Daiichi-Sankyo

# Clinical Results Summary

# A clinical study to learn more about the effects of quizartinib in people with a type of blood cancer called acute myeloid leukemia (AML)

**Protocol number:** AC220-002

**Thank You!**

Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study for quizartinib. Each participant helped to advance medical research for people affected with a type of blood cancer, called acute myeloid leukemia. Their contribution to medicine and healthcare is greatly appreciated.

**Important note:** This summary only shows the results of a single study. Other studies may have different findings. Researchers and health authorities look at the results of many studies to understand which treatments work and how they work. It takes a lot of people in many studies around the world to advance medical science and healthcare.

Do not use the results of this study to make health decisions. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

# What was the main purpose of this study?

## Acute myeloid leukemia (AML)

Researchers were looking for a better way to treat people with a type of blood cancer called acute myeloid leukemia, or AML.

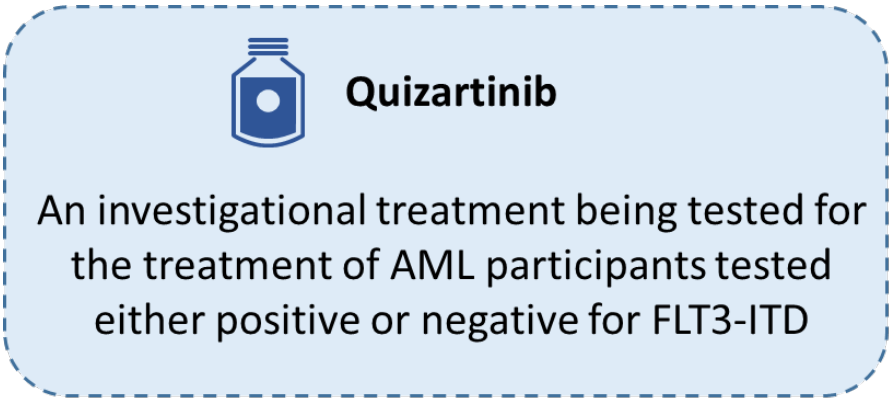
AML is a cancer of the blood and the bone marrow. The bone marrow is found in the center of most bones, where new healthy blood cells are made. AML starts in the bone marrow and prevents it from making normal blood cells. The abnormal (cancer) cells build up in the bone marrow, so there are fewer healthy blood cells. These cancerous cells can also enter the blood stream and circulate in the blood, and go to different parts of the body.

The main treatment for AML is chemotherapy. Chemotherapy uses medicines to kill cancer cells or stop them from growing and dividing. You can have chemotherapy through a drip into a vein, as a tablet you swallow, or by an injection under the skin. People with AML might also have a procedure called a stem cell transplant,

which attempts to remove the cancerous blood forming cells from the bone marrow and replace them with healthy cells taken, in most of the cases, from another healthy person (donor). The new cells can now multiply and produce healthy cells.

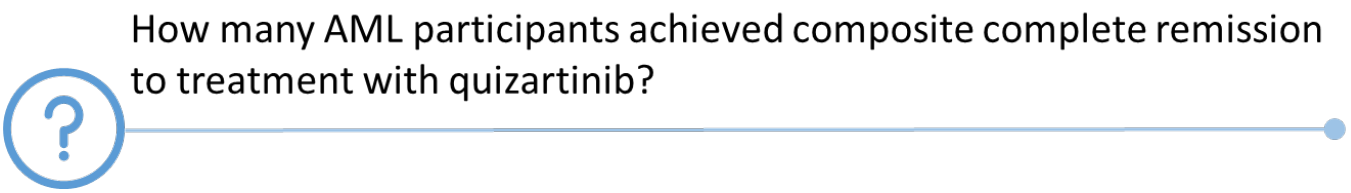
People with AML may or may not have certain gene alterations (or mutations). People with FLT3-ITD positive AML have an alteration (or mutation) in the FLT3 gene. FLT3-ITD positive AML is often severe, does not respond well to treatment and is likely to come back even after treatment. Quizartinib is designed to work against AML cells with this genetic mutation. Researchers wanted to see how effective quizartinib is at treating patients who tested either positive or negative for FLT3-ITD in AML.

## Treatment given in this study



## Main purpose of this study

The main question the researchers wanted to answer in this study was:




**Composite complete remission** was defined as the sum of:

- **Complete remission** which is also called **"CR":** CR meant less than 5% of cells in the participant's bone marrow were cancer cells, with complete recovery of neutrophils and platelets*. There were no signs of AML in the bone marrow or any parts of the body, and the participant's blood cells had recovered without the need of any transfusion; plus
- **Complete remission with incomplete platelet recovery**, which is also called **"CRp":** CRp meant less than 5% of cells in the participant's bone marrow were cancer cells, with incomplete recovery of platelets; plus
- **Complete remission with incomplete hematological recovery**, which is also called **"CRi":** CRi meant less than 5% of cells in the participant's bone marrow were cancer cells, with incomplete recovery of neutrophils, with or without complete recovery of platelets. The participants may or may not have needed blood or platelet transfusion.

*Neutrophils are a type of white blood cells that fight bacteria. Platelets are a type of blood cells that help in preventing/stopping bleeding.

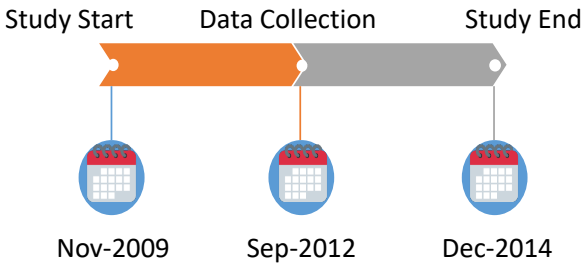
## Other purposes of this study

Researchers also wanted to answer the following questions:

- How long did participants who achieved composite complete remission to treatment with quizartinib continue to show remission? This is also called 'Duration of Composite Complete Remission'.
- How long did AML participants live after initiating treatment with quizartinib? This is also called 'Overall Survival'.
- How long the participants stayed free of disease before leukemia recurred again or they died due to any cause? This is also called 'Leukemia Free Survival'.
- What side effects did the participants develop during the study?

There were some additional questions that researchers wanted to answer but these are not discussed in this summary.

## How long was this study?

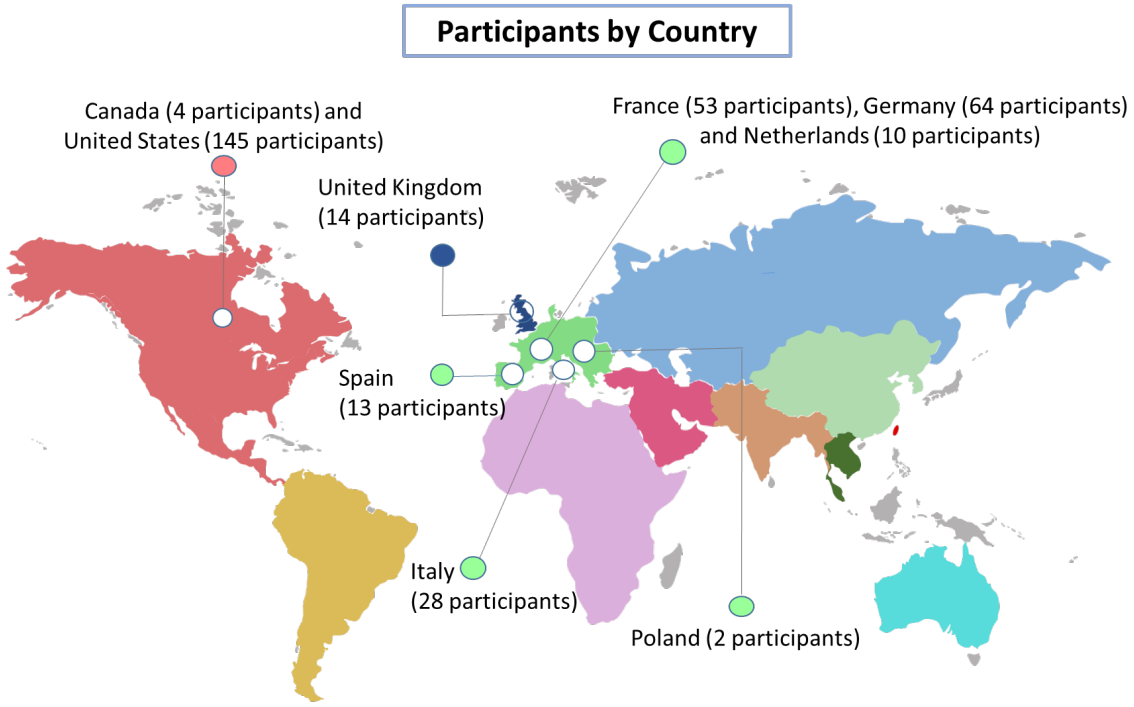



The study was designed in such a way that the participants could continue in it as long as they benefited from the treatment and their AML did not get worse, and they did not have any serious side effects. A serious side effect could have caused a participant to discontinue their treatment with quizartinib.

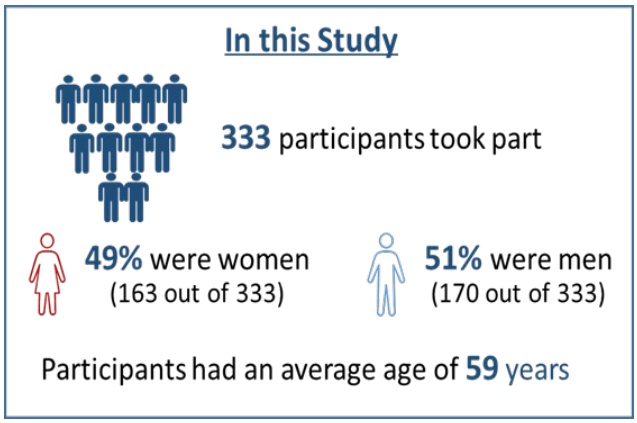
The first participant was enrolled in the study in November 2009. The results were collected up to September 2012 for the study report. This summary is based on that report. The study was completed as planned in December 2014. No further report is available.

## Who was in this study?

This study included 333 participants from the following countries:



Participants could take part in this study if they:




- were able to swallow quizartinib oral solution,
- were diagnosed with AML or had myelodysplastic syndrome (MDS – another type of blood cancer in which blood forming cells become abnormal) that progressed to AML,
- were at least 60 years and AML came back again within 12 months of receiving their first treatment, or did not respond to their first treatment,
  OR
  were at least 18 years and AML came back again or did not respond to their second treatment, or did not respond to stem cell transplant,
- were fully active, OR unable to do hard physical activity but able to walk and do light housework or office work, OR unable to work but able to walk and manage selfcare and be out of bed for more than 50% of waking hours,
- did not have any other diseases or abnormal lab tests that could prevent their meeting study requirements including study visits and assessments, and
- did not have any major heart problems such as a heart attack or irregular heart rhythm.

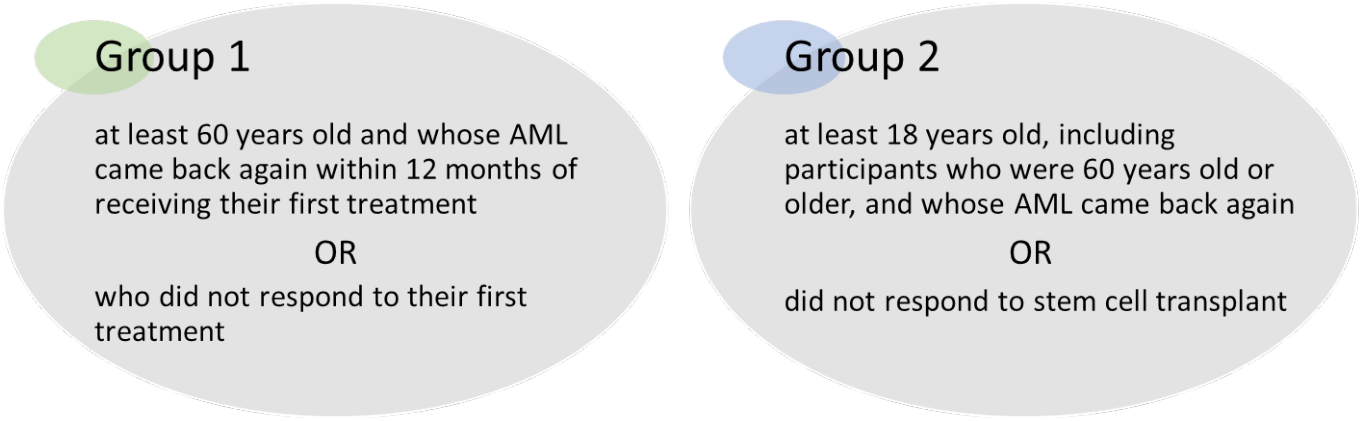
## What happened during this study?

This was a Phase 2 study to find out the effect of quizartinib in AML participants who tested positive or negative for FLT3-ITD mutation. Generally in Phase 2 studies, the study treatment is given to a small number of participants with the disease condition to gather information about the effects of the study treatment in patients.

This study was divided into 2 stages: Exploratory and Confirmatory.

The Exploratory Stage was to explore the effect of quizartinib in patients diagnosed with AML. It included the first 62 AML participants out of which 58 tested positive for FLT3-ITD. They received quizartinib for the first 28 days (1 cycle) of the study. An independent committee reviewed the data from the Exploratory Stage. They recommended continuing the study into the Confirmatory Stage.

The Confirmatory Stage was to confirm the effect seen with quizartinib in the Exploratory Stage on a larger number of patients. It included all the remaining participants. Participants in either stage were assigned to Group 1 or Group 2:

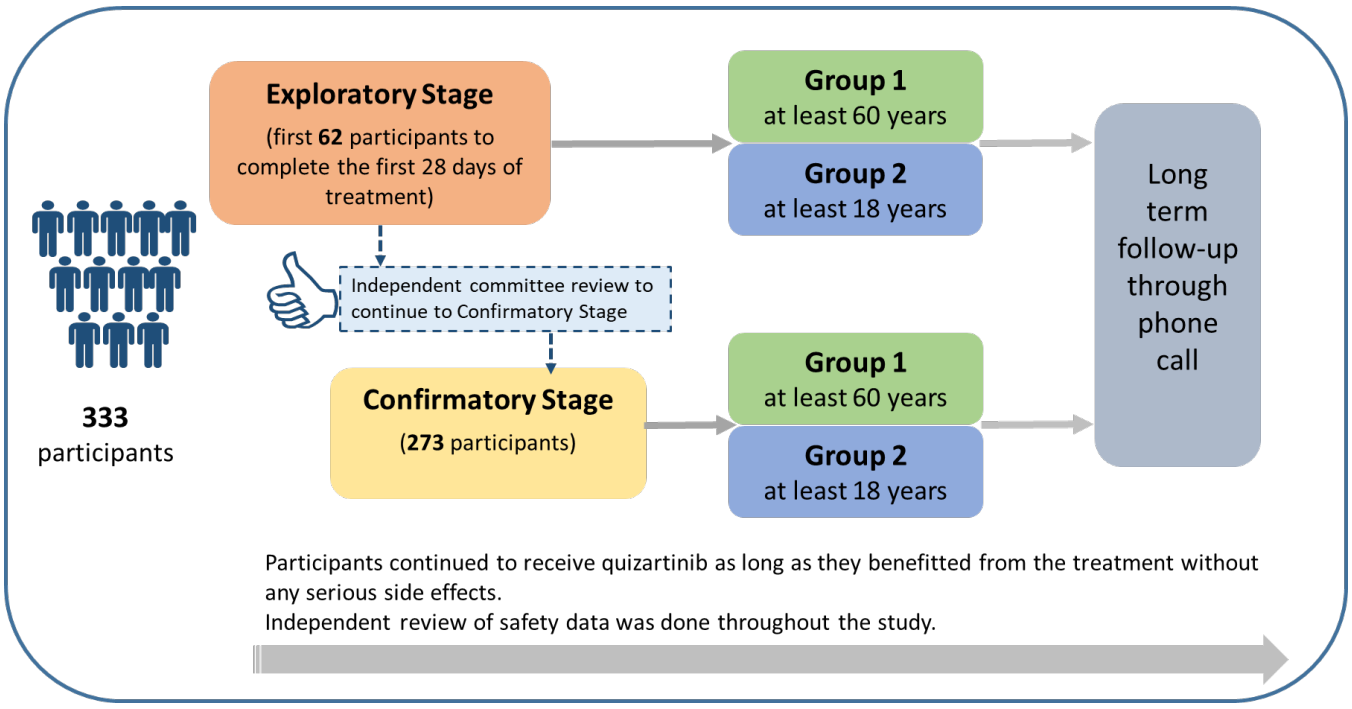



This study was “open label”. This means that everyone, including the researchers and the participants knew which treatment was given to which participants.

When the study started, a few of the participants received 200 milligrams (mg)/day of quizartinib solution by mouth. However, this dose level caused changes in electrical activity of the heart (electrocardiogram QT prolonged). Because of this side effect in these first few participants, the starting dose of quizartinib was reduced to:

- 135 mg/day for men, or
- 90 mg/day for women.

Participants took quizartinib on an empty stomach once every morning for 28 days. This cycle of treatment could be repeated for as long as they benefited from the treatment without any serious side effects. Researchers collected bone marrow and blood samples from the participants throughout the study to check the effect of quizartinib on AML. They also monitored the health of the participants throughout the study. A test called electrocardiogram was used to check the electrical activity of the heart of participants. During the long term follow-up, the participants received a phone call for a health check every 3 months.




# What were the key results of this study?

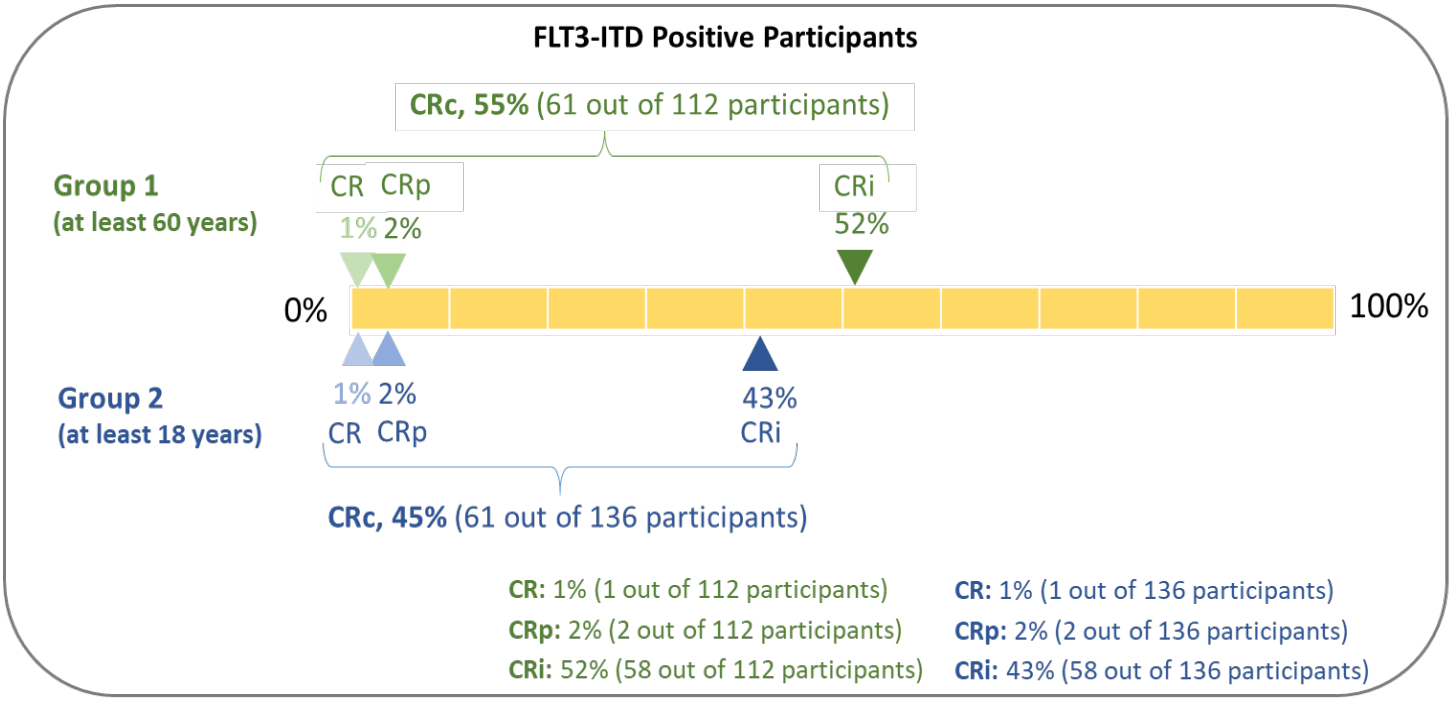
Key results from this study are shown for the total group of participants, from both stages, as average results. This summary does not show the results from each individual participant. An individual participant's results could be different from the total group of participants. A full list of the questions the researchers wanted to answer and a detailed presentation of the results can be found on the websites listed at the end of this summary.

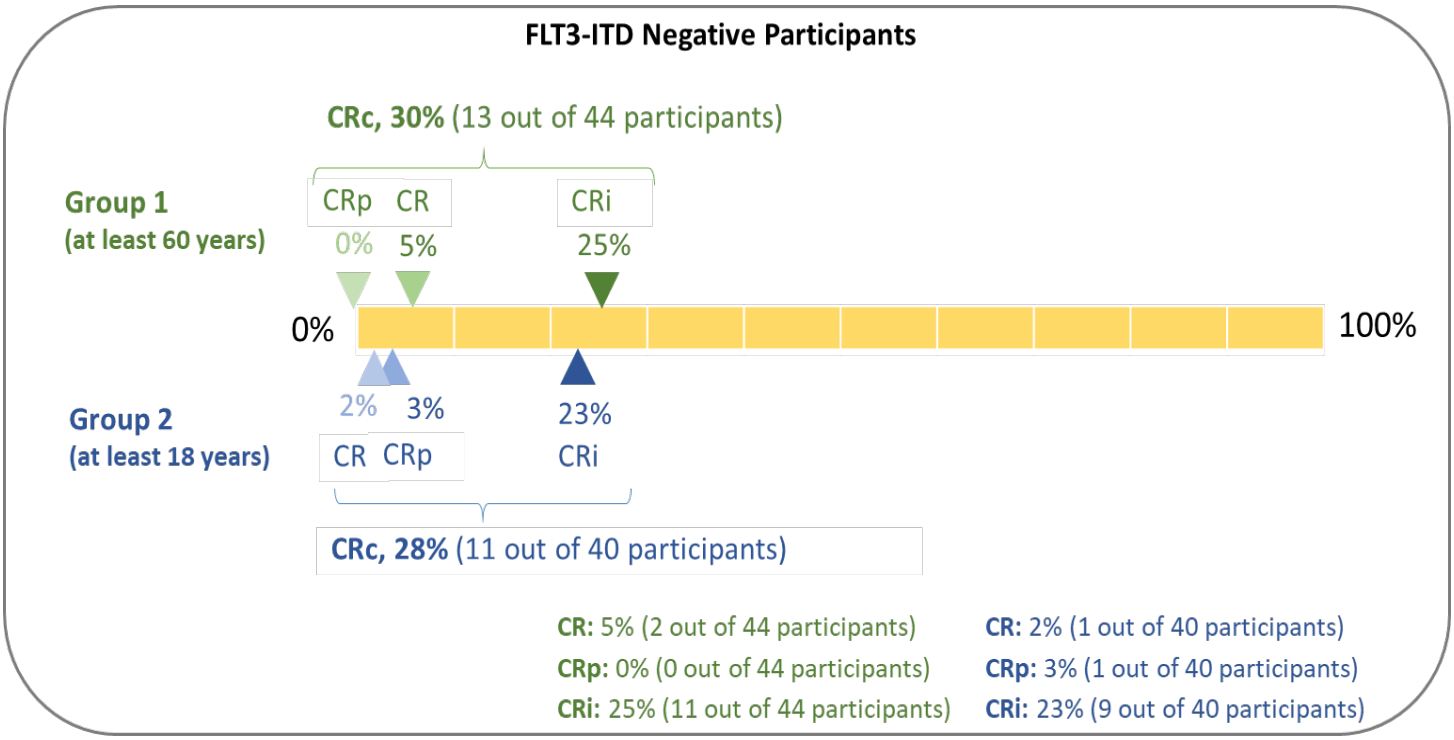
The researchers combined the data from both the Exploratory and Confirmatory Stages. The results are presented altogether so that researchers had clearer answers to the study questions.

## How many AML participants achieved composite complete remission to treatment with quizartinib?

To answer this question, researchers checked, after the first 3 cycles of treatment, how many AML participants had achieved complete remission (CR), complete remission with incomplete platelet recovery (CRp), and complete remission with incomplete hematological recovery (CRi). The results were assessed locally at the study site.

The percentage of participants who achieved composite complete remission (CRc) to treatment with quizartinib was:



# What were the other results of this study?

## How long did participants who achieved composite complete remission to treatment with quizartinib continue to show remission?

**FLT3-ITD positive:** About half of the participants in each group responded to quizartinib for at least 12.1 weeks (2.8 months) in Group 1 and at least 11.3 weeks (2.6 months) in Group 2.

**FLT3-ITD negative:** About half of the participants in each group responded to quizartinib for at least 20.4 weeks (4.7 months) in Group 1 and at least 7.0 weeks (1.6 months) in Group 2.

## How long did AML participants live after initiating treatment with quizartinib?

Researchers measured the time from starting the treatment until the patients died due to cancer or any other cause. At the end of this study, researchers found that:

**FLT3-ITD positive:** About half of the participants in both the groups lived for at least 25.4 weeks (5.8 months) in Group 1 and at least 24.0 weeks (5.5 months) in Group 2 after initiating treatment with quizartinib.

**FLT3-ITD negative:** About half of the participants in both the groups lived for at least 19.1 weeks (4.3 months) in Group 1 and at least 25.1 weeks (5.7 months) in Group 2.

## How long the participants stayed free of disease before leukemia recurred again or they died due to any cause?

**FLT3-ITD positive:** About half of the participants in both the groups lived cancer free for at least 12.1 weeks (2.7 months) in Group 1 and at least 12.9 weeks (2.9 months) in Group 2.

**FLT3-ITD negative:** About half of the participants in both the groups lived cancer free for at least 20.4 weeks (4.6 months) in Group 1 and at least 7.0 weeks (1.6 months) in Group 2.

# What side effects did the participants develop during the study?

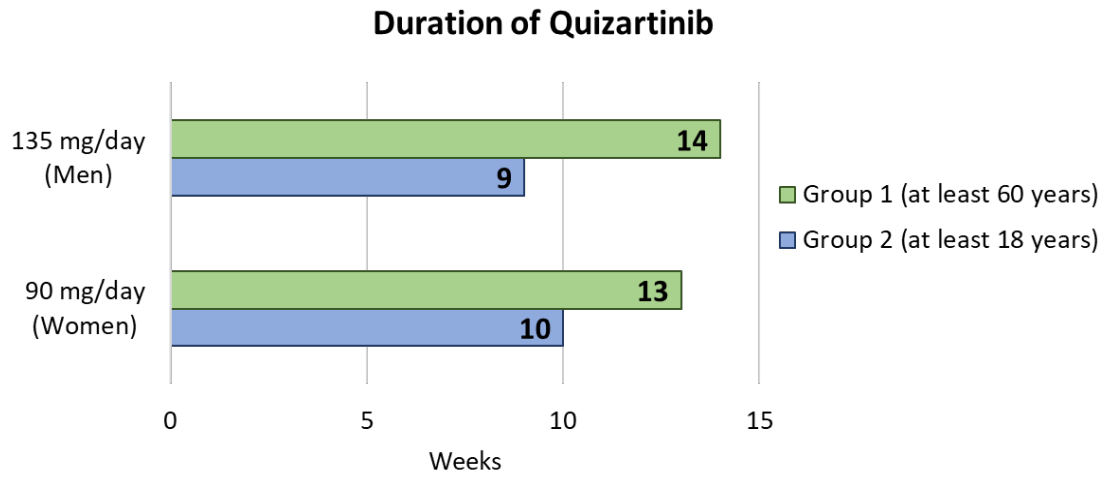
Side effects are medical problems (this may range from something mild such as feeling tired or something more severe like a severe infection or other medical problem) that happened during the study, which the study doctor thought could be related to the treatments in the study.

Side effects are considered serious if they cause death, are life-threatening, cause disability, cause lasting problems, cause birth defects, or require hospitalization. Some participants stopped study treatment because of side effects.

Side effects other than those related to study treatment are not reported here. For more information on medical problems, please visit the websites listed at the end of this summary.

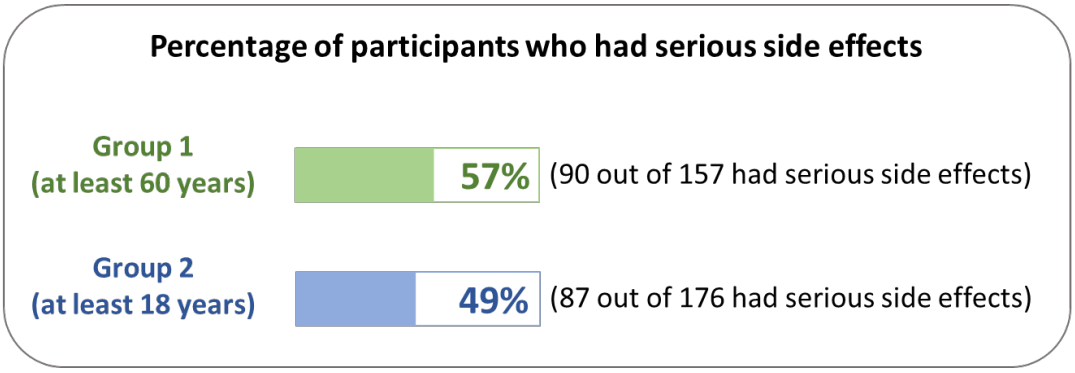
## How long did the participants receive treatment during the trial?

The participants in Group 1 were in the study longer than the participants in Group 2. The next figure shows the median duration for which the participants in either Group 1 or 2 received treatment, by dose level (women vs men). Median means the midpoint value for a group. For example, for the participants in Group 1 who took quizartinib 90 mg/day (all women), the duration of the treatment for half of them was less than 13 weeks, and for the other half it was more.




## How many participants had serious side effects?

In this study, side effects were monitored for 333 participants who took quizartinib.




The most common serious side effects that occurred in at least 2% (2 out of 100) of participants in any group were:

| Group 1 (at least 60 years) | | | Group 2 (at least 18 years) | |
|---|---|---|---|---|
| (34 out of 157) | 22% | Abnormally low number of neutrophils[a] accompanied with fever | 24% | (42 out of 176) |
| (17 out of 157) | 11% | Changes in electrical activity in the heart[b] (Electrocardiogram QT prolonged) | 9% | (15 out of 176) |
| (7 out of 157) | 5% | Lung infection (pneumonia) | 4% | (7 out of 176) |
| (6 out of 157) | 4% | Irregular heartbeat | 1% | (2 out of 176) |
| (5 out of 157) | 3% | Low number of red blood cells | 3% | (6 out of 176) |
| (5 out of 157) | 3% | Extreme response by the body to infection | 2% | (3 out of 176) |
| (5 out of 157) | 3% | Fever | 2% | (4 out of 176) |
| (4 out of 157) | 3% | Bleeding in upper part of digestive tract | 0% | (0 out of 176) |
| (3 out of 157) | 2% | Low number of platelets[c] | 3% | (5 out of 176) |
| (1 out of 157) | 1% | Feeling sick (the desire to vomit) | 3% | (5 out of 176) |
| (1 out of 157) | 1% | Bleeding in digestive tract | 2% | (4 out of 176) |
| (1 out of 157) | 1% | Vomiting | 2% | (4 out of 176) |

a: A type of white blood cells that fight bacteria
b: Detected using ECG of the heart
c: A type of blood cells that help in preventing/stopping bleeding

One serious case of change in electrical activity of the heart, called *Torsades de Pointes**, was reported in a 63 year old female participant. She was taking 90 mg/day of quizartinib. The study doctor considered that this change in the electrical activity of the heart was possibly caused by the treatment with quizartinib.

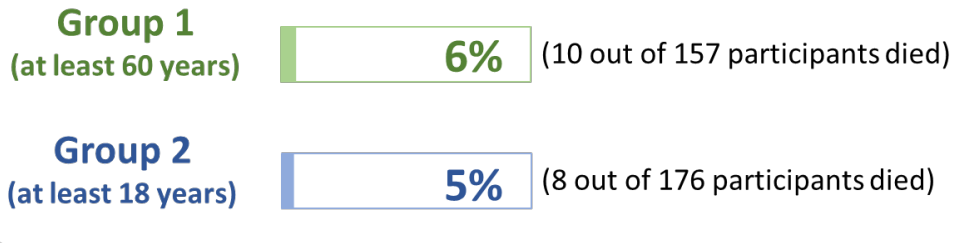
It is worth noting that, the participant also had other medical problems at the time of the event, including:

- history of irregular heart rhythm,
- a severe infection in her blood,
- periods of time where she stopped breathing, and
- some abnormalities in electrolytes (low calcium and potassium), all of which may have also contributed to the event.

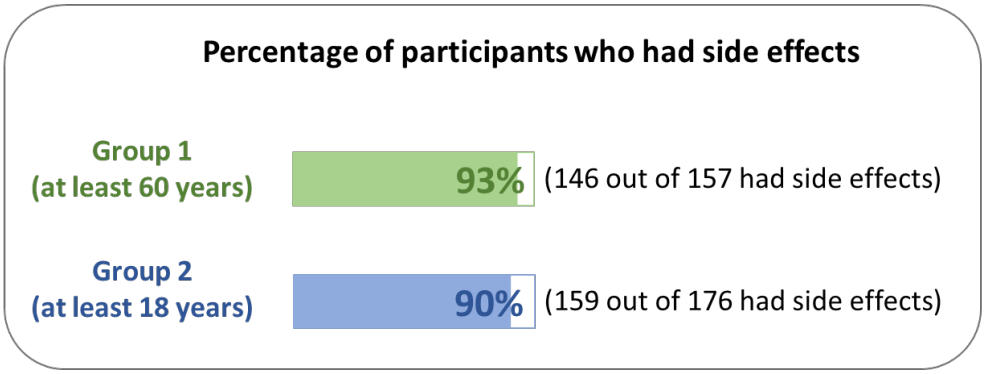
The participant stopped quizartinib and the electrical activity of her heart and heart rhythm returned to normal. She recovered from the event.

**Torsades de Pointes* is a serious type of change in electrical activity and heart rhythm. It is life-threatening and can lead to death.

In this study, 18 deaths (5%) reported by the researchers as related to quizartinib. The most common reason was infections.



## How many participants had side effects?




The most common side effects that occurred in more than 10% (10 out of 100) of participants in any group were:

| Group 1 (at least 60 years) | | | Group 2 (at least 18 years) | |
|---|---|---|---|---|
| (66 out of 157) | 42% | Feeling sick (the desire to vomit) | 36% | (64 out of 176) |
| (49 out of 157) | 31% | Feeling very tired | 22% | (39 out of 176) |
| (40 out of 157) | 26% | Changes in electrical activity in the heart[a] (Electrocardiogram QT prolonged) | 32% | (56 out of 176) |
| (39 out of 157) | 25% | Low number of red blood cells | 26% | (45 out of 176) |
| (39 out of 157) | 25% | Loose stools | 21% | (37 out of 176) |
| (37 out of 157) | 24% | Vomiting | 28% | (50 out of 176) |
| (38 out of 157) | 24% | Change in sense of taste | 18% | (31 out of 176) |
| (34 out of 157) | 22% | Abnormally low number of neutrophils[b] accompanied with fever | 25% | (44 out of 176) |
| (32 out of 157) | 20% | Decreased appetite | 18% | (31 out of 176) |
| (26 out of 157) | 17% | Swelling in lower legs and hands | 9% | (15 out of 176) |
| (23 out of 157) | 15% | Fever | 9% | (15 out of 176) |

| Group 1 (at least 60 years) | | | Group 2 (at least 18 years) | |
|---|---|---|---|---|
| (20 out of 157) | 13% | Indigestion | 11% | (20 out of 176) |
| (21 out of 157) | 13% | Weakness | 6% | (11 out of 176) |
| (20 out of 157) | 13% | Feeling dizzy | 6% | (10 out of 176) |
| (20 out of 157) | 13% | Red or purple spots on the skin due to bleeding | 5% | (8 out of 176) |
| (17 out of 157) | 11% | Low number of platelets[c] | 14% | (24 out of 176) |
| (17 out of 157) | 11% | Low levels of potassium in the blood | 9% | (16 out of 176) |
| (13 out of 157) | 8% | Low number of neutrophils[b] | 11% | (20 out of 176) |

a: Detected using ECG of the heart
b: A type of white blood cells that fight bacteria
c: A type of blood cells that help in preventing/stopping bleeding

## How many participants had to stop treatment because of side effects?

**Percentage of participants who stopped treatment due to side effects**

| | | |
|---|---|---|
| Group 1 (at least 60 years) | 15% | (23 out of 157 had stopped quizartinib) |
| Group 2 (at least 18 years) | 11% | (20 out of 176 had stopped quizartinib) |

## How was this study useful for patients and researchers?

This study helped researchers learn about the effects of quizartinib in AML patients with or without FLT3-ITD.

Findings from this study may be used to support review and approval of this study treatment in patients with AML who have tested positive or negative for FLT3-ITD mutation. Other studies on quizartinib are ongoing.

Please remember, this summary only shows the results of a single study. Other studies may have different findings. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

## Where can I learn more about this study?

You can find more information about this study on the following websites:

- www.clinicaltrials.gov: Use the NCT identifier NCT00989261 in the search field.
- https://www.clinicaltrialsregister.eu/ctr-search/search: Use the EudraCT identifier 2009-013093-41 in the search field.

Please remember that the results on these websites may be presented in a different way. If you were a study participant and have questions about the results of this study, please speak with the doctor or staff at your study site.

**Full study title:** A Phase 2 Open-Label, AC220 Monotherapy Efficacy (ACE) Study in Patients with Acute Myeloid Leukemia With and Without FLT3-ITD Activating Mutations (AC220-002)

**Sponsor:** Daiichi Sankyo, Inc.

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