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Plain Language Summary of Publication

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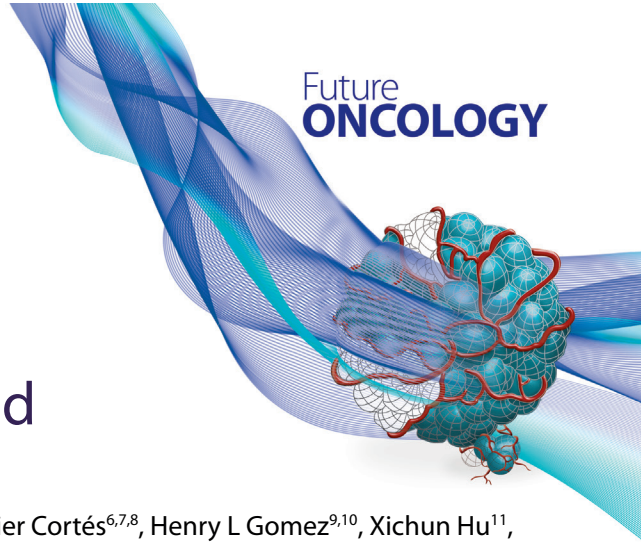

A plain language summary of the CAPItello-291 study: Capivasertib in hormone receptor-positive advanced breast cancer

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Where can I find the original article on which this summary is based?

The full title of the original publication in the *New England Journal of Medicine* is: 'Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer'. You can read the original article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa2214131

Summary

How to say (double click sound icon to play sound)...

- **Aromatase:** ah-ROH-muh-tayz
- **Capivasertib:** kap-i-va-ser'-tib
- **CAPItello-291:** kap-i-tello
- **Estrogen:** EH-struh-juhn
- **Fulvestrant:** ful-VES-trant

What is this summary about?

This is a summary of the article discussing the results of the CAPItello-291 study. In the study, participants had **advanced breast cancer** that could not be completely removed with surgery, and that was diagnosed as a type of breast cancer where tumor cells had **hormone** receptors (HR-positive) but did not have HER2 receptors (HER2-negative). All participants were also required to have previously received treatment with a type of therapy called an **aromatase inhibitor** (with or without a **CDK4/6 inhibitor**), but over time their cancer cells had still grown or spread. The CAPItello-291 study researchers wanted to find out if a treatment combination of the medications capivasertib plus fulvestrant worked better than **placebo** plus fulvestrant. Capivasertib is a drug that blocks the activity of a **protein** called AKT, which is found inside breast cancer cells.

What are the key takeaways?

The main finding was that participants who took capivasertib plus fulvestrant lived longer without their disease getting worse (progressing) compared with those treated with placebo plus fulvestrant. This is called **progression-free survival**. This result was seen across all participants

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(**median progression-free survival** of 7.2 months with capivasertib plus fulvestrant vs 3.6 months with placebo plus fulvestrant). It was also seen in participants whose tumors had detectable **genetic alterations** in **genes** called ***PIK3CA***, ***AKT1***, and/or ***PTEN*** (median progression-free survival of 7.3 months with capivasertib plus fulvestrant vs 3.1 months with placebo plus fulvestrant). The most common **side effects** experienced by participants included diarrhea and different types of rash. These were as expected (given how capivasertib works). The CAPItello-291 study is still ongoing, and more results are expected to be released in the future.

What were the main conclusions reported by the researchers?

Results from the CAPItello-291 study showed that capivasertib plus fulvestrant compared with placebo plus fulvestrant improved progression-free survival in participants with HR-positive/HER2-negative advanced breast cancer whose cancer had grown or spread despite hormone therapy (with/without a CDK4/6 inhibitor).

Advanced breast cancer: Cancer that has spread to local **lymph nodes** or outside of the breast.
Lymph nodes: A small bean-shaped structure that is part of the body's immune system.
Hormone: A chemical messenger that can travel around the body and bind to hormone receptors on cells, causing cells to act in a certain way.
Aromatase inhibitor: A type of hormone therapy that stops the body from making estrogen.
CDK4/6 inhibitor: A type of drug that blocks the activity of a protein called CDK4/6, reducing the growth of breast cancer cells. Also known in full as a cyclin-dependent kinase 4/6 inhibitor.
Placebo: An inactive substance that looks the same and is given in the same way as the active treatment being tested.
Protein: A large, complex molecule that plays many critical roles in the body.
Progression-free survival: The length of time after a participant starts treatment in a clinical study to when cancer grows, spreads, or gets worse, or until the participant dies for any reason. This is frequently used by researchers as a way of measuring how well one treatment works compared to another.
Median progression-free survival: Timepoint at which half of the participants' cancer progressed.
Genetic alterations: A mutated form of a gene.
Gene: The functional and physical unit of heredity passed from parent to child.
***PIK3CA*:** The gene that makes part of the PI3K protein (one of several proteins that are part of an important biological pathway that regulates cell growth and survival).
***AKT1*:** The gene that makes the AKT protein (one of several proteins that are part of an important biological pathway that regulates cell growth and survival).
***PTEN*:** The gene that makes the PTEN protein (one of several proteins that are part of an important biological pathway that regulates cell growth and survival).
Side effect: An effect of a medicine that is beyond its desired effect. Side effects can be harmful.

What is the purpose of this PLSP?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Capivasertib in combination with fulvestrant is used to treat the condition under study that is discussed in this summary. Approval varies by country; please check with your local provider for more details.

Who should read this article?

This summary may be helpful for people with HR-positive/HER2-negative advanced breast cancer and their family members or caregivers. It may also be helpful for patient advocates and healthcare professionals, including those helping someone find the best treatment for their diagnosis.

Who sponsored this clinical study?

The pharmaceutical company AstraZeneca (the manufacturer of the drugs being investigated) funded and was responsible for conducting this clinical study.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyses the information that was generated during the study.

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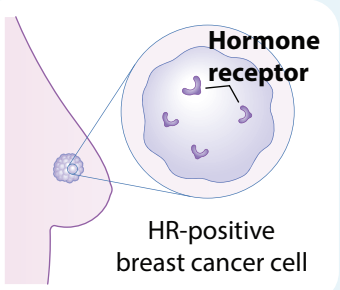
What is HR-positive/HER2-negative advanced breast cancer?

Breast cancer is a disease where breast cells grow out of control and form a tumor. There are three common proteins found in breast cancer cells. These proteins are also known as receptors:

- Estrogen receptors are hormone receptors
- Progesterone receptors are hormone receptors
- Human epidermal growth factor receptor 2 (also called HER2) is another type of receptor

Biopsy: A medical procedure to remove cells, tissue, or fluid for examination by a specialist.

During the process of a breast cancer diagnosis, scientists look at breast cancer cells (collected from a **biopsy**) under a microscope to see what type of receptors are on the cells. When a person has hormone receptors in their breast cancer cells, plus no/little amounts of the HER2 receptor, their breast cancer is known as HR-positive/HER2-negative. Breast cancer is called advanced when the breast cancer cells travel to local lymph nodes or outside the breast (for example, the bones).

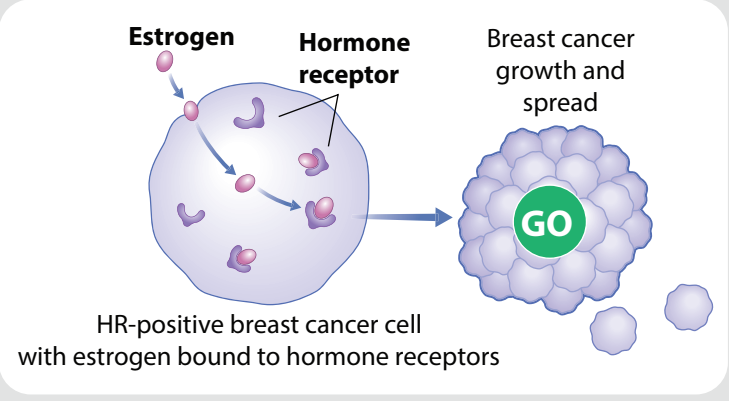


About 70% of advanced breast cancers are HR-positive/HER2-negative, of which approximately 50% of patients also have tumors with detectable genetic alterations in *PIK3CA*, *AKT1*, and/or *PTEN* genes. Knowing the type of breast cancer can help doctors decide on the most suitable treatment.

How is HR-positive/HER2-negative advanced breast cancer treated?

Hormone therapy

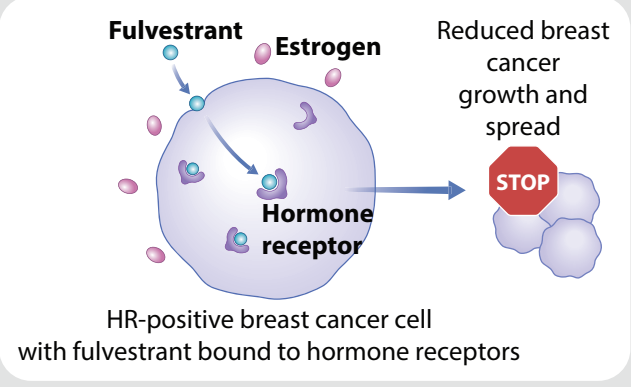
Estrogen is a hormone naturally present in the body. For people with HR-positive breast cancer, estrogen can bind to the receptors in the breast cancer cells and cause breast cancer to grow or spread. Hormone therapies (also known as endocrine therapies) are a standard treatment. Hormone therapies work by lowering the amount of hormone (estrogen) in the body or by blocking the effect the hormones have on breast cancer cells. For patients with HR-positive breast cancer, hormone therapies can be given alone or with other treatments.



First-line treatment

Aromatase inhibitors are a type of hormone therapy that stops the body from making estrogen. This means lower levels of estrogen in the body and fewer signals telling the breast cancer cells to grow. Aromatase inhibitors (such as anastrozole, letrozole, or exemestane) are often the first treatment given to people with HR-positive/HER2-negative advanced breast cancer. This is known as first-line treatment.

Often, doctors also give people with HR-positive/HER2-negative breast cancer a type of treatment called a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. A CDK4/6 inhibitor is a type of drug that blocks the activity of a protein called CDK4/6, reducing the growth of breast cancer cells. CDK4/6 inhibitors work in a different way than hormone therapies to slow or stop the growth of cancer.



Second-line treatment
Over time, breast cancer cells can change, and first-line therapies can stop working, meaning treatment needs to be changed. Doctors frequently use fulvestrant, a drug that blocks estrogen receptors in breast cancer cells, reducing their growth and spread, as a standard hormone therapy alone or with other treatments. However, the most appropriate second-line treatment to give people when first-line therapy has stopped working is unclear. Additional treatment options are needed.

Why was the CAPItello-291 study carried out?

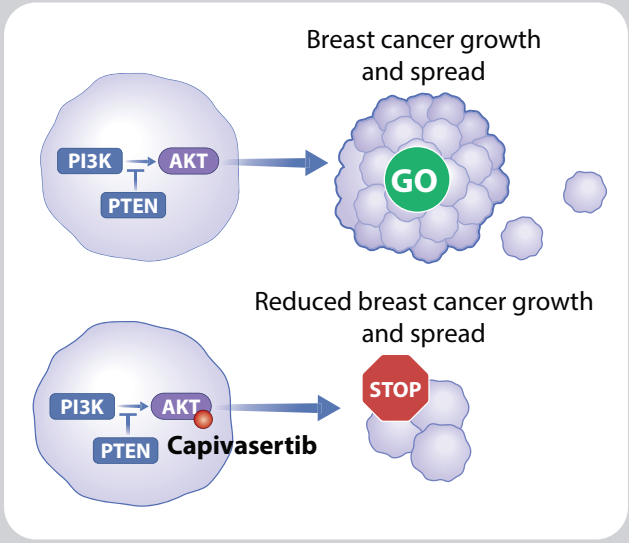
- Before the CAPItello-291 study began, researchers had already shown that combining a new drug, capivasertib, with fulvestrant may be effective in people with HR-positive advanced breast cancer who had previously been treated with hormone therapy for their advanced disease.
- The CAPItello-291 study researchers wanted to find out if the combination of capivasertib plus fulvestrant worked better than placebo plus fulvestrant in a large number of participants with HR-positive/HER2-negative advanced breast cancer.

What is capivasertib?

How does capivasertib work?
Capivasertib is a drug that blocks the activity of a protein called AKT, which is found inside breast cancer cells. The AKT protein is part of the PI3K/AKT pathway (also sometimes called the AKT pathway), a biological pathway made up of various proteins that regulate cell growth and survival. PI3K, AKT, and PTEN are important proteins that regulate the activity of the PI3K/AKT pathway. By blocking the activity of the AKT protein, capivasertib can slow down the growth of breast cancer cells. The PI3K/AKT pathway is often involved in the growth of breast cancer cells. When the pathway malfunctions, breast cancer cells can survive and reproduce more easily.

How is capivasertib taken?

- Capivasertib is taken by mouth at a dose of 400 mg twice a day (taken as two 200 mg tablets each time). In the study, doctors could give a lower dose, if needed, based on the side effects a patient may have.
- Capivasertib is not taken every day. It is taken twice a day for 4 days in a row, followed by a 3-day break every week. Treatment is taken like this because earlier research showed that the likelihood of experiencing side effects of treatment was lower than when taken every day.



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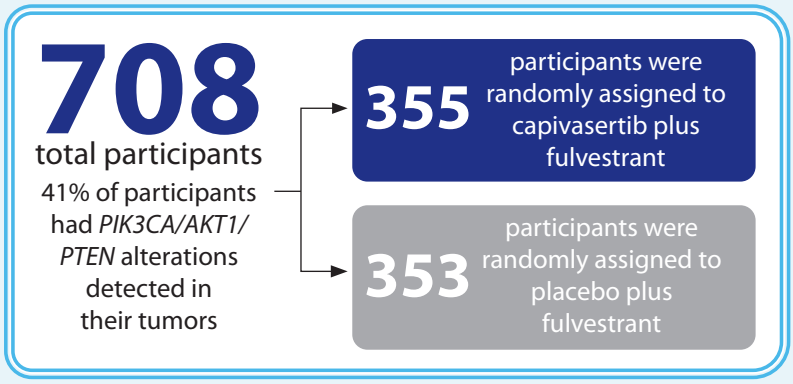
How was the CAPItello-291 study carried out?

- This was a double-anonymized clinical study, which means that neither the participants nor the researchers knew what treatment each participant was given while the study was ongoing.
- Participants with HR-positive/HER2-negative breast cancer were randomly assigned to two treatment groups.
- About half of the participants were given capivasertib plus fulvestrant, and about half were given a placebo plus fulvestrant. Fulvestrant is given as an injection into the muscle following the manufacturer's instructions.
- Half of the participants received capivasertib and the other half received placebo.



Who was included in the CAPItello-291 study?

Adults included in this study had:

- Advanced breast cancer (cancer that has spread to local lymph nodes or outside of the breast) that could not be completely removed with surgery
- Breast cancer where tumor cells had estrogen receptors (HR-positive) but did not have HER2 receptors (HER2-negative). Breast cancer where tumor cells had progesterone receptors (PR-positive) was allowed but not required
- Previously received treatment with aromatase inhibitors (with or without a CDK4/6 inhibitor), but their tumor had still grown or spread

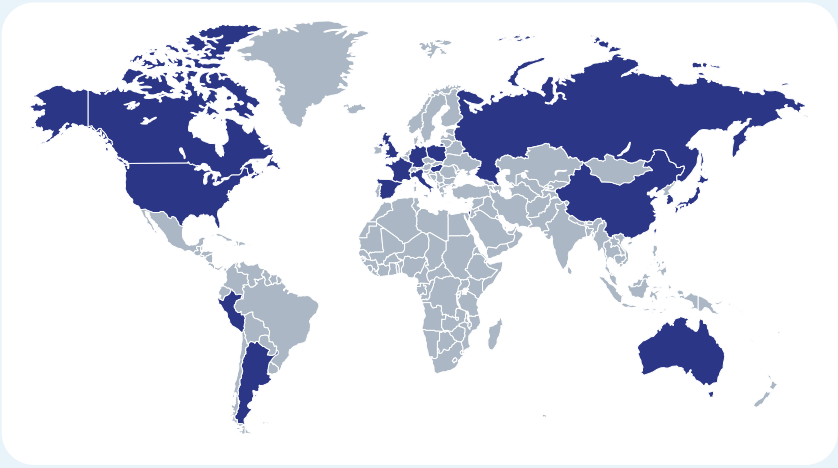
To be included in this study, participants also had to have tumor tissue available for researchers to test if their cancer had alterations in the *PIK3CA*, *AKT1*, and/or *PTEN* genes that make the proteins in the PI3K/AKT pathway.

People were not able to join the study if they had:

- Previously received treatment with fulvestrant or other approved or experimental treatments that work in a similar way to either fulvestrant or capivasertib
- Diabetes requiring insulin treatment
- Blood test results suggesting too much glucose in their blood and that the body isn't processing the sugar properly

Where did the study take place?

The study included 708 participants from 19 countries.



North America
Canada
United States

South America
Peru
Argentina

Asia
China
Israel
Japan
Republic of Korea
Taiwan

Europe
Belgium
France
Germany
Hungary
Italy
Poland
Russia
Spain
United Kingdom

Oceania
Australia

What were the main characteristics of participants at the start of the study?

- 99% of participants were female.
- The racial diversity of participants was as follows:
  - 57% of participants were White
  - 27% of participants were Asian
  - 1% of participants were Black or African-American
  - 15% of participants were of other or non-disclosed race
- White individuals comprised the majority of study participants, with Black or African-American individuals being under-represented.
- The most common places where cancer had spread from its original site (metastatic):
  - 68% of participants had cancer that had spread to the soft internal organs (known as the viscera) of the body, such as the lungs or liver
    - 43% of participants had cancer that had spread to the liver
  - 14% of participants had cancer that had spread to the bone only

What was the CAPItello-291 clinical study designed to look at?

The main question researchers wanted to answer in the CAPItello-291 study was:

- How long was it before a participant's cancer grew, spread, or got worse, or until the participant died for any reason while receiving capivasertib plus fulvestrant compared with placebo plus fulvestrant? The time this takes is also known as progression-free survival.

Researchers also asked the following questions:

- How long did participants live after entering the study with capivasertib plus fulvestrant compared with placebo plus fulvestrant? The time this takes is also known as overall survival.
- What were the side effects that patients experienced when taking capivasertib plus fulvestrant?

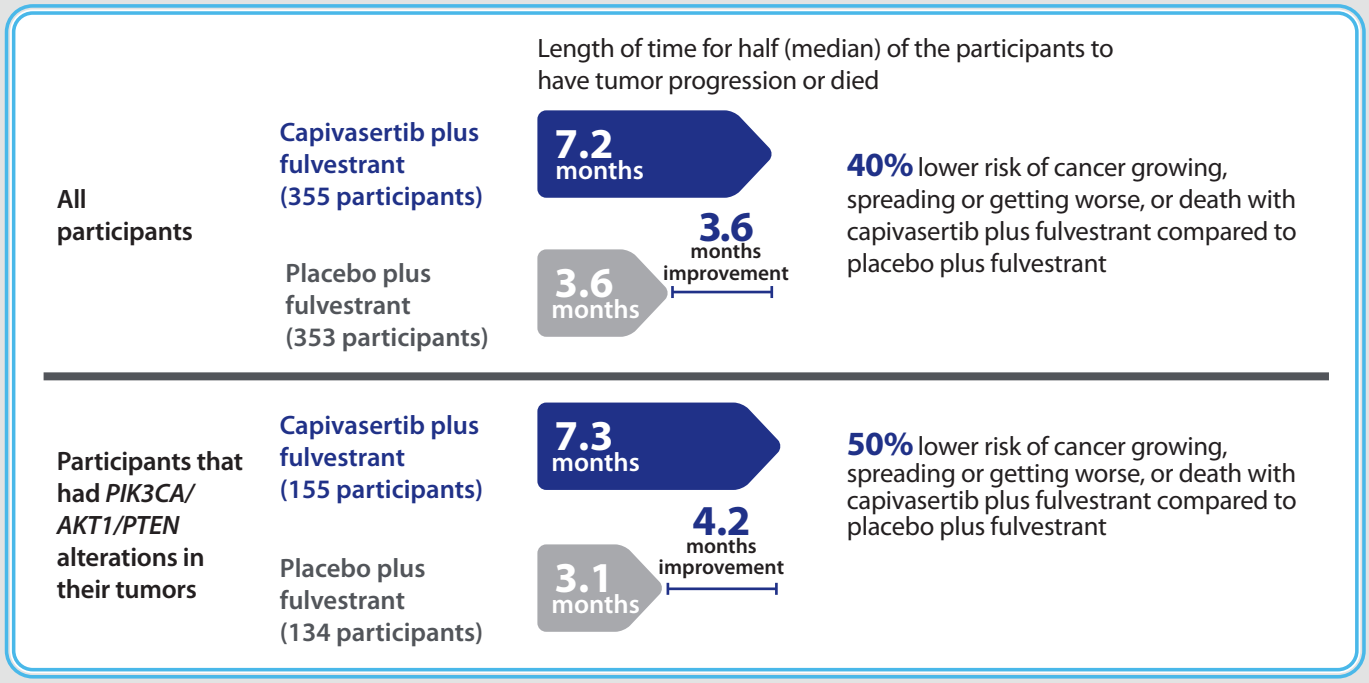
Researchers looked at the results in two different ways:

- Results of all participants (regardless of the genetic status of their tumor).
- Results of only participants who had at least one genetic alteration (*PIK3CA/AKT1/PTEN* alterations) in their tumors.

What were the main findings of the CAPItello-291 study?

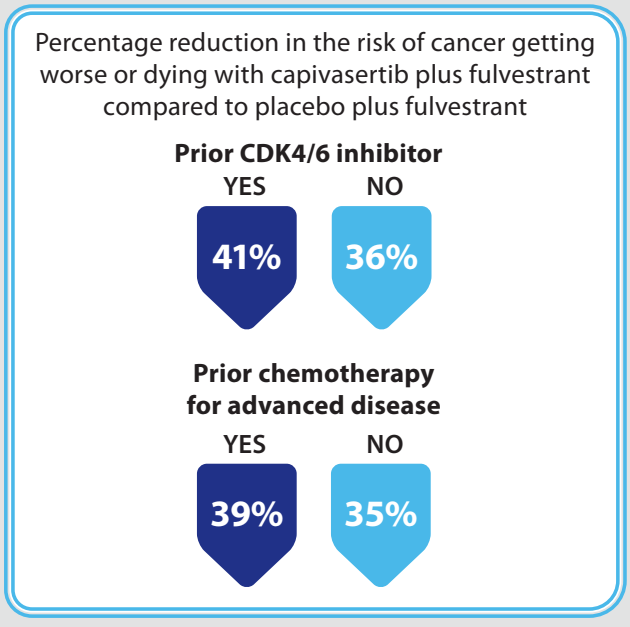
How long was it before a participant's cancer grew, spread, or got worse?

- Participants who took capivasertib plus fulvestrant lived longer with their disease without it getting worse (progressed) compared with those treated with placebo plus fulvestrant. This is called progression-free survival. This result was seen across all participants. It was also seen in participants whose tumors had detectable genetic alterations in genes called *PIK3CA*, *AKT1*, and/or *PTEN*.
- Participants who did not have *PIK3CA/AKT1/PTEN* alterations in their tumors (or had an unknown test result) also had longer progression-free survival when treated with capivasertib plus fulvestrant compared with placebo plus fulvestrant.



Did any important factors affect the benefit of capivasertib plus fulvestrant?

- The benefit of capivasertib plus fulvestrant was consistent whether or not participants had previously been treated with a CDK4/6 inhibitor or chemotherapy for advanced disease.
- The benefit of capivasertib plus fulvestrant was also consistent regardless of where the cancer had spread outside the breast.

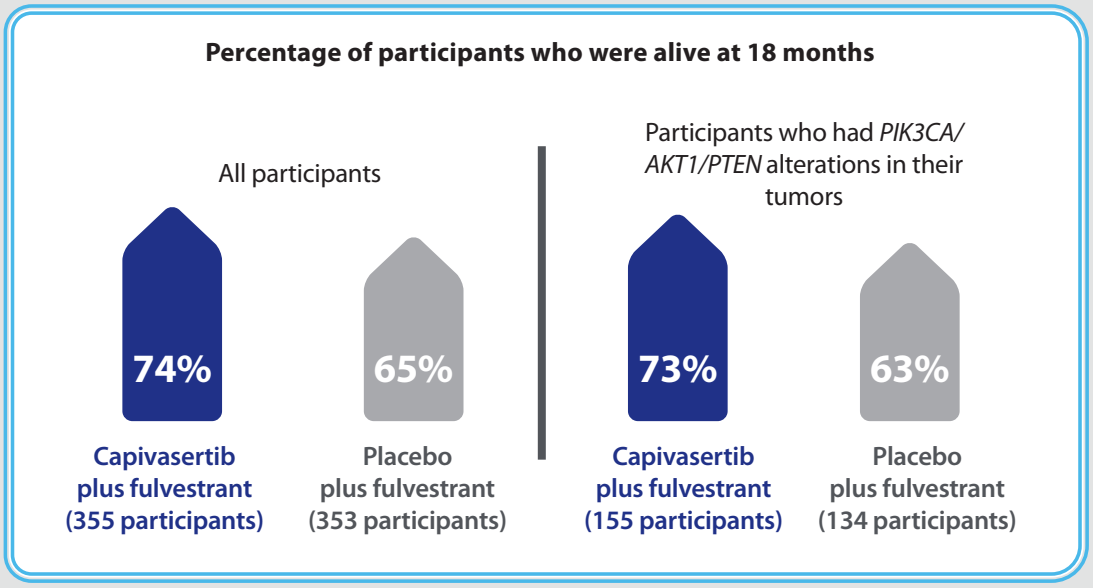


Were there any other measures of how well capivasertib plus fulvestrant treatment worked?

- Yes, other measures reported in the publication also favored capivasertib plus fulvestrant over placebo plus fulvestrant.

How long did participants live for?

- When the first results from this study were available (2022), it was too early for researchers to know the survival benefits of adding capivasertib to fulvestrant. This is because only a small percentage of participants in the study had died at that point.
- However, the percentage of participants who were alive at 18 months was numerically higher with capivasertib plus fulvestrant than with fulvestrant plus placebo.
- This study is still in progress. The future results will provide more information about how long people lived (also called overall survival).



How did treatment impact participants' well-being and ability to carry out their normal daily activities (known as health-related quality of life)?

- Participants in both treatment groups maintained their health-related quality of life (as measured by mean change in quality of life scores).
- Participants who took capivasertib plus fulvestrant had a median of 25 months before their health-related quality of life got worse compared to 12 months with those treated with placebo plus fulvestrant.

Health-related quality of life: A measure of a person's well-being and ability to carry out their normal daily activities. In order to measure this, participants in the study were asked to complete regular questionnaires.

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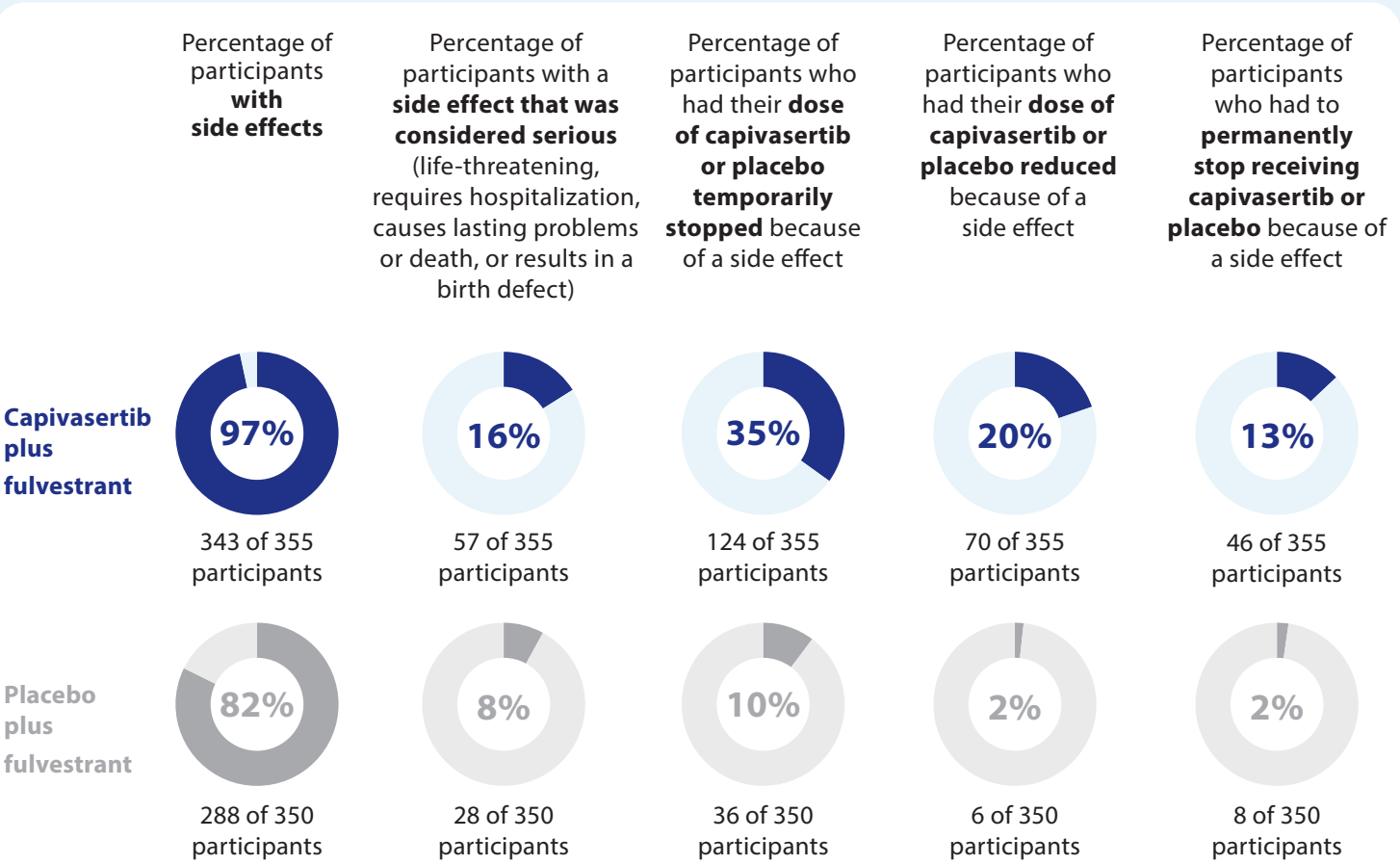
What were the side effects of this treatment?

How many participants had side effects?

This study monitored the side effects of treatments in all participants who took at least 1 dose of their study treatment. This included:

- A total of 355 participants who received capivasertib plus fulvestrant
- A total of 350 participants who received placebo plus fulvestrant



Note: Participants were able to be counted in more than 1 category

What were the most common side effects?

The most common side effects experienced by participants are shown below. The side effects that people reported were as expected (given how capivasertib works). There were other side effects reported, but these happened in fewer participants.

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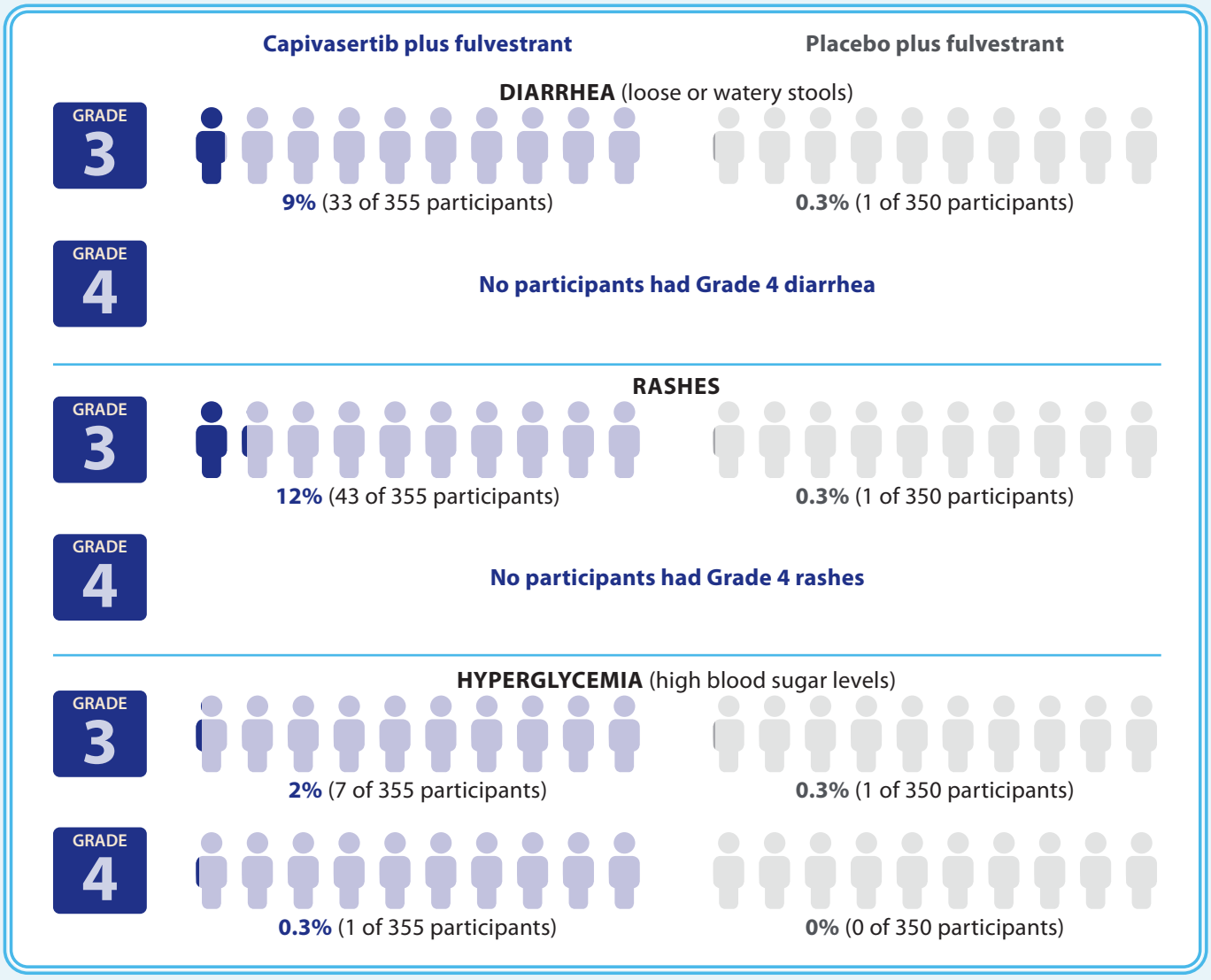
What were the most common severe and life-threatening side effects?

Side effects of treatment were measured using the following standardized descriptions:

GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
A side effect that has no or **mild** symptoms and does not require medical treatment	A **moderate** side effect that requires limited medical treatment or that limits some daily activities	A side effect that is **severe but not life-threatening** but may limit daily activities and – in some cases – could require hospital care	A side effect that is **life-threatening** and requires urgent medical treatment	A side effect that results in **death**

Most of the side effects in the study were mild (grade 1) or moderate (grade 2). The most common severe (grade 3) or life-threatening (grade 4) side effects experienced by participants are shown below and did not occur very often. Other side effects that participants experienced (such as nausea and fatigue) were mainly mild (grade 1) or moderate (grade 2) in both treatment groups.



What do the results of this study mean?

Based on the results of this study, capivasertib plus fulvestrant compared with placebo plus fulvestrant improved progression-free survival in participants with HR-positive/HER2-negative advanced breast cancer whose cancer has grown or spread despite hormone therapy (with/without a CDK4/6 inhibitor). Patients should always talk to a doctor before deciding about their treatment.

Where can I find more information on the CAPItello-291 study?

The full title of the original publication in the *New England Journal of Medicine* is: 'Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer'.

You can read the original article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa2214131 (Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, *et al.* Capivasertib in hormone receptor–positive advanced breast cancer. *N Engl J Med.* 2023; 388(22):2058-2070).

You can read more about the CAPItello-291 study on the following websites:

- ClinicalTrials.gov website at: https://clinicaltrials.gov/study/NCT04305496
- Type the EudraCT identifier 2019-003629-78 into the search field at: https://www.clinicaltrialsregister.eu/ctr-search
- More information about clinical trials in general can be found at: https://www.clinicaltrials.gov/ct2/about-studies/learn

Patients should ask their healthcare providers for more information about the benefits and risks of any treatment.

The study started in April 2020 and is currently ongoing. The estimated completion date is June 2024. Up-to-date information can be found at: https://clinicaltrials.gov/study/NCT04305496.

Information on the approval of capivasertib with fulvestrant by the US Food and Drug Administration can be found at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer.

Approval varies by country; please check with your local provider for more details.

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