AstraZeneca

Clinical Study Results

Research Sponsor: AstraZeneca

Drugs Studied: Olaparib, ceralasertib, and adavosertib

Study Purpose: This study was designed to understand how olaparib, ceralasertib, and adavosertib work in participants with metastatic triple negative breast cancer

Protocol Number: D5336C00001

Thank you

Thank you to the participants who took part in the clinical study for the study drugs olaparib, ceralasertib, and adavosertib.

All of the participants helped researchers learn more about olaparib, ceralasertib, and adavosertib to help people with triple negative breast cancer that has spread to other parts of the body or surrounding breast tissue.

AstraZeneca sponsored this study and believes it is important to share the results of the study with you and the public. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you. We hope it helps you understand and feel proud of your important role in medical research.

If you participated in the study and have questions about the results, please speak with the study doctor or staff at your study site.

Overview of this study

Why was the research needed?

Researchers are looking for a better way to treat triple negative breast cancer that has spread. They also want to understand more about how certain genetic changes, also called "mutations", affect potential cancer treatments. Before a treatment can be approved for people to take, researchers do clinical studies to find out how it works and how safe it is.

What treatments did the participants take?

At the start of this study, the participants took 1 of 3 treatments:

- **Olaparib on its own**
- **Olaparib and ceralasertib**
- **Olaparib and adavosertib**

What were the results of this study?

The main questions the researchers wanted to answer in this study were:

- **When the participants took study treatment, how long was it before their cancer got worse?**

  How long the participants lived with their cancer before it got worse was different between treatment groups. It was also different between participants with and without certain genetic mutations.

- **What medical problems happened during this study?**

  More than 80.0% of participants who took study treatment had medical problems that the study doctors thought might be related to the study treatments. The most common medical problems were nausea, and having a low level of red blood cells, which is also called anemia.

More details about the results of this study are included later in this summary.

Where can I learn more about this study?

You can find more information about this study on the websites listed on the last page. When a full report of the study results is available, it also can be found on those websites.

Who took part in this study?

The researchers asked for the help of people with a type of breast cancer called "metastatic triple negative breast cancer". The participants in this study were women who were 29 to 83 years old when they joined.

The study included 273 participants in 15 countries: Belgium, Canada, the Czech Republic, France, Germany, Ireland, Italy, South Korea, Netherlands, Poland, Portugal, Spain, Taiwan, the United States, and the United Kingdom.

Why was the research needed?

Researchers are looking for a better way to treat people with triple negative breast cancer that has spread. Before a treatment can be approved for people to take, researchers do clinical studies to find out how it works and how safe it is.

In this study, the researchers wanted to find out how olaparib, ceralasertib, and adavosertib work in participants with triple negative breast cancer. They also wanted to know if certain genetic changes affected how the study treatments worked. Genetic changes are also called "mutations".

In people with cancer, the body is not able to control the growth of cells. These cells can form tumors. When the cancer spreads to other parts of the body or surrounding tissue, it is called "metastatic" cancer.

Triple negative breast cancer is a type of breast cancer where the cells are unable to use hormones called "estrogen" and "progesterone" in the normal way, and they also don't have a protein called "HER2". Triple negative breast cancer is hard to treat because many of the treatments available for other types of breast cancer don't work for this type of cancer.

The study drugs olaparib, ceralasertib, and adavosertib are designed to make it harder for tumor cells to repair their DNA when damaged. This makes it harder for the tumor cells to grow and survive.

The researchers wanted to find out if olaparib on its own, or olaparib combined with ceralasertib or adavosertib, helped stop the participants' cancer from getting worse. They also wanted to find out if the participants had any medical problems during the study.

What was the purpose of this study?

The main questions the researchers wanted to answer in this study were:

- When the participants took study treatment, how long was it before their cancer got worse?
- What medical problems happened during this study?

The answers to these questions are important to know before other studies can be done to find out if olaparib on its own, or olaparib combined with ceralasertib or adavosertib, can help slow the growth of tumors in people with metastatic triple negative breast cancer.

What treatments did the participants take?

In this study, the participants took 1 of 3 treatments:

- Olaparib on its own
- Olaparib and ceralasertib
- Olaparib and adavosertib

This was an "open-label" study. This means the participants, researchers, study doctors, and other study staff knew what each participant was taking.

A computer program was used to randomly choose the treatment each participant took. This helps make sure the groups are chosen fairly. Researchers do this so that comparing the results of each treatment is as accurate as possible.

The participants took olaparib and ceralasertib as tablets by mouth. They took adavosertib as capsules by mouth. The participants took study treatments in 21-day or 28-day periods called "cycles". The doses of the treatments were measured in milligrams, also known as "mg".

The chart below shows the treatments the researchers planned to study. The olaparib and adavosertib group had fewer participants than the other 2 groups because it was stopped earlier, due to a high number of medical problems.

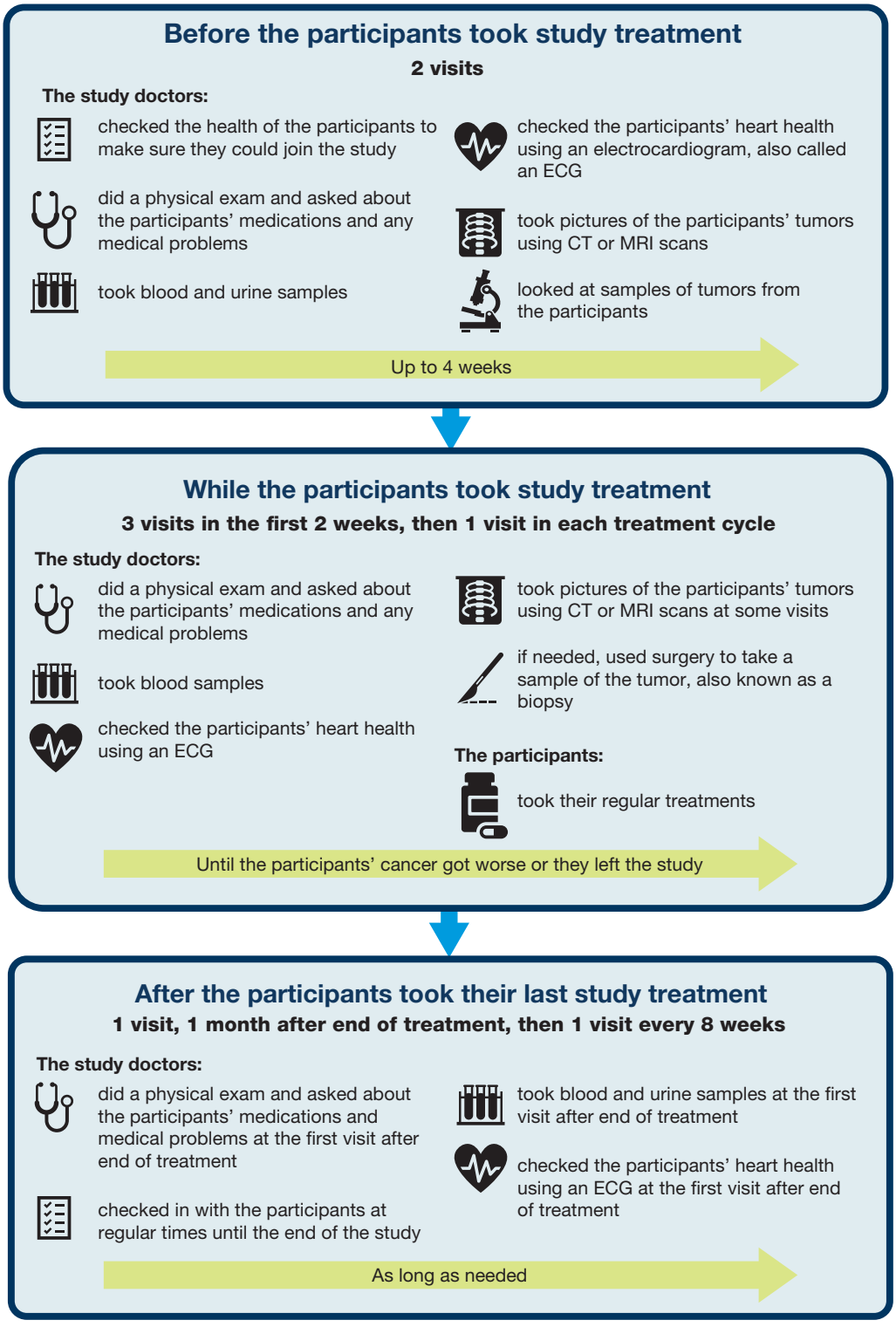
	Olaparib on its own	Olaparib and ceralasertib	Olaparib and adavosertib
	114 participants	112 participants	47 participants
	Treatment cycle: 28 days	Treatment cycle: 28 days	Treatment cycle: 21 days
	600 mg total of **olaparib** each day taken as tablets twice daily by mouth during each treatment cycle	600 mg total of **olaparib** each day taken as tablets twice daily by mouth during each treatment cycle	400 mg total of **olaparib** each day taken as tablets twice daily by mouth during each treatment cycle
		160 mg of **ceralasertib** taken as tablets once daily by mouth for the first week of each treatment cycle	300 mg or 350 mg total of **adavosertib** taken as capsules twice daily on days 1 to 3 and days 8 to 10 of each treatment cycle

The doctors could reduce the dose of the participants' assigned treatments if they had any medical problems during the study. The participants took their assigned treatments until their cancer got worse, until the study doctors thought they should stop study treatment, or until they left the study for another reason.

What happened during this study?

The study started in February 2018 and ended in November 2020.

The chart below shows what happened during the study.



What were the results of this study?

This is a summary of the main results from this study overall. The results each participant had might be different and are not in this summary. A full list of the questions that researchers wanted to answer can be found on the websites listed at the end of this summary. When a full report of the study results is available, it can also be found on these websites.

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.

When the participants took study treatment, how long was it before their cancer got worse?

To answer this question, a group of experts that were not a part of this study's research team looked at pictures of the participants' tumors using MRI or CT scans taken during the study. They measured the growth of the tumors using a set of rules called Response Evaluation Criteria in Solid Tumors, also known as "RECIST".

Then, the study researchers calculated the amount of time that the participants lived with their cancer without their tumors growing. This is called "progression-free survival".

The researchers also wanted to know if certain genetic mutations affected how the treatments worked. So, they looked at the results from participants with or without certain genetic mutations. These mutations were in a gene called "BRCA" and in a group of genes called "HRR".

During this study, a different group of experts recommended that the participants stop taking the combination of olaparib and adavosertib. This was due to a higher number of medical problems in that group than in the other 2 groups, and because the doctors did not think the study treatment was helping the participants. So, this section does not include the results for the olaparib and adavosertib group.

The researchers calculated the results as a median. This "median" is the time beyond which half of the participants had progression-free survival. Overall, the researchers found that the median for the time these participants lived before their cancer got worse was:

	Olaparib on its own	Olaparib and ceralasertib
Participants with a BRCA mutation	7.3 months (for 43 participants)	7.4 months (for 40 participants)
Participants who did not have a BRCA mutation but had an HRR mutation	1.9 months (for 20 participants)	3.9 months (for 20 participants)
Participants who did not have an HRR mutation	1.9 months (for 51 participants)	3.6 months (for 52 participants)

What medical problems happened during this study?

This section is a summary of the medical problems the participants had during the study that the study doctors thought might be related to the study treatments. These medical problems are called "adverse reactions". An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or requires hospital care.

These adverse reactions may or may not be caused by the study treatments. A lot of research is needed to know whether a treatment causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for olaparib, ceralasertib, and adavosertib.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this study.

The researchers reported adverse reactions **for each individual study drug**. The results below are for the **265** out of 273 participants **who took at least 1 dose of their study treatment**.

Did any adverse reactions happen during this study?

	Olaparib (out of 265 participants)	Ceralasertib (out of 109 participants)	Adavosertib (out of 46 participants)
How many participants had adverse reactions?	86.4% (229)	84.4% (92)	97.8% (45)
How many participants had serious adverse reactions?	8.3% (22)	6.4% (7)	30.4% (14)

A total of **23** participants stopped taking their assigned treatment due to medical problems that **may or may not have been related to the study treatments**, which means they may or may not be related to adverse reactions. This was:

- **1.8%** of participants who were taking **olaparib on its own**. This was 2 of 110 participants.
- **11.0%** of participants who were taking **olaparib** and **ceralasertib**. This was 12 of 109 participants.
- **19.6%** of participants who were taking **olaparib** and **adavosertib**. This was 9 of 46 participants.

The olaparib and adavosertib group was stopped early because of an adverse reaction that happened in some participants in that group. This adverse reaction was a condition called "febrile neutropenia". This is when a person has a fever and a low level of white blood cells called neutrophils, which help the body fight infections.

What serious adverse reactions happened during this study?

The most common serious adverse reaction was a fever and a low level of white blood cells called neutrophils, which is also called febrile neutropenia.

The table below shows the serious adverse reactions that happened in more than 1 participant who took each drug during the study. There were other serious adverse reactions, but these happened in fewer participants.

Most common serious adverse reactions

Serious adverse reaction	Olaparib (out of 265 participants)	Ceralasertib (out of 109 participants)	Adavosertib (out of 46 participants)
A fever and a low level of white blood cells called neutrophils, also called febrile neutropenia	1.9% (5)	0.9% (1)	10.9% (5)
Low levels of red blood cells, also called anemia	2.3% (6)	1.8% (2)	2.2% (1)
Low levels of white blood cells called neutrophils, which help the body fight infections	1.1% (3)	0.0% (0)	8.7% (4)
Low levels of white blood cells called leukocytes, which help the body fight infections	0.8% (2)	0.0% (0)	4.3% (2)
Decrease in the number of platelets in the blood, which are cells that help blood to clot	0.8% (2)	0.9% (1)	2.2% (1)
Low levels of platelets in the blood	0.4% (1)	0.0% (0)	6.5% (3)

None of the participants died because of serious adverse reactions.

What adverse reactions happened during this study?

The most common adverse reactions were nausea and having low levels of red blood cells, which is also called anemia.

The table below shows the adverse reactions that happened in 15.0% or more of participants during the study. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions

Adverse reaction	Olaparib (out of 265 participants)	Ceralasertib (out of 109 participants)	Adavosertib (out of 46 participants)
Nausea	46.0% (122)	48.6% (53)	43.5% (20)
Low levels of red blood cells, also called anemia	39.6% (105)	37.6% (41)	30.4% (14)
Fatigue	21.5% (57)	22.0% (24)	28.3% (13)
Vomiting	20.8% (55)	17.4% (19)	26.1% (12)
General weakness	20.4% (54)	24.8% (27)	6.5% (3)
Low levels of white blood cells called neutrophils, which help the body fight infections	14.7% (39)	14.7% (16)	41.3% (19)
Diarrhea	14.7% (39)	11.9% (13)	47.8% (22)
Decreased appetite	12.8% (34)	11.0% (12)	17.4% (8)
Decrease in the number of white blood cells, which help fight infections	7.9% (21)	8.3% (9)	15.2% (7)
Low levels of platelets in the blood, which are cells that help blood to clot	7.2% (19)	8.3% (9)	21.7% (10)
Decrease in the number of platelets in the blood	5.7% (15)	6.4% (7)	15.2% (7)
Low levels of white blood cells called leukocytes, which help the body fight infections	5.7% (15)	4.6% (5)	19.6% (9)
Constipation	4.5% (12)	2.8% (3)	17.4% (8)

How has this study helped patients and researchers?

This study helped researchers learn more about olaparib, ceralasertib, and adavosertib in participants with metastatic triple negative breast cancer. The study also helped researchers understand more about how patients with different genetic mutations respond to different potential cancer treatments.

Researchers look at the results of many studies to decide which treatments work best and are safest. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with the combination of olaparib and ceralasertib or olaparib and adavosertib for metastatic triple negative breast cancer were not planned at the time this summary was written.

Where can I learn more about this study?

You can find more information about this study on the websites listed below. When a full report of the study results is available, it can also be found here.

- www.clinicaltrials.gov Once you are on the website, type **"NCT03330847"** into the search box and click **"Search"**.
- www.clinicaltrialsregister.eu Once you are on the website, click **"Home and Search"**, then type **"2017-002361-22"** in the search box and click **"Search"**.
- www.AstraZenecaClinicalTrials.com Once you are on the website, type **"D5336C00001"** into the search box, and click **"Find a Study"**.

Full Study Title: A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including BRCA1/2)

AstraZeneca Protocol Number: D5336C00001

National Clinical Trials Number: NCT03330847

EudraCT Number: 2017-002361-22

AstraZeneca sponsored this study and has its headquarters in Cambridge, UK.

The phone number for the AstraZeneca Information Center is +1-877-240-9479.

Thank you

Clinical study 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.

CISCRP

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 participants for clinical studies, nor is it involved in conducting clinical studies.

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