Clinical Trial RESULTS

Roche

Research Sponsor: F. Hoffmann-La Roche, Ltd., and Genentech, Inc.

Drug Studied: Trastuzumab emtansine (T-DM1)

National Clinical Trial #: NCT01120184

Protocol #: BO22589/TDM4788g

Results from Study Dates: July 2010 to September 2014

Full Title of Your Study: A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer (MARIANNE)

Thank you!

Thank you for taking part in the global clinical study for the study drugs trastuzumab emtansine and pertuzumab. In the United States, trastuzumab emtansine is called ado-trastuzumab emtansine. Researchers studied these treatments for use in patients with breast cancer that came back after being treated or that spread to other parts of the body before treatment. You and the other patients helped researchers compare the effects of trastuzumab emtansine and pertuzumab to another combination of breast cancer drugs. The combination used is trastuzumab with a chemotherapy drug called a taxane.

Your study is still ongoing. F. Hoffmann-La Roche and Genentech, Inc., the sponsors of this study, think it is important for you to know the main results. The sponsors asked an independent non-profit organization called CISCRP to help prepare this summary for you. We hope it helps you understand the results and makes you feel proud of your key role in medical research. If you have questions about these results, please speak with your doctor, research nurse, or other team member at your study center.

WHAT'S HAPPENED SINCE I JOINED THE STUDY?

Your study began in July 2010. This summary tells you the results up to September 2014. Study doctors are still collecting information and some of the patients are still taking the study treatment.

Patients from 38 countries around the world were in your study. A total of 1,095 patients were enrolled in the study, and 1,080 patients at 241 study centers received at least 1 dose of a study drug. The sponsor presented the main results from this study at the American Society for Clinical Oncology conference in June 2015. This is one of the largest and most important conferences in the oncology community. This is a summary of those results.

WHY WAS THE RESEARCH NEEDED?

Researchers were looking for a different way to treat HER2-positive metastatic breast cancer. Metastatic means the cancer has spread to parts of the body other than the breast and surrounding lymph nodes. HER2-positive breast cancer has more of a protein called "human epidermal growth factor receptor 2", or HER2, than healthy breast tissue.

Researchers know that a drug called trastuzumab blocks the HER2 protein. In many countries, trastuzumab combined with another therapy is the standard treatment for metastatic HER2-positive breast cancer. For example, doctors might give trastuzumab with chemotherapy or hormone therapy. In the study, trastuzumab was given with a chemotherapy drug for breast cancer called a taxane.

In your study, researchers wanted to learn:

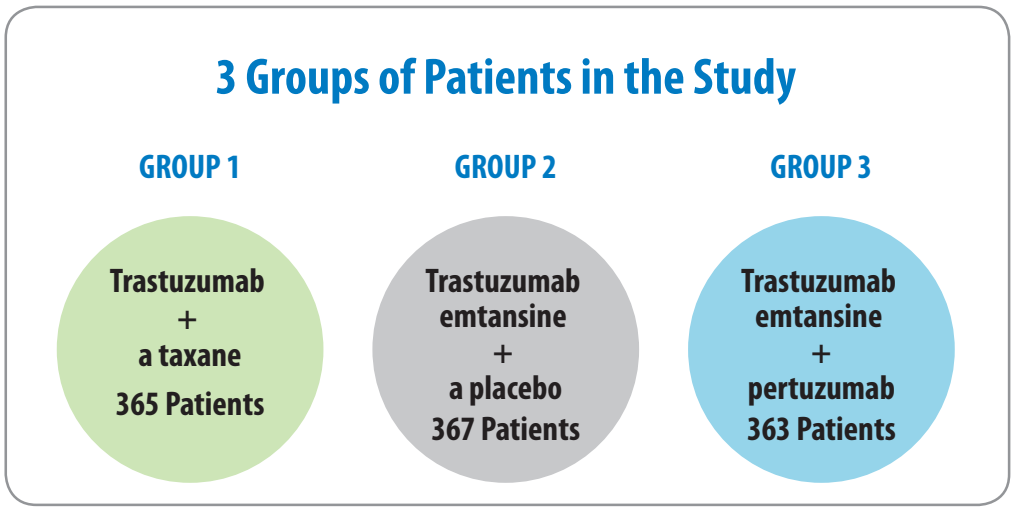
- How long did trastuzumab emtansine prevent breast cancer from getting worse compared to trastuzumab combined with a taxane?
- Did adding pertuzumab to trastuzumab emtansine prevent breast cancer from getting worse for a longer time than trastuzumab emtansine alone?
- Did patients taking trastuzumab emtansine, with or without pertuzumab, maintain their quality of life longer than patients taking trastuzumab combined with a taxane?
- Did patients taking trastuzumab emtansine, with or without pertuzumab, live longer? Researchers compared this treatment to trastuzumab combined with a taxane.
- What adverse events did patients have? An adverse event is a medical problem that may or may not be caused by the study drug.

WHAT KIND OF STUDY WAS THIS?

Patients in your study received 1 of the following treatment options. The treatments were assigned randomly:

- Trastuzumab with a taxane
- The study drug trastuzumab emtansine and a placebo
- Trastuzumab emtansine with another study drug called pertuzumab.

Patients were put into 3 groups.



Group 1, open label

Group 1, trastuzumab and a taxane, was "open label". This means patients, doctors, and study staff knew what drugs patients were taking. There are different taxanes that can be given to treat breast cancer. In your study, the taxanes that could be given were either docetaxel or paclitaxel. You and your doctor decided which taxane you would take with trastuzumab.

Group 2 and Group 3, blinded

Groups 2 and 3 were "blinded". This means patients in these groups all took trastuzumab emtansine but they did not know if they were also taking pertuzumab or a placebo. Doctors and study staff did not know either. If you were in Group 2, you took trastuzumab emtansine and a placebo. A placebo looks like a real drug, but does not contain any medicine. Researchers use a placebo to learn if the study medicine works better than no medicine at all. If you were in Group 3, you took trastuzumab emtansine and the other study drug, pertuzumab.

WHAT HAPPENED DURING THE STUDY?

Patients in all 3 groups received the drugs by IV (into a vein). You and other patients could have treatment until the cancer got worse or until you or the study staff decided to stop the treatment.

During the study, your doctors and nurses regularly checked your health and ability to do daily activities. You answered questions about how you were feeling, had physical examinations, and had blood, urine, and pregnancy tests. You also had heart tests and CT or MRI scans to check your tumors and learn if cancer got worse. The study doctors and nurses also kept track of all adverse events that you and other patients had.

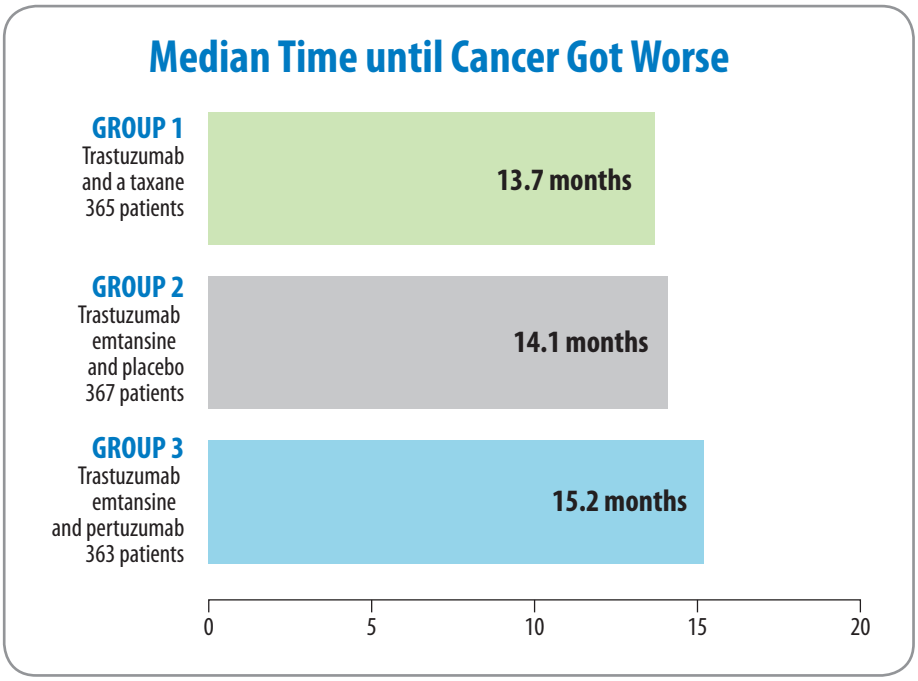
WHAT WERE THE STUDY RESULTS?

This section is a summary of the main medical questions that were asked in this study and the results so far.

How long did trastuzumab emtansine prevent breast cancer from getting worse compared to trastuzumab with a taxane?

The study doctors wanted to learn if trastuzumab emtansine treatment worked as well or better than a taxane and trastuzumab to prevent breast cancer from getting worse. They wanted to learn if it worked as well either alone or with pertuzumab. They found that trastuzumab emtansine with or without pertuzumab was not less effective than trastuzumab and a taxane at preventing cancer from getting worse over time. But it also was not substantially better. Breast cancer was considered to be "getting worse" if the tumor grew or spread during the study. Doctors did CT scans to check this.

The graph below shows the median time in each group until breast cancer got worse. Median means halfway between the shortest and the longest time.



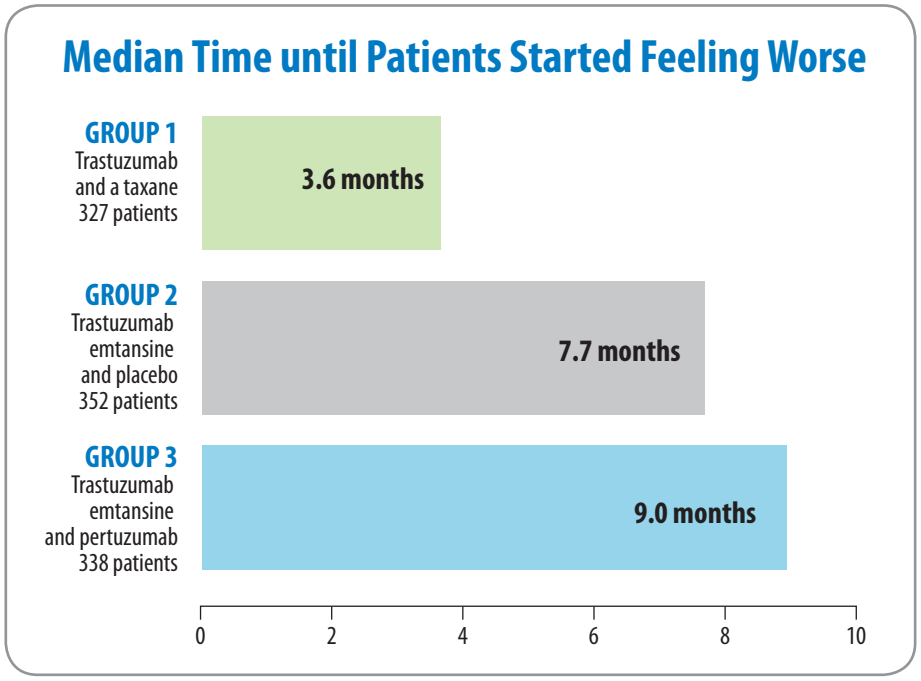
The median time until cancer got worse was about the same for each group. Some patients got worse sooner or later than this time. Patients in Group 1, trastuzumab and a taxane, had a median of 13.7 months until cancer got worse. Patients in Group 2, trastuzumab emtansine and a placebo, had a median of 14.1 months. Patients in Group 3, trastuzumab emtansine and pertuzumab, had a median of 15.2 months before cancer got worse.

Did adding pertuzumab to trastuzumab emtansine prevent breast cancer from getting worse for a longer time than trastuzumab emtansine alone?

The graph above shows that adding pertuzumab to trastuzumab emtansine (Group 3) did not substantially increase the median time until cancer got worse as compared to trastuzumab treatment without addition of pertuzumab (Group 1 and Group 2).

Did patients taking trastuzumab emtansine, with or without pertuzumab, maintain their quality of life longer than patients taking trastuzumab and a taxane?

Yes. Patients taking trastuzumab emtansine, with or without pertuzumab, felt better for a longer time than patients taking trastuzumab and a taxane. The graph below shows the median time from the start of the study until patients started feeling worse.



Did patients taking trastuzumab emtansine, with or without pertuzumab, live longer?

Researchers compared this treatment to trastuzumab combined with a taxane. Researchers do not know yet, because not enough time has passed. They need more information and are collecting it now.

WHAT ADVERSE EVENTS DID PATIENTS HAVE?

A lot of research is needed to know whether a drug causes a medical problem. So when new drugs are being studied, study doctors keep track of all medical problems that patients have. These medical problems are called "adverse events", and may or may not be caused by the study drug. This section tells you about the adverse events that happened in your study.

How many patients had adverse events?

Most patients had at least 1 adverse event. Some patients in each group stopped taking the study drugs because of an adverse event. More patients in Group 1, trastuzumab and a taxane, stopped taking study drugs due to an adverse event than in the other groups. The table below shows how many patients in each group had adverse events. It also shows how many stopped taking study drugs because of them.

Adverse Events in Each Group	Group 1 Trastuzumab and a taxane 353 Patients	Group 2 Trastuzumab emtansine and placebo 361 Patients	Group 3 Trastuzumab emtansine and pertuzumab 366 Patients
Had at least 1 adverse event	98.6%	98.9%	98.6%
Stopped taking study drugs because of an adverse event	29.7%	18.3%	19.1%

What adverse events did patients have?

The tables on the next page show the adverse events that happened in more than 2 out of every 10 patients (20%) in at least 1 group. The study doctors also wanted to learn which adverse events happened in each group and which happened more often.

This table shows adverse events that happened more often to patients taking trastuzumab and a taxane (at least 20% of patients).

Adverse Events that Happened More Often in Group Taking Trastuzumab and a Taxane	Group 1 Trastuzumab and a taxane 353 Patients	Group 2 Trastuzumab emtansine and placebo 361 Patients	Group 3 Trastuzumab emtansine and pertuzumab 366 Patients
Hair loss (Alopecia)	59.8%	6.6%	9.0%
Diarrhea	48.7%	25.2%	48.1%
Tingling, numbness, or pain in hands or feet	28.0%	13.3%	17.8%
Swelling in hands or feet	27.8%	9.4%	8.5%
Low white blood cell count	22.7%	11.4%	8.7%

Group 1 patients had more severe or life-threatening adverse events such as neutropenia (low white blood cell count) (19.8%), febrile neutropenia (low white blood cell count with fever) (6.5%), and diarrhea (4.2%) as compared to patients in the other 2 groups.

The table below shows adverse events that happened more often to patients taking trastuzumab emtansine, whether they also took a placebo (Group 2) or pertuzumab (Group 3).

Adverse Events that Happened More Often in Groups Taking Trastuzumab Emtansine	Group 1 Trastuzumab and a taxane 353 Patients	Group 2 Trastuzumab emtansine and placebo 361 Patients	Group 3 Trastuzumab emtansine and pertuzumab 366 Patients
Nausea	37.1%	47.1%	52.2%
Headache	22.1%	32.1%	32.2%
Nosebleed	14.7%	31.0%	34.7%
Fever	16.4%	27.7%	32.2%
Vomiting	19.0%	21.6%	30.1%
Chills	4.0%	15.5%	26.8%

Patients in Group 2 and Group 3 had more severe or life-threatening adverse events compared to patients in Group 1. These events included high blood pressure (4.4% for Group 2, 4.9% for Group 3), low red blood cell count (4.7% in Group 2, 6.0% in Group 3), liver enzyme problems (ALT enzymes, 4.4% in Group 2, 6.6% in Group 3, and AST enzymes 6.6% in Group 2 and 3.0% in Group 3) and lower platelet count (6.4% in Group 2, 7.9% in Group 3).

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

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

Researchers look at the results of many studies to decide which drugs work best and are safest for patients. It takes patients in many studies all around the world to advance medical science.

Address and telephone number for the sponsor of this trial:

F. Hoffmann-La Roche
Grenzacherstrasse 124 CH-4070 Basel,
Switzerland
+41-61-688-1111

Thank you

It is said that the greatest gift is one which is given anonymously, giving when you do not know whether you will get direct personal benefit.

This is the gift that you have given by taking part in a clinical trial. It is a brave and selfless act, one that advances medical knowledge and benefits public health. Thank you for the gift of your participation in clinical research.

CISCRP
THE CENTER FOR INFORMATION & STUDY ON CLINICAL RESEARCH PARTICIPATION

The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting patients for clinical trials, nor is it involved in conducting clinical trials.