Clinical Trial Results

Research Sponsor:	F. Hoffmann-La Roche Ltd.
Research Partner:	Breast International Group (BIG)
Drug Studied:	RO4368451 (Pertuzumab)
National Clinical Trial #:	NCT01358877
EudraCT #:	2010-022902-41
Protocol #:	APHINITY (BIG 4-11/BO25126/TOC4939g)
Results from Study Dates:	November 2011 to December 2016
ClinicalTrials.gov Study Title:	A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants with Human Epidermal Growth Receptor 2 (HER2)-Positive Primary Breast Cancer (APHINITY)

Thank you!

Thank you for taking part in the APHINITY global clinical study. You helped researchers learn about adding pertuzumab to chemotherapy and trastuzumab to treat patients with HER2-positive breast cancer. Chemotherapy and trastuzumab was the standard treatment for HER2-positive breast cancer when you received it in this study. Trastuzumab is also called Herceptin and pertuzumab is also called Perjeta.

F. Hoffmann-La Roche Ltd. sponsored this study and worked with Breast International Group (BIG), Frontier Science Ltd. (FSS), and Breast European Adjuvant Study Team (BrEAST) to run this study. Two patient representatives also helped decide how the study would be done and reviewed this summary.

We believe it is important for you to know the main results from the study so far. An independent nonprofit organization called CISCRP and a medical writing organization called Synchrogenix helped prepare this summary for you. We hope it helps you understand the results and makes you feel proud of your important role in clinical research.

If you have questions after reading this summary, please ask your doctor, research nurse, or another team member at your study center.

This summary tells you:

- Why the research was needed
- The main results of the study so far
- The medical problems that happened during the study
- What happened during the study and what is happening now

Why was the research needed?

Researchers were looking for a new way to treat patients with HER2-positive breast cancer. HER2 is a protein in the body that is involved in normal cell growth. It is also called human epidermal growth factor receptor 2. Patients with HER2-positive breast cancer have high levels of the HER2 protein. Higher levels of HER2 can lead to the growth of breast cancer.

Surgery can be performed to remove breast cancer tumors. After surgery, chemotherapy drugs can be given in combination with a drug that blocks HER2. This helps treat the cancer and prevent it from coming back after surgery. One drug that is used to block HER2 is called trastuzumab.

In this study, the researchers are studying a drug called pertuzumab. This drug also blocks HER2, and it works together with trastuzumab. The researchers wanted to know if using pertuzumab together with chemotherapy and trastuzumab would help patients more than using chemotherapy and trastuzumab alone.

All the patients received trastuzumab and chemotherapy during the study. About half of the patients in the study also received treatment with pertuzumab, and the other half took a placebo. The placebo looked like pertuzumab but did not have any medicine in it. The researchers and patients did not know who received pertuzumab or the placebo. This was done to avoid bias in reporting any effects related to the study treatment.

The researchers wanted to answer the following questions:

- Did more patients receiving pertuzumab live and not have their cancer come back?
- Did patients receiving pertuzumab live longer?
- Did patients with a higher risk of cancer coming back live longer and with no cancer?
- What medical problems did the patients have?
- How many patients in this study had medical problems related to the heart?

What were the study results?

This section tells you the results of the APHINITY study based on information collected up to December 2016. The results are a summary of the information from all participants in the trial. Individual participant results are not included in this summary.

Researchers look at the results of many studies to decide which treatments work best and are safest. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

Did more patients receiving pertuzumab live and not have their cancer come back?

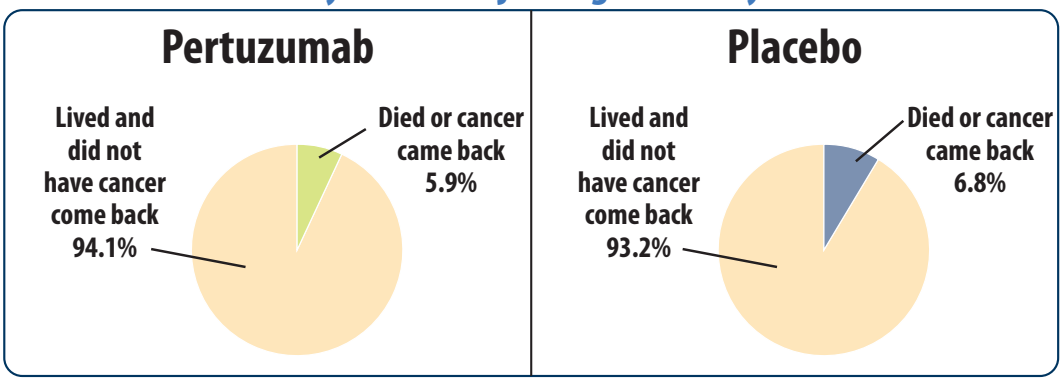
Yes. More patients receiving pertuzumab lived and did not have their cancer come back compared to patients receiving the placebo. The chances of dying or cancer coming back was 19% less for the patients who received pertuzumab.

The results for patients 3 years after joining the study show:

- 94.1% of the patients receiving pertuzumab lived and did not have their cancer come back 3 years after joining the study.
- 93.2% of the patients receiving the placebo lived and did not have their cancer come back 3 years after joining the study.

The chart below shows how many patients lived and did not have their cancer come back 3 years after joining the study.

Patients who lived and did not have their cancer come back 3 years after joining the study



It is important to know that the results above are for the main question the researchers asked. This study was designed to get the most accurate answers to the main question.

The results below are for other questions the researchers asked to learn more about the effects of pertuzumab on cancer. These were not the main question the study was designed to answer.

Did patients receiving pertuzumab live longer?

It is too soon for researchers to know if patients receiving pertuzumab lived longer compared to patients receiving the placebo. Not enough time has passed.

The researchers are still collecting more information. The results for all the patients up to December 2016 show that a similar number of patients receiving pertuzumab were still alive compared to patients receiving the placebo:

- 96.7% of the patients receiving pertuzumab were alive. This was 2,320 out of 2,400 patients.
- 96.3% of the patients receiving the placebo were alive. This was 2,315 out of 2,404 patients.

Some of the patients who died had their cancer come back, while some died for reasons not related to their cancer.

Did patients with a higher risk of cancer coming back live longer and with no cancer?

The researchers also wanted to know more about how pertuzumab worked in patients who had a higher risk of their cancer coming back. Some of these patients had cancer tumors in both their breast and lymph nodes, also called “lymph node-positive”. Other patients had a type of breast cancer that does not have hormone receptors on tumors, called “hormone receptor-negative”. Hormone-receptors are proteins that bind hormones in the body that can make cancer grow.

Patients with hormone receptor-negative tumors have fewer treatment options available because cancer treatments that use hormones to stop tumors from growing are unlikely to work against their tumors.

The patients with lymph node-positive or hormone receptor-negative tumors who received pertuzumab lived longer without their cancer coming back compared to the patients receiving the placebo. The chance of dying or cancer coming back was reduced by approximately 25% for the patients who received pertuzumab.

What medical problems did the patients have?

When new drugs are being studied, researchers keep track of all of the medical problems that patients develop during the study. These medical problems are called "adverse events". This section tells you about the adverse events that happened during the treatment period. These adverse events may or may not be caused by the study treatments. An adverse event is considered serious when it is life-threatening, leads to hospitalization, or causes lasting problems.

During the treatment period, the patients received either pertuzumab or the placebo, but all the patients also received chemotherapy and trastuzumab. The treatment period includes all of the time a patient was receiving study treatment up until 28 days after the final dose of study treatment. It is possible that some of the adverse events were caused by chemotherapy and/or trastuzumab.

How many patients had adverse events?

During the treatment period:

- Most of the patients had at least 1 adverse event. Adverse events happened about as often in patients receiving pertuzumab as patients receiving the placebo.
- Some of the adverse events were serious, but most were not. Serious adverse events happened more often in patients receiving pertuzumab.
- Some patients had adverse events that the doctors thought were related to either trastuzumab or pertuzumab. These happened more often in patients receiving pertuzumab.
- Some patients stopped taking study treatments due to adverse events. This happened more often in patients receiving pertuzumab.

The table below shows how many patients had adverse events.

Adverse events in the treatment period

	Pertuzumab added to chemotherapy and trastuzumab (Out of 2,364 patients)	Placebo added to chemotherapy and trastuzumab (Out of 2,405 patients)
Had at least 1 adverse event	99.9% (2,361)	99.5% (2,393)
Had at least 1 serious adverse event	29.3% (692)	24.3% (585)
Had an adverse event related to trastuzumab, pertuzumab, or the placebo	65.1% (1,538)	56.9% (1,369)
Stopped taking any of the study treatments because of an adverse event	13.1% (309)	11.5% (277)

What were the most common serious adverse events?

The most common serious adverse event during the treatment period was having a fever with abnormally low levels of a type of white blood cell called neutrophils. This happened about as often in patients receiving pertuzumab as in patients receiving the placebo. Diarrhea and heart failure happened more often in patients receiving pertuzumab.

Some patients died due to serious adverse events:

- 0.4% of patients receiving pertuzumab died due to a serious adverse event (10 of 2,364 patients)
- 0.6% of patients receiving the placebo died due to a serious adverse event (14 of 2,405 patients)

The table below shows the serious adverse events that happened in at least 1% of patients receiving either pertuzumab or the placebo. There were other serious adverse events, but fewer patients had them.

Serious adverse events in the treatment period

	Pertuzumab added to chemotherapy and trastuzumab (Out of 2,364 patients)	Placebo added to chemotherapy and trastuzumab (Out of 2,405 patients)
Fever with abnormally low levels of a type of a white blood cell called neutrophils	8.8% (208)	8.1% (196)
Diarrhea	2.5% (58)	0.7% (18)
Fever	1.6% (39)	1.9% (45)
Heart failure	1.4% (33)	0.7% (17)
Abnormally low levels of neutrophils	1.1% (26)	1.3% (32)
Pneumonia	0.7% (16)	1.0% (23)

What were the most common adverse events?

The most common adverse events during the treatment period were diarrhea and nausea. Diarrhea happened more often in patients receiving pertuzumab. Nausea happened about as often in patients receiving pertuzumab as the patients receiving placebo.

The table on the next page shows the most common adverse events. These events happened to at least 30% of patients receiving either pertuzumab or the placebo. There were other adverse events, but fewer patients had them.

Most common adverse events in the treatment period		
	Pertuzumab added to chemotherapy and trastuzumab (Out of 2,364 patients)	**Placebo added to chemotherapy and trastuzumab (Out of 2,405 patients)**
Diarrhea	71.2% (1,683)	45.2% (1,086)
Nausea	69.0% (1,632)	65.5% (1,575)
A hair loss condition called Alopecia	66.7% (1,577)	66.9% (1,610)
Tiredness	48.8% (1,154)	44.3% (1,065)
Vomiting	32.5% (768)	30.5% (733)

How many patients in this study had medical problems related to the heart?

It is known that treatment containing trastuzumab and pertuzumab may affect the heart. Researchers wanted to learn if patients who received pertuzumab together with trastuzumab and chemotherapy were more likely to have heart problems.

In this study, severe heart failure or death because of a heart problem happened in:

- 0.7% of patients receiving pertuzumab (17 of 2,364 patients)
- 0.3% of patients receiving the placebo (8 of 2,405 patients)

Researchers also wanted to learn how many patients had a drop in how much blood their heart was pumping out with each beat at any time in this study. This may have happened with no symptoms or with mild symptoms present. This happened in:

- 2.7% of patients receiving pertuzumab (64 of 2,364 patients)
- 2.8% of patients receiving the placebo (67 of 2,405 patients)

What's happened since you joined the study?

The APHINITY study you are involved in started in November 2011 and will last up to about 12 years from that date. You might have joined any time between November 2011 and August 2013. There were 4,804 patients included in the study. The study is taking place at nearly 600 study clinics in 42 countries around the world.

This study is taking place in:

- 13 countries in Western Europe
- 10 countries in Central and Eastern Europe, Middle East, Africa, and Indian Subcontinent region
- 9 countries in the Asia Pacific Region
- 8 countries in Latin America
- 2 countries in North America

This study had 2 parts:

- Part 1 was the treatment period and lasted about 1 year for each patient.
- Part 2 is the follow-up period, which is still going on. Researchers are collecting information until 2023.

The sponsor and the study partners BIG, FSS, and BrEAST reviewed all the information collected until December 2016 in Parts 1 and 2 and reported the results.

What happened during the study?

Before the study began, you had surgery to remove your cancer. The study doctors took a sample of your cancer tissue to make sure you had HER2-positive breast cancer. Then they did tests to check your heart and overall health. They also took blood samples.

Part 1 started within 8 weeks of your surgery:

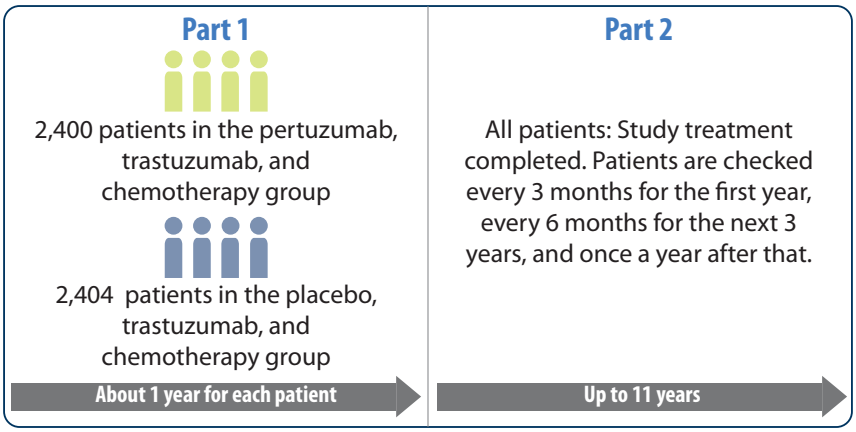
- You received chemotherapy and trastuzumab with either pertuzumab or a placebo every 3 weeks. You received trastuzumab with either pertuzumab or a placebo for up to 1 year.
- You may have received what is called “hormonal therapy” if your tumor was a “hormone receptor positive” tumor. This would have been started once you had completed your chemotherapy. You may have also received radiotherapy. Your study doctor would have recommended this for you, and it would have been started once you had completed chemotherapy.

Part 2 started about 1 month after your last treatment when you had a follow-up visit at the study clinic. The study doctors checked your heart and overall health. They also checked if your cancer had come back and asked if you were taking any medicines to treat it.

There are more follow-up visits at the study clinic after you stop getting treatment. Study doctors are continuing to see how you are doing since treatment ended. Follow-up visits should still be happening:

- Every 3 months during the first year
- Every 6 months during the next 3 years
- Once a year after that

The chart below shows what happened during each part of the study.



How has this study helped patients and researchers?

The APHINITY study is still going on. The researchers are still collecting information from all the participants that are in the study. If you are still in the study, continued study visits will give researchers more results and help them learn important information about the study treatments.

Doctors and researchers look at results of many studies to decide which drugs work best and are safest for patients. The results presented here are for a single large study. Further studies may provide new information.

Where can you learn more about this study?

You can find more information about the APHINITY study online at:

- https://clinicaltrials.gov/ct2/show/NCT01358877
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2010-022902-41

If you have questions about the results, please speak with the doctor, research nurse, or another team member at your study center.

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

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Thank you

Clinical trial participants belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.

Thank you for the gift of your participation in clinical research.