Clinical Trial Results – Layperson Summary

A study to compare "ipatasertib + chemotherapy" with "placebo + chemotherapy" – in patients with inoperable or metastatic triple negative 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 a clinical trial called a "study" in this document. This summary is written for:

- members of the public
- **participants** – these are patients with breast cancer who took part in the study

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

The study started in August 2014 and finished in July 2019. This summary was written after the study had ended.

No single study can tell us everything about the risks and benefits of a medicine. Information from many studies is often needed to answer such questions. 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

Thank you to the people who took part in this study

The patients who took part have helped researchers to answer important questions about breast cancer and the study medicine.

Key information about this study

- In this study, all patients with triple-negative breast cancer were prescribed the same chemotherapy.
- In addition to chemotherapy, half of the patients were prescribed an experimental medicine (ipatasertib), and the other half - pills that had no medicine (placebo).
- This study was done to find out if adding ipatasertib to chemotherapy was better than when no medicine (placebo) was combined with chemotherapy.
- This study included 124 patients in 8 countries.
- This study found that ipatasertib + chemotherapy was better than placebo + chemotherapy.
- There were more side effects in patients who got ipatasertib than in patients who got the placebo.
- This report was written after the study was completed.

1. General information about this study

Why was this study done?

Triple-negative breast cancer (TNBC) affects 15-20% of all patients with breast cancer. A biopsy sample will show certain features of the tumor tissue:

- The absence of estrogen hormone receptors.
- The absence of progesterone hormone receptors.
- The absence of human epidermal grown factor 2.

Patients who are diagnosed with metastatic disease (cancer that has spread to other parts of the body) have a shortened life-span, with approximately 15 of 100 patients (15%) surviving 5 years from diagnosis.

There is a need for new medicines that can improve the life-span of patients with TNBC.

Researchers wanted to know what would be the effects – good, bad, or none – when a new cancer medicine was given to patients with TNBC in combination with chemotherapy.

What was the study medicine?

Ipatasertib, also known as GDC-0068, is a medicine that has been given to people in other studies and found to be safe for humans. Here is how the medicine works:

- **The Akt pathway** is one of several pathways inside the human cell to promote cell growth and survival.
- When patients receive chemotherapy to kill cancer cells, sometimes the cancer cells can mutate (change) and increase the activity of the Akt pathway.
- This means chemotherapy would not be able to kill cancer cells that have increased Akt pathway activity and are better able to grow and survive.
- Ipatasertib inhibits the Akt pathway, causing the death of cancer cells.

Ipatasertib was compared to a "**placebo**".

- In this study, some patients got ipatasertib while others got a placebo.
- The placebo looked the same as ipatasertib but did not contain any real medicine.

What did researchers want to find out?

Researchers did this study to compare the study medicine against the placebo.

The main question that researchers wanted to answer were:

1. Does adding ipatasertib to chemotherapy improve the outcome for patients with TNBC?

Other questions that researchers wanted to answer were:

2. What effect does ipatasertib have on patients with TNBC with certain genetic mutations (PTEN-low tumors)?
3. What effect does ipatasertib have on patients with TNBC with certain genetic mutations (PI3K/Akt pathway activated tumors)?
4. Is ipatasertib safe and could patients tolerate the side effects when combined with chemotherapy?

What kind of study was this?

There are several ways to describe this study.

- **Phase 2 study**
  Phase 2 studies are carried out to find out if a study medicine is effective for patients.
- **Placebo-controlled study**
  Some people got ipatasertib while others got a placebo. This was done so that all patients got a treatment, and the real effect of the medicine could be compared against the placebo.
- **Randomized study**
  A computer randomly decided which patient joined the medicine group and which patient joined the placebo group. Researchers and patients had no control over this.
- **Double-blind study**
  The researchers and patients did not know which patient was getting the study medicine and which patient was getting the placebo. That made this a double-blind study.
- **Combination treatment study**
  Patients got ipatasertib or placebo in combination with chemotherapy.

When and where did the study take place?

The study started in August 2014 and finished in July 2019. The study took place in:

- Belgium
- France
- Italy
- Singapore
- South Korea
- Spain
- Taiwan
- United States

This summary was written after the study had ended.

2. Who took part in this study?

Patients who had TNBC that was confirmed by a tumor biopsy test could take part in this study if:

- Their tumors could not be operated on.
- They had cancer that was advanced while in its original site, or if it had spread to other parts (metastasized).

There were 124 patients with TNBC who participated in this study. A total of 122 patients received study treatment and 2 enrolled but did not receive any treatment in the study.

All patients were female (100%). Most of the patients were Asian (47%) or White (44%). The average age of patients was 54 years. The youngest patient was 26 years old. The oldest patient was 81 years old.

There were 2 treatment groups:

Placebo + Chemotherapy	Ipatasertib + Chemotherapy
Total = 62 patients Average age = 53 years Asian: 48%; White: 44%	Total = 62 patients Average age = 54 years Asian:45%; White:42%

What was required in order for patients to participate in this study

1. Provide written consent to volunteer in this study.
2. Be at least 18 years old.
3. Agree to undergo a tumor biopsy before starting treatment.
4. Take a blood test within 2 weeks before starting, and results must indicate patients are otherwise healthy.
5. Agree to use family planning methods to prevent pregnancies while on study.

What conditions disqualified patients from participating in this study

1. Patients who received certain cancer treatments at any time.
2. Patients who received certain treatments following diagnosis of locally advanced tumor or metastasized tumor could not take part in this study.
3. Patients who did not meet general health criteria for enrolling in this study.

3. What happened during the study?

The "**treatment**" was either the study medicine or the placebo in combination with chemotherapy. Patients did not know if they were getting ipatasertib or placebo.

How and when were treatments administered?

Patients joined the study and started their treatments at different times.

It took 4 weeks (Day 1–28) to get 1 cycle of treatment:

- Starting on Day 1, each patient got chemotherapy intravenously (by IV) once a week for a total of 3 treatments in one cycle (Days 1, 8, 15). Patients showed up at the clinic for chemotherapy (paclitaxel 80 mg/m^2).
- Starting on Day 1, each patient took one pill a day, by mouth (oral), for 3 weeks (Days 1–21). The pill was either ipatasertib (400 mg) or placebo. Patients could take their pills at home.
- Patients did not receive any treatment during the last week in each cycle.

Each cycle of treatment was repeated until patients stopped the treatment.

What happened after treatment started?

Patients could stop the treatment for any of the following reasons:

- Their disease became worse.
- They could not tolerate the side effects of the treatment.
- They chose to withdraw from the study.
- The study came to an end or was completed.

Patients were examined and got medical tests throughout the study. They were treated for side effects when it was needed.

When patients stopped their treatment, they were followed until they decided to stop participating in the study, they passed away, or were lost to the follow-up process – such as a patients who moved to another address.

4. What were the results of the study?

While patients did not know if they were getting ipatasertib or the placebo, they could stop the treatment at any time for any reason.

Therefore, the length of time that patients were treated for varied. Here are the time comparisons for the two treatment groups:

Placebo + Chemotherapy	Ipatasertib + Chemotherapy
Half of this group continued their treatment for **3.5 months** (median)	Half of this group continued their treatment for **5.3 months** (median)
Longest time on treatment for any patient: 27 months	Longest time on treatment for any patient: 43 months

Question 1: Does adding ipatasertib to chemotherapy improve the outcome for patients with TNBC?

Researchers measured the time from starting treatment until the patient's breast cancer became worse. This is known as **progression-free survival (PFS)**.

PFS tells you how long the patient is able to live without the disease becoming worse or the patient dying, since starting the treatment. It is an average number, calculated from results from the entire group.

Placebo + Chemotherapy	**Ipatasertib + Chemotherapy**
All patients: **PFS = 4.9 months**	All patients: **PFS = 6.2 months**

Patients who got ipatasertib + chemotherapy had a longer PFS than those who got placebo + chemotherapy.

Question 2: What effect does ipatasertib have on patients with TNBC with a certain genetic mutation (PTEN-low tumors)?

Placebo + Chemotherapy	**Ipatasertib + Chemotherapy**
Patients with PTEN-low tumors: **PFS = 3.6 months**	Patients with PTEN-low tumors: **PFS = 6.2 months**

This analysis only included patients who had a certain mutation (PTEN-low tumors). Patients who got ipatasertib + chemotherapy had a longer PFS than those who got placebo + chemotherapy.

Question 3: What effect does ipatasertib have on patients with TNBC with a certain genetic mutation (PI3K/Akt pathway activated tumors)?

Placebo + Chemotherapy	**Ipatasertib + Chemotherapy**
Patients with PI3K/Akt pathway activated tumors: **PFS = 4.9 months**	Patients with PI3K/Akt pathway activated tumors: **PFS = 9.0 months**

This analysis only included patients whose tumors had a certain mutation (PI3K/Akt pathway activated tumors). Patients who got ipatasertib + chemotherapy had a longer PFS than those who got placebo + chemotherapy.

Question 4: Is ipatasertib safe and could patients tolerate the side effects when combined with chemotherapy?

Overall, researchers thought ipatasertib was safe and could be tolerated.

5. What were the side effects?

Side effects are unwanted medical problems (such as a headache) that happen during the study and are related to the treatment given during the study.

- Not every patient in a study has all or any of the side effects seen in the study.
- Common side effects and serious side effects are listed in the following sections.

Most common side effects

The most common side effects are listed here – seen in 10% or more patients in either group. Side effects are any symptoms thought to be related to any of the study treatments.

Side effects	Placebo + chemotherapy group	Ipatasertib + chemotherapy group
Diarrhea	10 patients (16%)	56 patients (92%)
Hair loss (alopecia)	29 patients (47%)	33 patients (54%)
Feeling sick to stomach (nausea)	17 patients (27%)	29 patients (48%)
Feeling tired (fatigue)	19 patients (31%)	16 patients (26%)
Tingling and sensitive feeling in body parts (peripheral sensory neuropathy)	10 patients (16%)	16 patients (26%)
Feeling weak (asthenia)	6 patients (10%)	14 patients (23%)
Rash	11 patients (18%)	14 patients (23%)
Low white blood cell count (neutropenia)	14 patients (23%)	13 patients (21%)
Muscle pain (myalgia)	13 patients (21%)	13 patients (21%)
Vomiting	10 patients (16%)	12 patients (20%)
Inflammation of the mucous membrane of the mouth (stomatitis)	5 patients (8%)	11 patients (18%)
Nerve pain in body parts (neuropathy peripheral)	14 patients (23%)	11 patients (18%)
Not hungry (decreased appetite)	10 patients (16%)	11 patients (18%)
Low white blood cell count (neutrophil count decreased)	9 patients (15%)	9 patients (15%)
Pimple-like bumps in large areas of the body (dermatitis acneiform)	5 patients (8%)	9 patients (15%)
Strong itch of the skin (pruritus)	3 patients (5%)	9 patients (15%)
Dizziness	6 patients (10%)	8 patients (13%)
Stomach (abdominal) pain	4 patients (7%)	8 patients (13%)
Constipation	3 patients (5%)	6 patients (10%)
Low red blood cell count (anemia)	7 patients (11%)	6 patients (10%)
Numbness or a burning feeling in body parts (paresthesia)	7 patients (11%)	5 patients (8%)
Indigestion (dyspepsia)	6 patients (10%)	4 patients (7%)

Serious side effects

A side effect is considered “serious” if it is life threatening, needs hospital care, or causes lasting problems.

All serious side effects are listed here. Serious side effects are any serious symptoms thought to be related to any of the study treatments.

Serious side effects	Placebo + chemotherapy group	Ipatasertib + chemotherapy group
Diarrhea	0	3 patients (5%)
Pneumonia	0	2 patients (3%)
Fever with low white blood cell count (febrile neutropenia)	0	2 patients (3%)
A type of pneumonia that is less severe (atypical pneumonia)	0	1 patient (2%)
Blockage in a major blood vessel (embolism)	0	1 patient (2%)
Feeling sick to the stomach (nausea)	0	1 patient (2%)
Fever (pyrexia)	0	1 patient (2%)
White blood cell (neutrophil) decreased	0	1 patient (2%)
Altered liver function (cholestasis)	1 patient (2%)	0
Cell death	1 patient (2%)	0
Decrease in red cells, white cells, and platelets in blood (pancytopenia)	1 patient (2%)	0
Inflammation of the urinary bladder (cystitis)	1 patient (2%)	0

Deaths

At the end of the study, 87 patients (70%) had died. This included 46 patients (74%) in the placebo + chemotherapy group, and 41 patients (66%) in the ipatasertib + chemotherapy group. The most common cause of death was progression of disease, which accounted for 38 patients (61%) in the placebo + chemotherapy group and 39 patients (63%) in the ipatasertib + chemotherapy group.

6. How has this study helped research?

This study investigated the effect of adding an experimental medicine (ipatasertib) to chemotherapy for treatment of patients with TNBC that cannot be treated with surgery, or that has spread to other parts of the body.

Researchers found out that adding ipatasertib to chemotherapy improved PFS for patients, in comparison to adding placebo to chemotherapy.

Researchers also learned that the side effects from the study medicine could be tolerated by patients.

Overall, researchers gathered enough evidence to support continuing further with other investigations of the study medicine for cancer patients. The results of this phase 2 study led to a phase 3 study of this same treatment combination for patients with TNBC.

7. Are there plans for other studies?

There are several studies for ipatasertib.
They can be found here:

https://clinicaltrials.gov/ct2/results?cond=&term=ipatasertib&cntry=&state=&city=&dist=

8. Where can I find more information?

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

- World Health Organization clinical trials registry:
  http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02162719
- USA clinical trials registry:
  https://clinicaltrials.gov/ct2/show/NCT02162719
- EU clinical trials registry:
  https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000469-35

If you would like to find out more about the results of this study:

- The full title of the relevant scientific paper is:
  “Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial”.
- The authors of the scientific paper are:
  Sung-Bae Kim, Rebecca Dent, Seock-Ah Im, Marc Espié, Sibel Blau, and others.
- The paper is published in the journal:
  Lancet, volume number 18, on pages 1360-1372.

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/About.html
  or 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.

Who organized and paid for this study?

This study was organized and paid for by Genentech, Inc., South San Francisco, CA, USA. Genentech is part of F. Hoffmann-La Roche Ltd., with headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is:
"Randomized, Phase II, Multicenter, Placebo-Controlled Study of Ipatasertib (GDC-0068), an Inhibitor of Akt, in Combination with Paclitaxel as Front-Line Treatment for Patients with Metastatic Triple-Negative Breast Cancer".

- The protocol number for this study is **GO29227**.
- This study is known by a short name, which is "**LOTUS**".
- The ClinicalTrials.gov identifier for this study is **NCT02162719**.
- The EudraCT number for this study is **2014-000469-35**.