Clinical Trial Results – Layperson Summary

A study to look at how safe different doses of atezolizumab were for patients – and how this medicine was processed through the body

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; we will refer to the clinical trial as a "study" in this document.

This summary is written for:

- members of the public
- patients who took part in the study

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

The study started in June 2011 and finished in September 2018. This summary was written after the study had ended.

No single study can tell us everything about the risks and benefits of a medicine. Many patients volunteer in several studies to help us find out everything we need to know. The results from this one study may be different from other studies with the same medicine.

- 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 gather information about the study medicine and also answer important questions about cancers in different parts of the body.

Key information about this study

This study was done to find out what the safe dose was for a new medicine for cancer.

- In this study, patients got a new medicine called atezolizumab – different patients got different amounts of the medicine.
- Researchers wanted to know what dose or how much of the medicine was safe for patients to get into their bodies through IV.
- Researchers also wanted to know what happened to the medicine in the body and whether the medicine had any effect on the cancer.
- This study included 660 patients in 4 countries.
- The main discovery was that this medicine (atezolizumab) was safe for patients at all the different doses tested.
- Around 46% of patients (46 of every 100 people) taking atezolizumab had serious side effects.
- The researchers looked at all the doses and picked a single dose that they thought would be useful to study in future studies.

1. General information about this study

Why was this study done?

There are several different kinds of blood cells that together make up the immune system. The purpose of the immune system in the human body is to fight off diseases. Some blood cells have the job of setting off an alarm when they sense the presence of something that isn't normal. Other blood cells respond to the alarm and start the process of defending the body.

There are different proteins that can be released by certain blood cells to communicate to other blood cells. We can refer to the cells that release the proteins as "signaling cells". Then, the released proteins are detected by another type of blood cells – let's call these the "responder cells".

Signaling cells can talk to the responder cells by using specific types of proteins. The type of protein that is released by the signaling cells directs what the response will be in the responder cells. In this manner, signaling cells can affect how responder cells behave in the immune system.

Let's talk about one group of cells in particular, called "**T cells**". T cells are a type of blood cells that can release signaling molecules to communicate with other cells. They can also respond to signals. One way that T cells respond is as follows:

- **PD-L1** is a signaling protein that can be detected by T cells.
- **PD-1** is a structure on T cells used for detecting PD-L1.

When PD-L1 signaling protein is bound to the PD-1 docking structure on T cells, this is what happens:

- T cells cannot multiply to make more T cells.
- T cells cannot make other signaling proteins to communicate with cells in the immune system.
- T cells cannot kill disease-causing cells, such as cancer cells.

PD-L1 basically tells T cells to shut down. This is important because your immune system needs to turn itself off after it has fought off infections and other diseases.

Unfortunately, cancer cells can produce PD-L1 and trick the immune system. PD-L1 produced by cancer cells binds to the PD-1 docking structure on T cells. In this way, cancer cells can prevent T cells from multiplying, communicating with other immune cells, and killing the cancer cells. By using the same signaling proteins as those in the immune system, cancer cells can tell the cancer-fighting blood cells to leave the cancer cells alone.

Because scientists have found PD-L1 in many different kinds of cancers, PD-L1 can be a good target for designing a medicine to fight different kinds of cancer. If a medicine could block the PD-L1 proteins made by cancer cells from binding to the PD-1 docking structure on T cells, then T cells could still kill the cancer cells.

This study was done to test whether a drug that blocks the interaction between PD-L1 and PD-1 can be a useful cancer medicine.

What was the study medicine?

Atezolizumab is a new medicine designed to work on the immune system, and this type of medicine is known as an **immunotherapy**. There are different kinds of immunotherapies and atezolizumab is an **antibody immunotherapy**.

- Antibodies are proteins that only bind to one target. Atezolizumab was designed to only bind to PD-L1.
- By binding to PD-L1 produced by cancer cells in the human body, atezolizumab could prevent the interaction between PD-L1 from cancer cells and PD-1 on T cells.
- If PD-1 on T cells remained unoccupied, then the T cells would actively fight the cancer cells and not be tricked into becoming unresponsive.

What did researchers want to find out?

- Researchers did this study to compare different doses of the new medicine that was given to patients once every 3 weeks by IV infusion into their blood veins.
- Researchers wanted to find out how many people had side effects at each dose after getting the medicine during this study.

The main questions that researchers wanted to answer were:

1. What doses of atezolizumab could be considered safe for patients?
2. What was the largest dose of atezolizumab that could be tolerated?
3. Were there any side effects that limited how much medicine a patient should get?
4. Based on the results of this study, what dose of atezolizumab do researchers recommend should be given to patients in future studies?

Other questions that researchers wanted to answer included:

5. What happened to atezolizumab in the body when patients took this medicine?
6. Does atezolizumab cause any reactions in the immune system?
7. Does atezolizumab have any effect on cancer?

What kind of study was this?

This was a "**Phase 1**" study, which means that this was one of the first studies for atezolizumab. If fact, this was the first time that this medicine was given to patients.

This study was considered "**open label**" because doctors and patients knew what medicine the patients were getting and which dose they were getting.

The study design was called "**dose escalation**", which means that new patients kept getting higher doses of the medicine. The first set of patients were given the lowest dose and observed by the investigators. Following this, new sets of patients were given a slightly higher dose of the medicine but only if the previous sets of patients did not get sick from the medicine. This means that if patients got certain side effects after taking the medicine, then the investigators did not give new patients a higher dose.

During dose escalation, patients got different doses of atezolizumab. Researchers studied results for the different doses and then they decided on a single dose that they thought was useful. Following this, patients were enrolled in the "**dose expansion**" group to study a single dose of atezolizumab. This allowed the researchers to study a particular dose of this medicine in a larger number of patients.

When and where did the study take place?

The study started in June, 2011, and finished in September, 2018. This summary was written after the study had ended.

The study took place at 16 centers in the USA, 3 centers in France, 1 center in Great Britain, and 1 center in Spain.

2. Who took part in this study?

There were **660 patients** who took part in this study. Among them, 658 patients provided results on the safety of the medicine, and 652 patients provided results on whether the medicine was effective for cancer patients.

- The youngest patient was 20 years old while the oldest patient was 89 years old. Most patients (53%) were between 40 to 64 years old.
- The majority of the patients (77%) were white. Just over half of the patients (53%) were men and less than half of the patients (47%) were women.
- Patients with several different kinds of cancers could take part in this study but only if doctors thought that there was no other medicine that could be useful.
- Patients had metastatic cancer – which means that their cancer had spread to other parts of the body. Patients with advanced blood cancers also took part in this study.

Patients could take part in this study if:

- They were over 18 years old.
- They had cancer tissue (biopsy samples) available.
- They were healthy enough for the study, with functioning liver, kidney, and blood system.

Those patients who joined the study later and were in the dose expansion groups had to agree to provide biopsy samples at different times during the study.
Patient could not take part in the study if:

- They had received another type of cancer treatment within the last 3 weeks before the start of this study.
- They had certain blood diseases, brain diseases, or autoimmune diseases.
- Mothers who were nursing or who were pregnant were not allowed to take part in the study.

3. What happened during the study?

Patients joined the study at different times starting in 2011.

- During the study, patients received atezolizumab by IV once every 3 weeks.
- One dose at a time was studied in one group of patients before the next group of patients who joined the study got the next higher dose.
- Those patients who joined the study earlier got smaller doses of the medicine while patients who joined later received higher doses.
- Patients were allowed to get off the study at any time if they chose to do so or if their doctors thought that that was the right decision.
- Patients were taken off the study if their disease got worse.

Study drug dose
Of the 660 patients who enrolled in this study, 658 patients received atezolizumab treatment. Most patients received more than one treatment, and up to 99 treatments per patient were given.

Patients joined one of six groups, with each group receiving a different dose of the study medicine:

Atezolizumab – dose of medicine	Number of patients who got this dose
1 mg/kg	9
3 mg/kg	3
10 mg/kg	36
15 mg/kg	236
20 mg/kg	146
1200 mg total regardless of body weight	228

Time on study
Most patients stayed on the study for just under 3 months while others left early or stayed longer. The longest time on the study was just over 6 years.

What was done on the study
Patients were seen by their doctors on a regular basis. The doctors collected samples from patients for lab analyses and also did tests and spoke with patients to find out how patients were reacting to the medicine. Doctors took note of any side effects due to atezolizumab. If the side effects were minor, doctors gave out treatments for the side effects. Patients were taken off the medicine treatment if side effects were serious.

4. What were the results of the study?

Question 1: What doses of atezolizumab could be considered safe for patients?

Researchers looked at six different doses of atezolizumab. This study showed that all doses were safe for patients and that the side effects could be managed by doctors.

Question 2: What was the largest dose of atezolizumab that could be tolerated?

During dose escalation, the largest dose was 20 mg/kg. Researchers did not go beyond this dose, so they did not find the largest dose that patients should not exceed.

Question 3: Were there any side effects that limited how much medicine a patient should get?

Researchers did not find any side effects that would limit giving atezolizumab to patients at the doses tested.

Question 4: Based on the results of this study, what dose of atezolizumab do researchers recommend should be given to patients in future studies?

Based on results from 1-20 mg/kg tested during dose escalation, researchers decided on a fixed dose of 1200 mg given by IV once every 3 weeks, for future studies. Therefore, patients who joined the study later were assigned to the dose expansion part of the study, and they received atezolizumab at the recommended dose of 1200 mg given by IV once every 3 weeks.

Question 5: What happened to atezolizumab in the body when patients took this medicine?

Patients received their treatment once every 3 weeks. Researchers found that atezolizumab remained in the body throughout the 3-week period.

Question 6: Does atezolizumab cause any reactions in the immune system?

At the start of the study, researchers found that 3% of patients (3 out of every 100 patients) had immune systems that reacted against atezolizumab. These patients had anti-drug antibodies (ADAs) in their immune systems. The ADAs could remove atezolizumab from the body, thereby reducing the effectiveness of this medicine.

After taking the medicine, 28% of patients (28 out of every 100 patients) became positive for ADAs.

However, researchers found that the amount of atezolizumab removed by the ADAs in the immune system was very small. In fact, when patients were given 10 mg/kg and higher doses, the amount removed was not noticeable.

Question 7: Does atezolizumab have any effect on cancer?

Researchers looked to see if there was any effect of this medicine on cancer in patients on the study. They found that some types of cancers had improvements in response to atezolizumab while other cancers did not respond.

Type of cancer	Number of patients who were evaluated	How many patients saw improvements	How many months did improvements last
Breast cancer (HR+)	20	0	0
Bladder cancer	95	25	22
Head and neck cancer	32	7	7
Skin cancer	43	13	62
Lung cancer	89	20	16
Prostate cancer	25	1	1
Kidney cancer	72	10	13
Breast cancer (Triple negative)	115	11	21
Cancer types where less than 20 patients enrolled	140	6	8

5. What were the side effects?

Side effects (also known as “adverse reactions”) are unwanted medical problems (such as a headache) that happen during the study.

- All the side effects that occurred during the study were reported.
- Not all side effects were due to the study medicine.
- No one in this study had all of the side effects.
- Some patients had a few of the side effects.

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, or causes lasting problems. During this study, 46% of patients (46 out of every 100 patients) reported having a serious side effect. While there were several serious effects, the most frequent ones (or the ones that happened the most) are listed below.

Serious side effect	How many patients among 100 patients had this side effect?
Being short of breath	4
Fever	3
An infection that affects the kidney, bladder or the tubes in which people pass water from the body (UTI)	2
Pain in the stomach area	2
Pneumonia	2
Fluid around the lungs	2
Infection just below the skin (cellulitis)	2
Not enough water in the body (dehydration)	2
Feeling tired	2
Lower than normal concentration of oxygen in blood	2
Low levels of red blood cells	1
Serious reaction to an infection sometimes called "blood poisoning" or "sepsis"	1
Back pain	1
Injury to the kidney	1
General changes in brain function	1
Blood clot in lungs	1

Deaths

A total of 13 patients out of 660 died while on the study due to side effects.

- Two patients died as a result of infections (sepsis), and another two patients died due to heart attacks.
- A total of 9 patients – one patient each – suffered death due to the following causes:
  1) Death with no cause reported
  2) Liver failure
  3) Blood clot in liver
  4) Collection of pus in the body (empyema)
  5) Pneumonia
  6) Head injury
  7) Overdose
  8) High blood pressure affecting the lungs (pulmonary hypertension)
  9) Insufficient delivery of oxygen to the body (respiratory failure)

Among the 13 deaths, the one death due to liver failure and one death due to high blood pressure affecting the lungs were considered to be related to atezolizumab treatment by the investigators.

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

- Among every 100 patients, 5 patients stopped the treatment because of side effects.
- Among every 100 patients, 28 patients stopped their treatments for a while because of side effects, and then restarted their treatment.

Most common side effects

During this study, around 99 out of every 100 patients (99%) had a side effect that was not considered serious.

Several side effects were reported, but this summary only lists the most common ones that happened to more than 20 out of every 100 patients.

Common side effects	How many patients among 100 patients had this side effect?
Feeling tired	42
Feeling sick (nausea)	30
Not feeling hungry	27
Diarrhea	23
Constipation	23
Being short of breath	23
Fever	22
Cough	22
Low level of red blood cells (anemia)	21
Being sick (vomiting)	21

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 results presented here are from a single study of 660 patients with several different kinds of cancer. These results helped researchers learn more about atezolizumab:
What dose of this medicine can be used safely in future studies
Which types of cancers are more likely to respond to this treatment

No single study can tell us everything about the risks and benefits of a medicine. 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?

Several studies with patients who have different kinds of cancers and who are given atezolizumab are being carried out. Some studies are looking at combining atezolizumab with other cancer medicines.

Clinical studies of atezolizumab can be found at:

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

https://www.clinicaltrialsregister.eu/ctr-search/search?query=atezolizumab

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/NCT01375842
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-001422-23/GB
- https://forpatients.roche.com/en/search.html?query=atezolizumab

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

If you have any further questions after reading this summary:

- 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 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: “A phase 1, open label, dose escalation study of the safety and pharmacokinetics of atezolizumab (MPDL3280A) administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies”.

- The protocol number for this study is: GO27831.
- The ClinicalTrials.gov identifier for this study is: NCT01375842.
- The EudraCT number for this study is: 2011-001422-23.