participants with the medical problem
Diarrhea	17 out of 41 participants (42%)
Being sick (vomiting)	15 out of 41 participants (37%)
Feeling sick (nausea)	14 out of 41 participants (34%)
Problem with eyesight	13 out of 41 participants (32%)
ROS1-positive NSCLC (53 participants)	
Problem with eyesight	46 out of 53 participants (87%)
Feeling sick (nausea)	34 out of 53 participants (64%)
Swelling/fluid retention (edema)	32 out of 53 participants (60%)
Being sick (vomiting)	28 out of 53 participants (53%)
Diarrhea	25 out of 53 participants (47%)
Constipation	24 out of 53 participants (45%)
Dizziness	24 out of 53 participants (45%)
High levels of liver enzymes (transaminases)	21 out of 53 participants (40%)
Feeling tired (fatigue)	20 out of 53 participants (38%)
Nerve pain (neuropathy)	20 out of 53 participants (38%)
Nose and throat infection (upper respiratory tract infection)	20 out of 53 participants (38%)
Breathlessness (dyspnea)	17 out of 53 participants (32%)
Not feeling hungry	16 out of 53 participants (30%)
ALK-positive NSCLC (154 participants)	

Table 3. Commonly reported medical problems by study participants

Study group	Participants with the medical problem
Problem with eyesight	109 out of 154 participants (71%)
Feeling sick (nausea)	97 out of 154 participants (63%)
Diarrhea	93 out of 154 participants (60%)
Swelling/fluid retention (edema)	88 out of 154 participants (57%)
Being sick (vomiting)	83 out of 154 participants (54%)
Constipation	68 out of 154 participants (44%)
Dizziness	68 out of 154 participants (44%)
Nose and throat infection (upper respiratory tract infection)	60 out of 154 participants (39%)
Feeling tired (fatigue)	59 out of 154 participants (38%)
Nerve pain (neuropathy)	53 out of 154 participants (34%)
Not feeling hungry	50 out of 154 participants (33%)
MET Exon 14-positive NSCLC (85 participants)	
Swelling/fluid retention (edema)	54 out of 85 participants (64%)
Diarrhea	50 out of 85 participants (59%)
Feeling sick (nausea)	49 out of 85 participants (58%)
Constipation	45 out of 85 participants (53%)
Problem with eyesight	42 out of 85 participants (49%)
Feeling tired (fatigue)	35 out of 85 participants (41%)
Being sick (vomiting)	35 out of 85 participants (41%)

Table 3. Commonly reported medical problems by study participants	
Study group	**Participants with the medical problem**
Nerve pain (neuropathy)	34 out of 85 participants (40%)
Breathlessness (dyspnea)	29 out of 85 participants (34%)
Dizziness	26 out of 85 participants (31%)
Other cancers (66 participants)	
Feeling sick (nausea)	41 out of 66 participants (62%)
Being sick (vomiting)	35 out of 66 participants (53%)
Diarrhea	32 out of 66 participants (49%)
Problem with eyesight	32 out of 66 participants (49%)
Feeling tired (fatigue)	26 out of 66 participants (39%)
Swelling/fluid retention (edema)	21 out of 66 participants (32%)
Not feeling hungry	20 out of 66 participants (30%)

Note: There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interactions group. These data were reported in 2011 and are not discussed in this summary.

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.

A total of 271 participants (48%, or 271 out of the 566 participants that were treated in this study and for whom data were available) had serious medical problems as shown in Table 4. The doctors thought that many of these serious medical problems were not linked to crizotinib.

Below are instructions on how to read Table 4.

Instructions for Understanding Table 4.

- The **1st** column of Table 4 lists the group of participants who were treated with crizotinib in the study.
- The **2nd** column in tells how many of the participants in each group reported serious medical problem. Next to this number is the percentage of the participants in that group who reported the serious medical problem.
- Using these instructions, you can see that 9 out of the 36 participants (25%) in the Dose escalation – Low dose group had serious medical problems.

Table 4. Participants with serious medical problems

Study group	Serious medical problems
Dose escalation – Low dose	9 out of 36 participants (25%)
Dose escalation – High dose	11 out of 29 participants (38%)
Drug-drug interaction with Rifampin	6 out of 18 participants (33%)
Drug-drug interaction with Itraconazole	7 out of 18 participants (39%)
ALK-negative NSCLC - Group 1	22 out of 48 participants (46%)
ALK-negative NSCLC - Group 2	9 out of 18 participants (50%)
MET amplified NSCLC	25 out of 41 participants (61%)
ROS1-positive NSCLC	24 out of 53 participants (45%)
ALK-positive NSCLC	75 out of 154 participants (49%)
MET Exon 14-positive NSCLC	54 out of 85 participants (64%)

Table 4. Participants with serious medical problems

Study group	Serious medical problems
Other cancers	29 out of 66 participants (44%)

Note: There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interactions group. These data were reported in 2011 and are not discussed in this summary.

There were 97 participants (17%, or 97 out of the 566 participants that were treated in this study and for whom data were available) who passed away within 28 days of their last dose of crizotinib as shown in Table 5. Most of the participants who died during the study passed away because of their cancer.

Below are instructions on how to read Table 5.

Instructions for Understanding Table 5.

- The **1st** column of Table 5 lists the group of participants who were treated with crizotinib in the study.
- The **2nd** column in tells how many of the participants in each group passes away within 28 days of their last dose of crizotinib. Next to this number is the percentage of the participants in that group who passed away.
- Using these instructions, you can see that 3 out of the 36 participants (8%) in the Dose escalation – Low dose group passed away within 28 days of their last dose of crizotinib.

Table 5. Participants who died within 28 days of the last dose of crizotinib

Study group	Participants who died within 28 days of the last dose
Dose escalation – Low dose	3 out of 36 participants (8%)
Dose escalation – High dose	4 out of 29 participants (14%)

Table 5. Participants who died within 28 days of the last dose of crizotinib

Study group	Participants who died within 28 days of the last dose
Drug-drug interaction with Rifampin	1 out of 18 participants (6%)
Drug-drug interaction with Itraconazole	0 out of 18 participants (0%)
ALK-negative NSCLC - Group 1	13 out of 48 participants (27%)
ALK-negative NSCLC - Group 2	3 out of 18 participants (17%)
MET amplified NSCLC	8 out of 41 participants (20%)
ROS1-positive NSCLC	10 out of 53 participants (19%)
ALK-positive NSCLC	25 out of 154 participants (16%)
MET Exon 14-positive NSCLC	15 out of 85 participants (18%)
Other cancers	15 out of 66 participants (23%)

Note: There were no updated results provided in the final study report for the 12 participants treated with crizotinib and midazolam in the drug-drug interactions group. These data were reported in 2011 and are not discussed in this summary.

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:

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

www.clinicaltrials.gov	Use the study identifier **NCT00585195**
www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number **A8081001**

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!