Summary of Clinical Trial Results

A study to look at the effectiveness of idasanutlin plus cytarabine vs cytarabine in people with relapsed or refractory acute myeloid leukemia (the MIRROS study)

See the end of the summary for the full title of the study.

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) – written for:

- members of the public and
- people who took part in the study.

This summary is based on information known at the time of writing.

The study started in December 2015 and this summary includes the complete results that were collected and analysed in January 2020. The study stopped in April 2020.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

Contents of the summary

Glossary

- AML = Acute myeloid leukaemia, a type of blood cancer

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about acute myeloid leukaemia (AML) and the medicines studied – idasanutlin and cytarabine.

Key information about this study

- This study was done to find a new way to treat people with AML.
- In this study, people were given either the experimental combination being studied (idasanutlin plus cytarabine) or cytarabine plus a placebo – it was decided by chance which treatment each person was given.
- This study included 447 people in 19 countries.
- The main finding was that idasanutlin plus cytarabine was no better at treating people with AML than cytarabine plus a placebo.
- Slightly more people taking idasanutlin plus cytarabine had serious side effects, compared to people taking cytarabine plus a placebo.

1. General information about this study

Why was this study done?

This study was done in people with acute myeloid leukaemia (AML).

Leukaemia is a type of blood cancer, and 'myeloid' leukaemia affects a particular type of white blood cell called the 'myeloid cells'. These cells have an important role in fighting infections, but also help with tissue development and repair. Acute myeloid leukaemia is an aggressive cancer of the myeloid cells.

Many people with AML are first treated with intensive chemotherapy (also known as 'induction'). This treatment is effective in treating most people in the short term, but AML often comes back (known as 'relapsed' AML). People who do not improve with induction chemotherapy treatment are known as 'refractory'.

There is no standard treatment for people with relapsed or refractory AML. Cytarabine is a medicine most often used as part of intensive chemotherapy treatment, and many clinical trials are testing it in combination with other medicines. This study looked at another medicine called idasanutlin in combination with cytarabine to see if it helped to improve outcomes for people with relapsed or refractory AML.

What were the study medicines?

This study looked at 2 medicines:

- **Cytarabine** – existing medicine
- **Idasanutlin** – the medicine that was studied.

'Cytarabine' is an existing medicine given to people with AML.

- You say this as 'sy-TARE-a-been'.
- Cytarabine works by stopping the replication of genetic material in cells. By preventing duplication of genetic material, its stops duplication of cancer cells, further growth and helps to prevent spread of cancer cells in the body

'Idasanutlin' is the medicine that was studied here – it works in a different way to cytarabine

- You say this as 'eye-dess-ah-NUT-lin'.
- Idasanutlin works by activating signals that tell cancer cells to die
- This may mean that it could help treat people with AML

Idasanutlin plus cytarabine was compared to cytarabine plus a 'placebo'.

- You say this as 'plah – see – bo'
- The placebo looked the same as idasanutlin but did not contain any real medicine. This means it had no medicine-related effect on the body.
- Researchers compared idasanutlin plus cytarabine to cytarabine plus a placebo so they could show which benefits or side effects are actually caused by idasanutlin

What did researchers want to find out?

- Researchers did this study to compare idasanutlin plus cytarabine with cytarabine plus a placebo to see how well idasanutlin plus cytarabine worked (see section 4 "What were the results of the study?").
- They also wanted to find out how safe the medicine was – by checking how many people had side effects and seeing how serious they were, when taking each of the medicines during this study (see section 5 "What were the side effects?").

The main question that researchers wanted to answer was:

1. Did people treated with idasanutlin plus cytarabine live longer than those treated with cytarabine plus a placebo?

Other questions that researchers wanted to answer included:

2. How many people responded to the treatments?
3. What were the side effects of the treatments?

What kind of study was this?

This study was a 'Phase 3' study. In this study, a large number of people with AML either took idasanutlin plus cytarabine or cytarabine plus a placebo – this was to find out about the side effects of idasanutlin plus cytarabine and if idasanutlin plus cytarabine worked to help people with AML live longer. It could then be decided whether the treatment can be approved for medical professionals to give to people.

The study was 'randomised'. This means that it was decided by chance which of the medicines people in the study would have. Randomly choosing which medicine people take makes it more likely that the types of people in both groups (for example, age, sex) will be a similar mix. Apart from the exact medicines being tested in each group, all other aspects of care were the same between the groups.

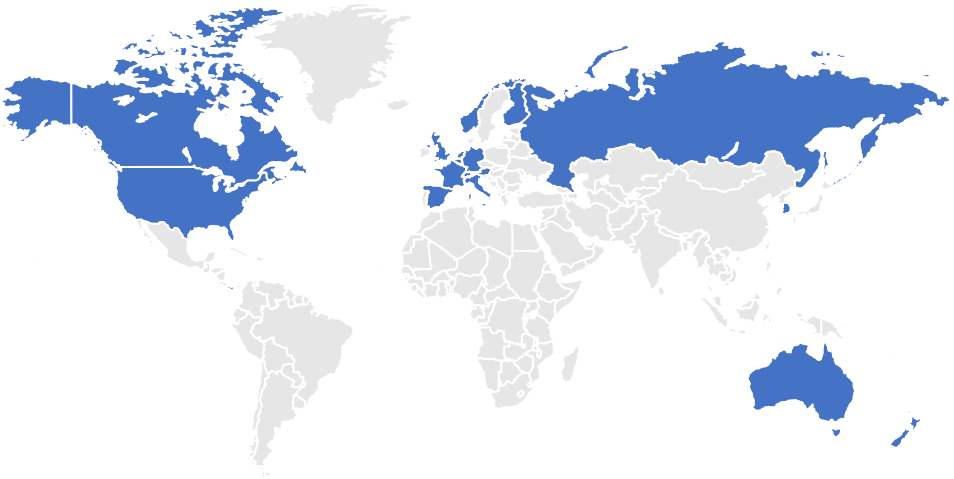
The study was 'double-blind'. 'Blinding' of a study is done so that any effect seen from the medicine is not due to something people expected to happen – if they had known which medicine they were taking. This means that no one involved in the study (both doctors and

people taking part) knew which treatments each person was receiving. However, doctors could find out which group a person was in if they were worried about side effects.

When and where did the study take place?

The study started in December 2015 and this summary includes the complete results up until January 2020. The study stopped in April 2020.

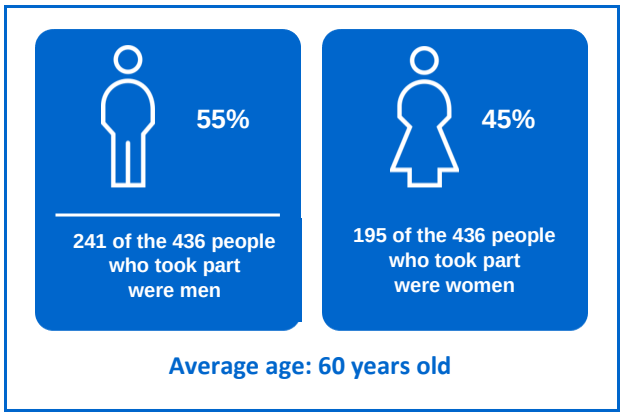
The study took place at 79 study centres – across 19 countries. The following map shows the countries where this study took place.



Australia
Austria
Belgium
Canada
Finland
France
Germany
Israel
Italy
Korea (Republic of)
The Netherlands
Norway
New Zealand
Panama
Russia
Spain
Switzerland
United Kingdom
United States of America

2. Who took part in this study?

In this study, 447 people with AML took part and this summary includes the complete results up until January 2020 for 436 people. The average age of people who took part was 60 years. 241 of the 436 people (55.3%) were male and 195 of the 436 people (44.7%) were female.



People could take part in the study if:

- They had been diagnosed with AML
- They had received up to 2 previous treatments that either did not work (refractory), or did work for a while but the cancer has since come back (relapsed)

People could not take part in the study if:

- Their AML had developed from an earlier diagnosed blood disease that worsened to AML
- Their AML had developed after they had been given chemotherapy to treat another cancer

Genetic testing was also done to look for any changes in genetic material (called a mutation). Doctors in this study were looking for a mutation in a gene called *TP53*. This gene provides instructions to make a protein called 'tumour protein 53', which helps to regulate cell growth and is important in stopping cells from growing out of control. Although the study did not exclude people with this mutation, some analyses in this summary only looked at people who did not have the mutation (known as wild type).

3. What happened during the study?

During the study, people were selected by chance to get one of two treatments. The treatments were selected at random – by a computer.

The treatments in this study were given in cycles, with each cycle lasting 28 days. The treatment groups were:

- **Idasanutlin plus cytarabine** – idasanutlin given as a tablet taken by mouth twice a day for the first 5 days of each cycle and cytarabine given as an infusion into the vein once a day for the first 5 days of each cycle
- **Cytarabine plus placebo** – placebo given as a tablet taken by mouth twice a day for the first 5 days of each cycle and cytarabine given as an infusion into the vein once a day for the first 5 days of each cycle

After people had completed the first cycle of treatment, they were checked for any change in their AML. People who were found to have responded to treatment were given up to 2 further cycles of treatment.

4. What were the results of the study?

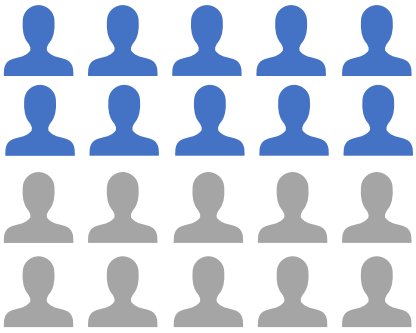
Question 1: Did people treated with idasanutlin plus cytarabine live longer than those treated with cytarabine plus a placebo

Researchers looked at how long people who were *TP53*-wild type lived when treated with idasanutlin plus cytarabine compared with cytarabine plus a placebo. Analysis showed that idasanutlin plus cytarabine was not better at treating people with AML than cytarabine plus a placebo, and length of survival was similar for both. Half of the people given idasanutlin plus cytarabine were still alive after 8.3 months, compared with people treated with cytarabine plus a placebo, of whom half were still alive after 9.1 months.

Half of the people treated with **idasanutlin plus cytarabine** were still alive after

8.3

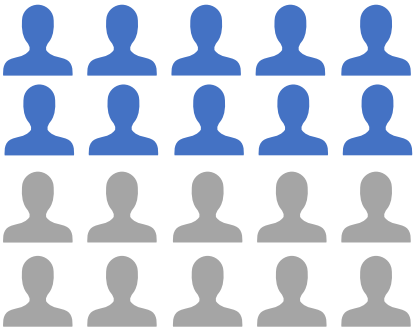
months



Half of the people treated with **cytarabine plus a placebo** were still alive after

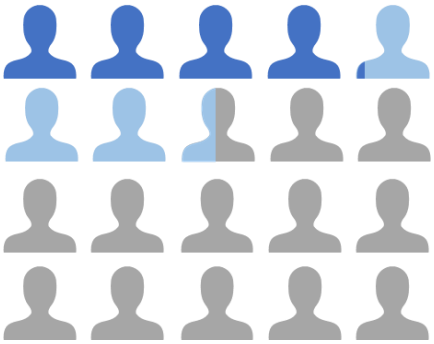
9.1

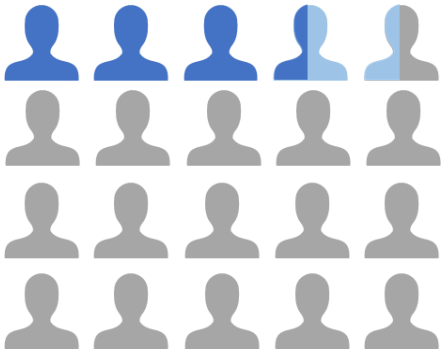
months



Question 2: How many people responded to the treatments?

Another piece of information that researchers collected was how many people responded to the treatment. Overall, 47 out of 232 (20.3%) of people treated with idasanutlin plus cytarabine had a 'complete response' at the end of treatment, meaning there was no longer any sign of their AML in their blood. By comparison, 21 out of 123 (17.1%) of patients people who received cytarabine plus a placebo had a complete response.





20.3% of people treated with **idasanutlin plus cytarabine** had a 'complete response'

The overall response rate was **38.8%** in people treated with **idasanutlin plus cytarabine**

17.1% of people treated with **cytarabine plus a placebo** had a 'complete response'

The overall response rate was **22.0%** in people treated with **cytarabine plus a placebo**

The overall response rate, which includes people who only had some improvement in their AML as well as those who achieve a complete response, was 90 out of 232 (38.8%) for people treated with idasanutlin plus cytarabine and 27 out of 123 (22.0%) for people treated with cytarabine plus a placebo.

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

5. What were the side effects?

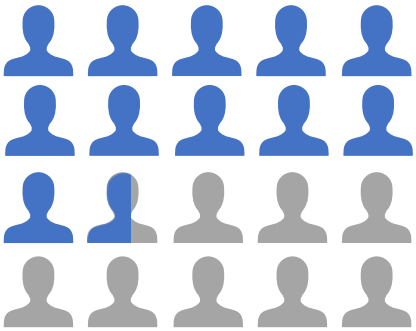
Side effects are medical problems (such as feeling dizzy) that happen during the study.

- Not all of the people in this study had all of the side effects
- Side effects may be mild to very serious and can be different from person to person
- It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies
- Serious and common side effects are listed in the following sections

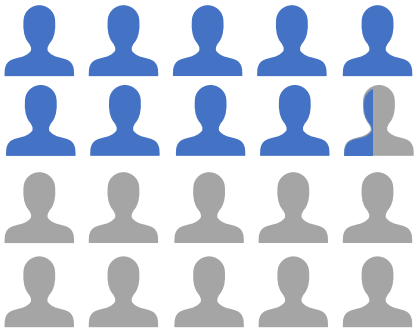
Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care, causes lasting problems or is considered medically significant by the doctor. The safety analysis was done on all people included in the study (both people who were *TP53*-wild type and who had the *TP53* mutation)

During this study, a number of people experienced serious side effects:



58.5% of people treated with **idasanutlin plus cytarabine** had at least one serious side effect



46.6% of people treated with **cytarabine plus a placebo** had at least one serious side effect

The most common serious side effects that happened in more than 5% of people in either group are shown in the table below:

Serious side effects reported in this study	**People taking idasanutlin plus cytarabine** (284 people total)	**People taking cytarabine plus placebo** (146 people total)
Sepsis (blood poisoning)	11.3% (32 out of 284)	4.8% (7 out of 146)
Fever with low neutrophil (a type of	9.5% (27 out of 284)	8.9% (13 out of 146)

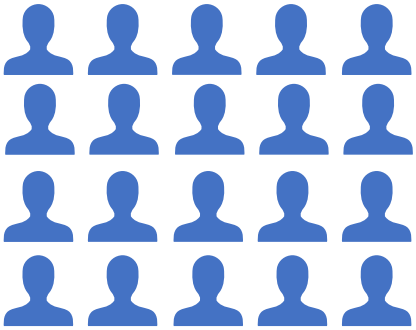
blood cell that fights infections) count		
Pneumonia	6.3% (18 out of 284)	8.9% (13 out of 146)
Septic shock	3.2% (9 out of 284)	5.5% (8 out of 146)

During the study, some people decided to stop taking their medicine because of side effects:

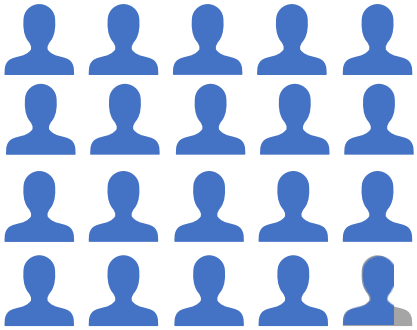
- In the idasanutlin plus cytarabine group, 11 out of 284 people (3.9%) stopped taking either or both treatments.
- In the cytarabine plus placebo group, 2 out of 146 people (1.4%) stopped taking either or both treatments.

Most common side effects

During this study, a number of people experienced common side effects:



100% of people treated with **idasanutlin plus cytarabine** had at least one side effect



99.3% of people treated with **cytarabine plus a placebo** had at least one side effect

The most common side effects were gastrointestinal toxicities, which includes, for example, nausea, vomiting and abdominal pain.

- 96.1% of people treated with idasanutlin plus cytarabine experienced gastrointestinal toxicities.
- 86.3% of people treated with cytarabine plus a placebo experienced gastrointestinal toxicities.

Side effects can also be graded by their severity, with more severe side effects having a higher grade (5 being the highest).

- 94.7% of people treated with idasanutlin plus cytarabine had at least one side effect that was Grade 3–5

95.2% of people treated with cytarabine plus a placebo had at least one side effect that was Grade 3–5

The most common Grade 3–5 side effects are shown in the table below:

Most common Grade 3–5 side effects	**People taking idasanutlin plus cytarabine** (284 people total)	**People taking cytarabine plus placebo** (146 people total)
Fever with low neutrophil (a type of blood cells that fight infections) count	52.5% (149 out of 284)	49.3% (72 out of 146)
Low platelet count	40.8% (116 out of 284)	47.9% (70 out of 146)
Low red blood cell count	23.2% (66 out of 284)	28.1% (41 out of 146)

Other side effects

You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

6. How has this study helped research?

The information presented here is from a single study of 447 people with relapsed or refractory AML. These results helped researchers learn more about idasanutlin and cytarabine when used to treat relapsed or refractory AML.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at idasanutlin plus cytarabine in adults are planned.

8. Where can I find more information?

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

- https://clinicaltrials.gov/ct2/show/results/NCT02545283

- https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-003065-15/AT
- https://forpatients.roche.com/en/trials/cancer/leukemia/a-study-of-idasanutlin-with-cytarabine-versus-cytarabine-plus-pl.html

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/cancer/leukemia/a-study-of-idasanutlin-with-cytarabine-versus-cytarabine-plus-pl.html
- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own treatment:

- Speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PHASE III STUDY OF IDASANUTLIN, AN MDM2 ANTAGONIST, WITH CYTARABINE VERSUS CYTARABINE PLUS PLACEBO IN PATIENTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA (AML)".

The study is known as 'MIRROS'.

- The protocol number for this study is: WO29519.
- The ClinicalTrials.gov identifier for this study is: NCT02545283
- The EudraCT number for this study is: 2014-003065-15.