Summary of Clinical Trial Results

A study looking at the use of pertuzumab in combination with trastuzumab and chemotherapy in HER2-positive early breast cancer

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

About this summary

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

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

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

The study started in November 2011 and this summary includes the results that were collected and analysed in June 2019. At the time of writing this summary, the study is still ongoing – this summary presents the complete results for one part of the study. Study doctors are still collecting information, and this summary will be updated when new information becomes available.

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 those of 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

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about HER2-positive breast cancer and the medicines being studied.

1. General information about this study

Why was this study done?

Receptors are a type of protein found on cells. Some breast cancer cells have higher-than-normal levels of a receptor called 'HER2' (human epidermal growth factor receptor 2) on their surface, which stimulates them to grow. This type of breast cancer is called 'HER2-positive breast cancer', and it is classed as 'early' if the cancer cells have not spread to other parts of the body.

Surgery can be performed to remove breast cancer tumours. After surgery, chemotherapy drugs can be given in combination with anti-cancer medicines that block the HER2 receptor. This helps treat the cancer and prevent it from coming back after surgery.

Anti-cancer medicines that block the HER2 receptor are known as 'HER2-targeted therapies' and include drugs such as 'trastuzumab'. The combination of trastuzumab and chemotherapy was the 'standard of care' (that is, the accepted treatment for a particular disease, according to medical experts) for people with HER2-positive early breast cancer at the time this study was designed.

In this study, researchers were looking for a new way to treat people with HER2-positive breast cancer, using a drug called 'pertuzumab', which also targets HER2 and works together with trastuzumab. The study was designed to look at whether adding pertuzumab to trastuzumab and chemotherapy helped people with HER2-positive early breast cancer more than using trastuzumab and chemotherapy alone.

What were the study medicines?

'Trastuzumab'

- You say this as 'trass-too-za-mab'.
- Trastuzumab is an existing medicine that works by attaching to the HER2 protein on the surface of HER2-positive cancer cells. When trastuzumab attaches to HER2, it stops the protein from sending signals that make the cancer cells grow and make copies of themselves. It also makes cells in the immune system become active so that they can help attack the cancer.

'Pertuzumab'

- You say this as 'per-too-za-mab'.
- Pertuzumab is the medicine being studied in APHINITY. It works together with trastuzumab but attaches to a different part of the HER2 protein.

Pertuzumab was compared to trastuzumab and chemotherapy plus a 'placebo'.

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

What did researchers want to find out?

- Researchers did this study to find out how effective pertuzumab (the study medicine) was when combined with trastuzumab and chemotherapy, compared with placebo, trastuzumab and chemotherapy (see section 4, "What are the results of the study at 6 years?").

- They also wanted to find out how safe this combination of medicines was – by checking how many people had side effects related to the heart when taking either the combination of pertuzumab, trastuzumab and chemotherapy, or placebo, trastuzumab and chemotherapy (see section 5, "What heart-related side effects have been seen in the study so far?").

The main question that researchers wanted to answer was:

1. Did people who were given pertuzumab live longer, compared with those given placebo?

Other questions that researchers wanted to answer included:

2. Did more people who were given pertuzumab live without their cancer coming back, compared with placebo?
3. In people with a higher risk of their cancer coming back, did more who were given pertuzumab live without their cancer coming back, compared with placebo?
4. How many people in this study had medical problems related to the heart?

What kind of study was this?

This study was a 'Phase 3' study. This means that the combination of pertuzumab, trastuzumab and chemotherapy had been tested in a smaller number of people with HER2-positive early breast cancer before this study.

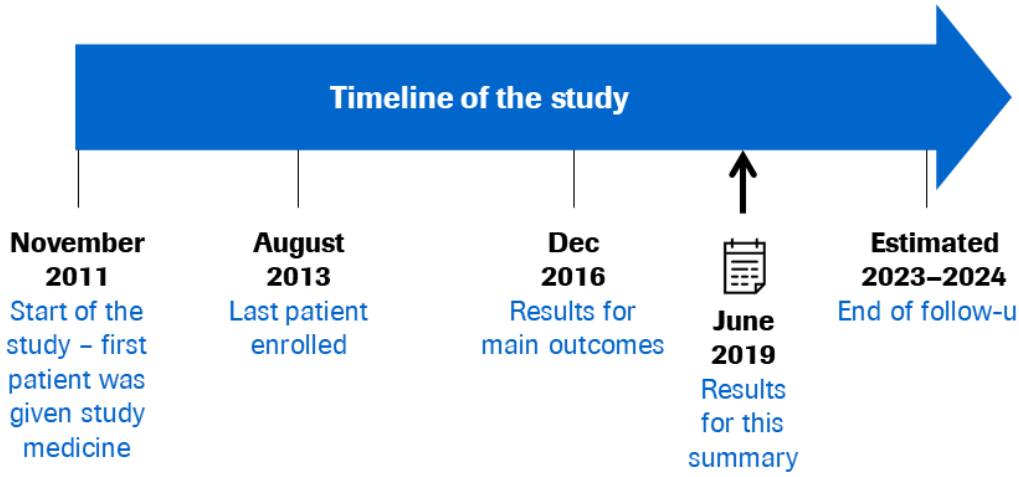
In this study, a larger number of people with this cancer either took pertuzumab or placebo in addition to trastuzumab and chemotherapy. This was to find out about the side effects of pertuzumab, and whether adding pertuzumab to trastuzumab and chemotherapy is more effective at helping people to live without their cancer coming back, than trastuzumab and chemotherapy alone.

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 (with regard, for example, to age or race) will be similar and comparable. Apart from the exact medicines being tested in each group, all aspects of care were the same between the groups.

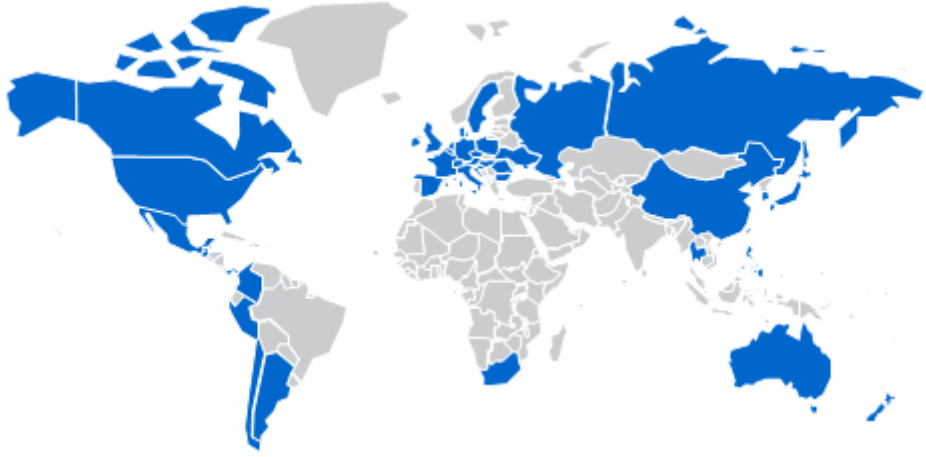
This was a 'double-blind' study. This means that neither the people taking part in the study nor the study doctors knew whether people were taking pertuzumab or placebo. This type of trial helps to lower the chance of having a result influenced by other factors, rather than the medicine itself.

When and where did the study take place?

The study started in November 2011. The primary analysis results (main outcome results) were collected in 2016 and have been reported previously (you can find the previous summary here: https://forpatients.roche.com/content/dam/patient-platform/lps/Aphinity%20Lay%20Summary.pdf). This summary includes the results up until June 2019 – the symbol on the timeline ( ) shows when the information in this summary was collected. At the time of writing this summary, further information is being collected.



The study took place at 548 study centres – across 42 countries in Africa, Asia, Australia, Europe, North America and South America. The following map shows the countries where this study took place.



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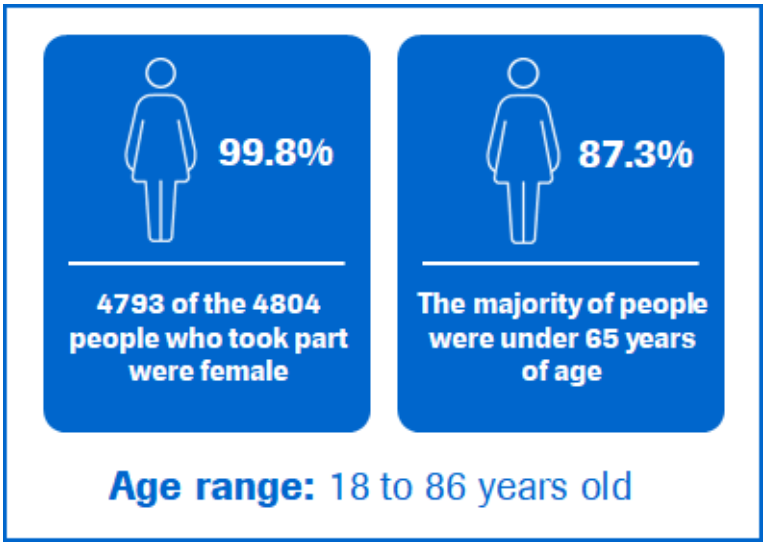
- Peru
- Philippines
- Poland
- Republic of Korea
- Romania
- Russia
- Slovenia
- South Africa
- Spain
- Sweden
- Switzerland
- Taiwan
- Thailand
- Ukraine
- United Kingdom
- United States

2. Who is taking part in this study?

In this study, 4804 people (4793 pre- and post-menopausal women and 11 men) with HER2-positive early breast cancer took part. More information on the people who took part is given below.



People could take part in this study if they had:

- **HER2-positive breast cancer, confirmed by a specific test**
- **Surgery to remove the tumour**
- **At diagnosis: cancer cells in the armpits (axillary lymph nodes) and a detectable tumour, OR no cancer cells in the armpits AND either a tumour bigger than 1 cm or a tumour size of 0.5–1 cm and at least one of the following: age <35 years, no hormone receptor proteins* on cancer cells, cancer cells do not look like normal cells**

People could NOT take part in this study if they had:

- **Previous history of invasive breast cancer**
- **Breast cancer that could not be removed by surgery or had spread to other parts of the body**
- **Heart disease or heart problems**
- **Previously been treated with anti-cancer therapies**

* Hormone receptors are proteins that bind hormones in the body that can make cancer cells grow.

3. What is happening during the study?

Before joining the study, people had to have surgery to remove their cancer. During the study, people were then selected by chance to get one of two treatments. The treatments were selected at random – by a computer.

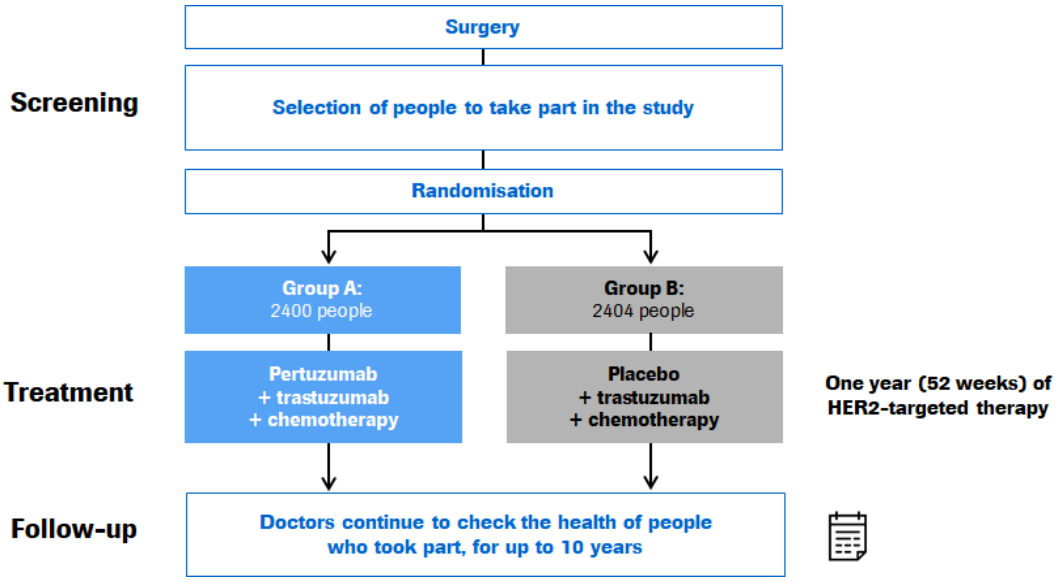
The treatment groups were:

- **Group A** – pertuzumab (study medicine) and trastuzumab were infused into a vein (intravenous) every 3 weeks for 1 year.
- **Group B** – the placebo (inactive substance) and trastuzumab were infused into a vein every 3 weeks for 1 year.

People in both groups were also given chemotherapy (for up to 6 months).

This study is still ongoing – people have finished taking their study medicines and are being monitored in the 'follow-up' phase for their health and safety. When the study

finishes, the people who took part will be asked to go back to their study centre for more visits – to check their overall health. Look below to see more information about what has happened in the study so far – and what the next steps are. The symbol on the timeline (📋) shows when the information presented in this summary was collected – almost 8 years after the study started.



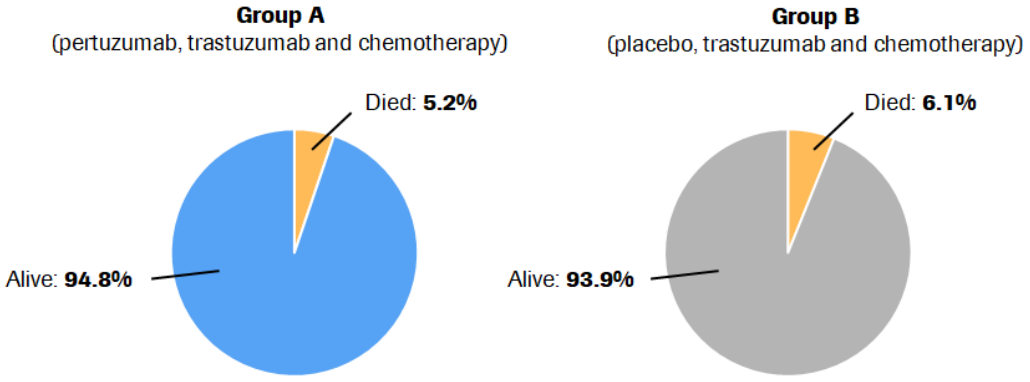
4. What are the results of the study at 6 years?

Question 1: Did people who were given pertuzumab live longer, compared with those given placebo?

Researchers wanted to know whether adding pertuzumab to trastuzumab and chemotherapy helped people to live longer. Overall, at June 2019, 94.8% (2275 out of 2400) of people given pertuzumab were still alive, compared with 93.9% (2257 out of 2404) of people given placebo, as shown in the figure below.

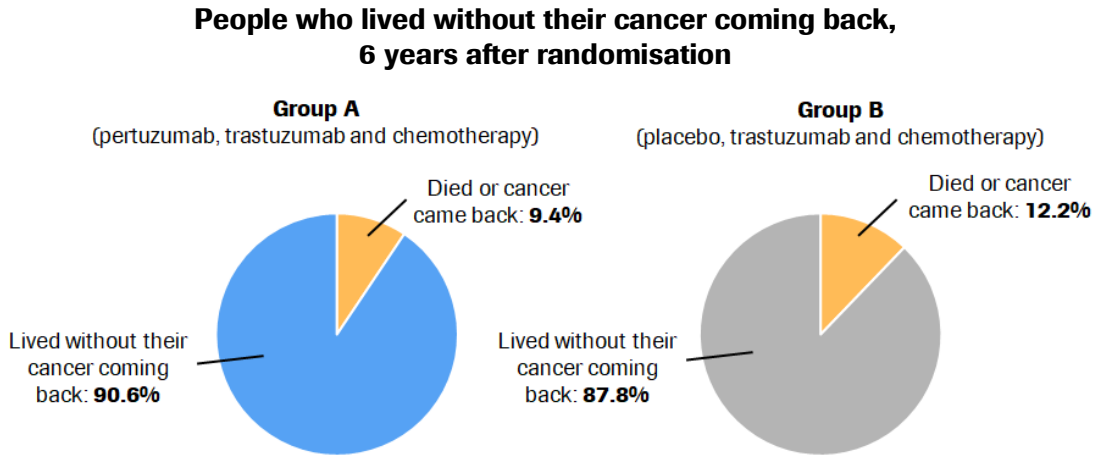
It is still too soon for researchers to say for certain whether adding pertuzumab to trastuzumab and chemotherapy helps people to live longer – not enough time has passed. Doctors are continuing to collect information on those who are taking part in the study during the follow-up phase.

People in the study who were still alive, up to June 2019



Question 2: Did more people who were given pertuzumab live without their cancer coming back, compared with placebo?

Yes – the results show that 6 years after people were randomised in APHINITY, 90.6% of people given pertuzumab lived without their cancer coming back, compared with 87.8% of people given placebo, as shown in the figure below.



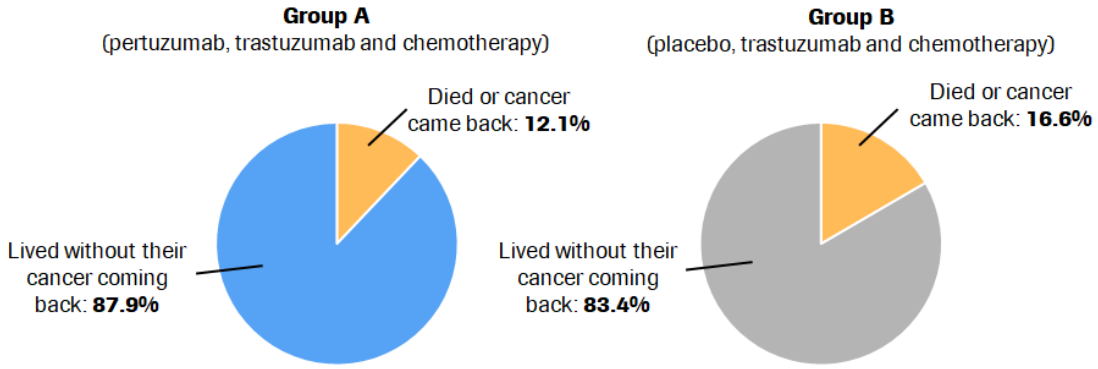
Question 3: In people with a higher risk of their cancer coming back, did more people who were given pertuzumab live without their cancer coming back, compared with placebo?

Researchers wanted to understand whether adding pertuzumab to trastuzumab and chemotherapy helped people who had a higher risk of their cancer coming back (this is called 'high-risk', HER2-positive early breast cancer), more than trastuzumab and chemotherapy alone.

Some of the people in the study had cancer in the breast and in the axillary lymph nodes in the armpits (the cancer is then classed as 'node-positive'). Other people either had a type of breast cancer that does not have hormone receptors (classed as 'hormone receptor-negative') or does have hormone receptors (classed as 'hormone receptor-positive'). Hormone receptors are proteins that bind hormones in the body that can make cancer cells grow. People with hormone receptor-negative cancer have fewer treatment options available because cancer treatments that target hormone receptors are unlikely to work against their tumours.

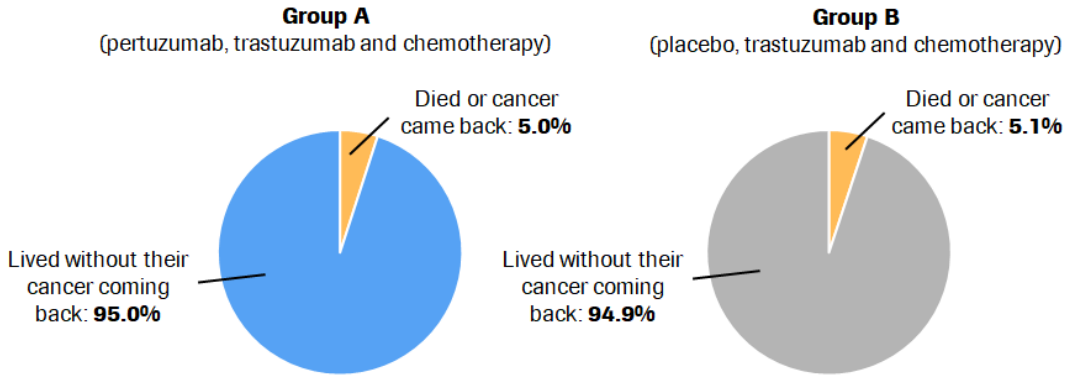
Six years after randomisation, more people with node-positive breast cancer lived without their cancer coming back when given pertuzumab (87.9%), compared with placebo (83.4%), as shown in the figure below.

People with node-positive breast cancer who lived without their cancer coming back, 6 years after randomisation



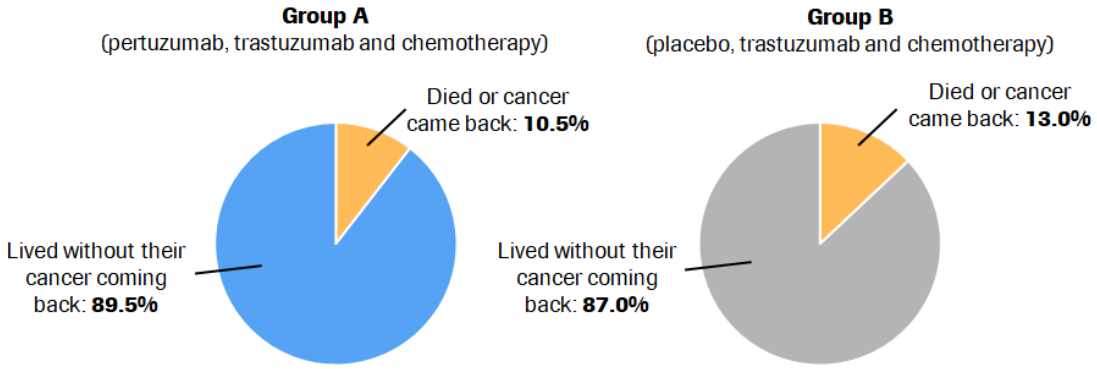
The number of people without cancer cells in the axillary lymph nodes in the armpits (node-negative breast cancer) who lived without their cancer coming back 6 years after randomisation was similar whether they were given pertuzumab (95.0%) or placebo (94.9%), as shown in the figure below.

People with node-negative breast cancer who lived without their cancer coming back, 6 years after randomisation

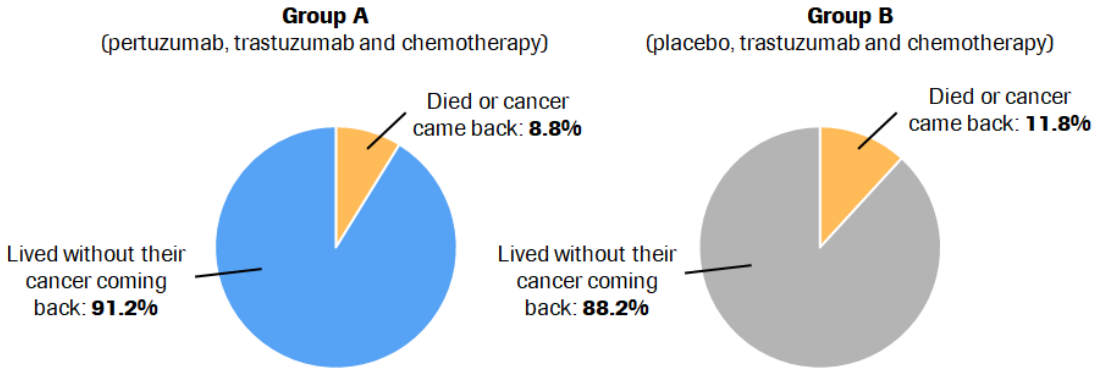


Researchers also found that adding pertuzumab to trastuzumab and chemotherapy helped more people live longer without their cancer coming back, whether their cancer was hormone receptor-positive or -negative. This is different from the results from the primary analysis (treatment part of the study), which seemed to show that adding pertuzumab helped people more if their cancer was hormone receptor-negative. Taken together, these results, collected over a longer period of time (up to June 2019), show that pertuzumab is effective, regardless of the hormone receptor status of the cancer (positive or negative), as shown in the figures below.

People with hormone receptor-negative breast cancer who lived without their cancer coming back, 6 years after randomisation



People with hormone receptor-positive breast cancer who lived without their cancer coming back, 6 years after randomisation



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).

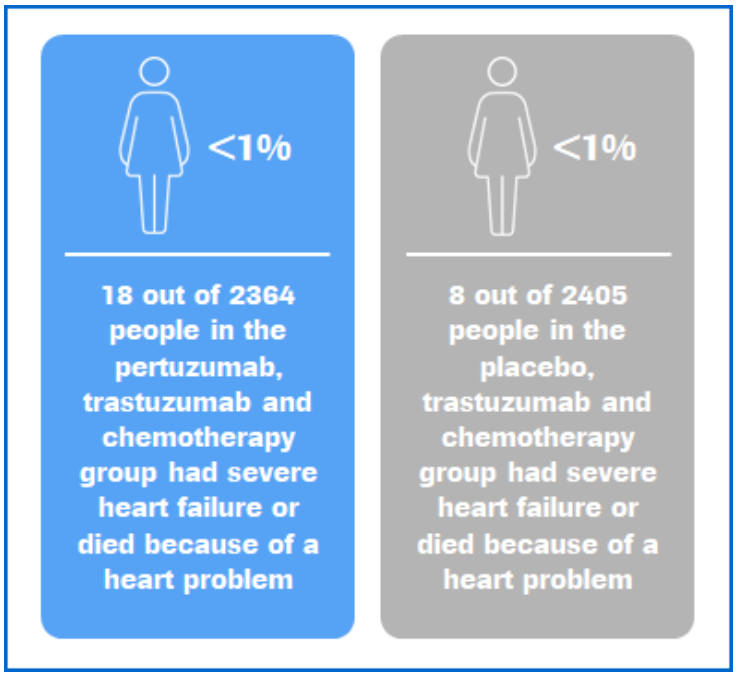
5. What heart-related side effects have been seen in the study so far?

Side effects (also known as 'adverse reactions') are unwanted 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.

Question 4: How many people in this study had medical problems related to the heart?

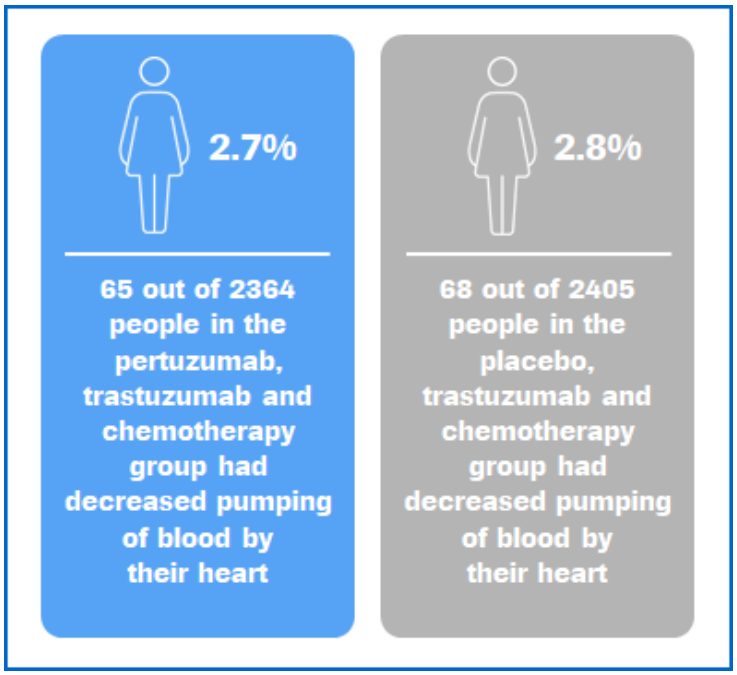
Researchers wanted to learn if pertuzumab, trastuzumab and chemotherapy treatment affected the heart. In this study, up to June 2019, 0.8% of people in the pertuzumab, trastuzumab and chemotherapy group had severe heart failure or died because of a heart problem, compared with 0.3% in the placebo, trastuzumab and chemotherapy group, as shown in the figure below.

People who had severe heart failure or died because of a heart problem, up to June 2019



Researchers also wanted to learn how many people had decreased pumping of blood by their heart at any time in this study. This may have happened with no symptoms or with mild symptoms present. This happened in 2.7% of people in the pertuzumab, trastuzumab and chemotherapy group, compared with 2.8% of people in the placebo, trastuzumab and chemotherapy group, as shown in the figure below.

People who had decreased pumping of blood by their heart, at any time in the study



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 4804 people with HER2-positive early breast cancer. These results, obtained around 6 years after people joined the study, helped researchers understand that adding pertuzumab to trastuzumab and chemotherapy for people with HER2-positive early breast cancer helped them to live longer without their cancer coming back, compared with trastuzumab and chemotherapy alone.

The benefit of adding pertuzumab was even higher in the group of people whose HER2-positive early breast cancer was node-positive. Pertuzumab was effective regardless of whether the cancer was hormone receptor-positive or -negative.

It is still too soon to tell if people live longer when given pertuzumab, compared with placebo – doctors are still collecting this information, and this summary will be updated in the future.

Based on the results from the primary analysis (main study outcomes), which were collected up to December 2016, the combination of pertuzumab, trastuzumab and chemotherapy was approved by drug regulatory authorities for use in people with high-risk, HER2-positive early breast cancer. This combination is now the current standard-of-care for people who are at high risk of their cancer coming back. The results presented in this summary (collected up to June 2019) further support the findings from the main study outcomes.

7. Are there plans for other studies?

At the time of writing this summary, other studies with pertuzumab are still happening, and further studies are planned.

8. Where can I find more information?

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

- https://forpatients.roche.com/en/trials/cancer/bc/a-study-of-pertuzumab-in-addition-to-chemotherapy-and-trastuzuma.html
- https://clinicaltrials.gov/ct2/show/NCT01358877
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022902-41/results

If you would like to find out more about the results of this study, the full title of the relevant scientific paper is: “Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up”. The authors of the scientific paper are: Martine Piccart, Marion Procter, Debora Fumagalli, Evandro de Azambuja, Emma Clark, and others. The paper is published in the ‘Journal of Clinical Oncology’, year 2021, volume number 39, on pages 1448 to 1457.

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/bc/a-study-of-pertuzumab-in-addition-to-chemotherapy-and-trastuzuma.html

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 paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland, and organised by F. Hoffmann-La Roche Ltd, Breast International Group (BIG), Frontier Science Ltd (FSS) and Breast European Adjuvant Study Team (BrEAST).

Full title of the study and other identifying information

The full title of this study is: "A Randomized Multicenter, Double-Blind, Placebo-Controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients With Operable HER2-Positive Primary Breast Cancer".

The study is known as 'APHINITY'.

- The protocol numbers for this study are: BIG 4-11 / BO25126 / TOC4939g.
- The ClinicalTrials.gov identifier for this study is: NCT01358877.
- The EudraCT number for this study is: 2010-022902-41.