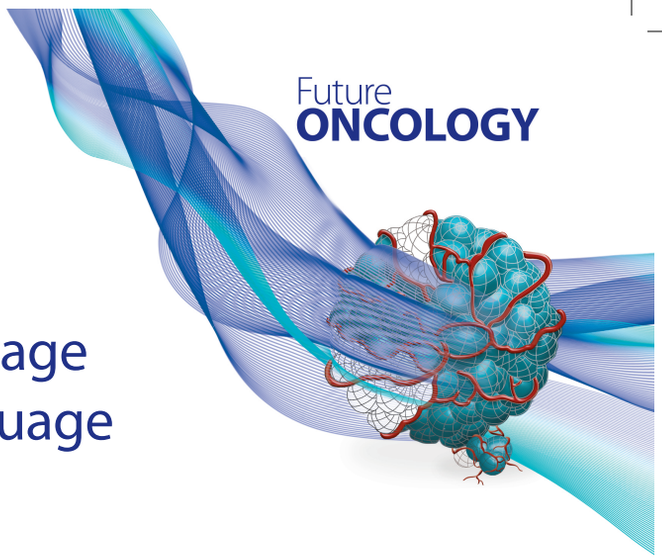
Future ONCOLOGY

Plain Language Summary of Publication

Trastuzumab and pertuzumab without chemotherapy in early-stage HER2+ breast cancer: a plain language summary of the PHERGain study



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Summary

What is this summary about?

This is a summary of a publication about the PHERGain study, which was published in *The Lancet Oncology* in May 2021. The study includes 376 women with a type of breast cancer called HER2-positive breast cancer that can be removed by surgery. In the study, researchers wanted to learn if participants could be treated with two medicines called trastuzumab and pertuzumab without the need for chemotherapy. To identify HER2-positive tumors with more sensitivity to anti-HER2 therapies, the researchers used a type of imaging called a FDG-PET scan to check how well the treatments were working.

How to say (double-click on the icon to play sound)…

- **Trastuzumab:** tras-tuh-ZUH-mab
- **Pertuzumab:** per-tuh-ZUH-mab
- **Docetaxel:** doe-se-TAX-el
- **Carboplatin:** kar-boe-PLA-tin

What happened in the PHERGain study?

Participants took a treatment before surgery, consisting of either chemotherapy (docetaxel and carboplatin) plus trastuzumab and pertuzumab (group A) or trastuzumab and pertuzumab alone (plus hormone therapy if the tumor was hormone receptor-positive; group B). After two cycles of treatment, participants underwent a FDG-PET scan. Participants assigned to group A completed 6 cycles of treatment regardless of ^{18}F-FDG-PET results. Participants in group B continued the same treatment until surgery if their FDG-PET scan showed the treatment was working. While participants who did not show a response started treatment with chemotherapy in addition to trastuzumab and pertuzumab. All participants then had surgery.

What were the results?

The results revealed that, of the participants in group B who showed a response using FDG-PET scan, 37.9% achieved a disappearance of all invasive cancer in the breast and axillary lymph nodes. This rate appears to be higher than those reported in previous studies evaluating the same treatment. These participants also had less side effects and improved overall quality of life compared with participants taking chemotherapy plus trastuzumab and pertuzumab.

What do the results of the study mean?

Early monitoring of how well participants respond to treatment by FDG-PET scan seems to identify participants with operable HER2-positive breast cancer who were more likely to benefit from trastuzumab and pertuzumab without the need to have chemotherapy. The PHERGain study is still ongoing and results on long-term survival are expected to be released in 2023.

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Who is this article for?

This summary may be helpful for patients with HER2-positive breast cancer and their family members or caregivers. It may also be very useful for patient advocates and healthcare professionals. This includes those who are looking for treatment options for patients with HER2-positive breast cancer that can be removed by surgery.

What is HER2-positive breast cancer?

HER2 stands for ´human epidermal growth factor receptor 2´. It is a type of protein, called a receptor, present on the surface of both healthy and cancer cells that can control how cells growth.

HER2-positive breast cancer is a type of breast cancer which has high levels of the HER2 protein. Breast cells with too much of the HER2 protein grow and divide at an uncontrolled rate, forming tumors. About one in five breast cancers are HER2-positive.

Whether breast cancer is HER2-positive is commonly measured as part of usual care for breast cancer. Breast cancer cells collected during a biopsy are analyzed under a microscope to check if they have too much HER2 protein and are HER2-positive.

What is hormone receptor-positive breast cancer?

About 70–80% of all breast cancers are classified as hormone receptor (HR)-positive. That means the tumor cells grow and proliferate in response to the hormones produced in the body called estrogen and progesterone. These tumors have on the surface of their cells a significant number of receptors for either estrogen or progesterone (from now on called HR-positive).
The remaining 20–30% of all breast cancers are classified as HR-negative. This means they have few or no hormone receptors for the estrogen or progesterone.

What is an FDG-PET scan and how does it work?

The type of scan used in the PHERGain study is called a ^{18}F-FDG-PET scan. It is one of the most accurate and sensitive imaging procedures for diagnosing cancer diseases in the earliest stages of growth before it may be seen on other imaging tests.

^{18}F-FDG-PET

^{18}F
Fluorine-18 radioisotope

This is radioactive isotope, which is a chemical element with an excess energy in their nucleus that is spontaneously released by emitting radiation.

FDG
Fluorodeoxyglucose

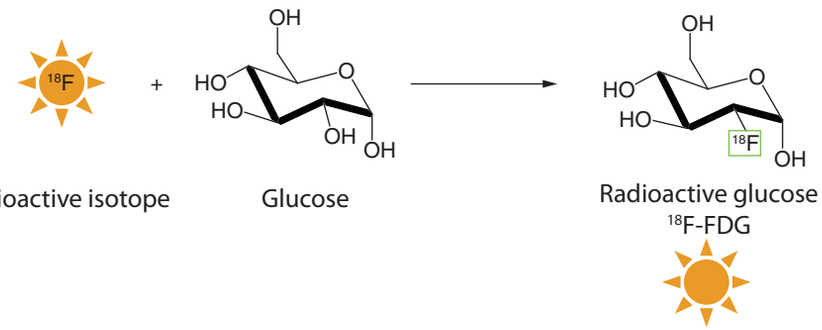
This is similar to naturally occurring glucose (a type of sugar) and acts as a type of 'radiotracer' when injected into the body. Because cancer cells use glucose at a much faster rate, it can identify which cells in the body are cancerous.

PET
Positron emission tomography

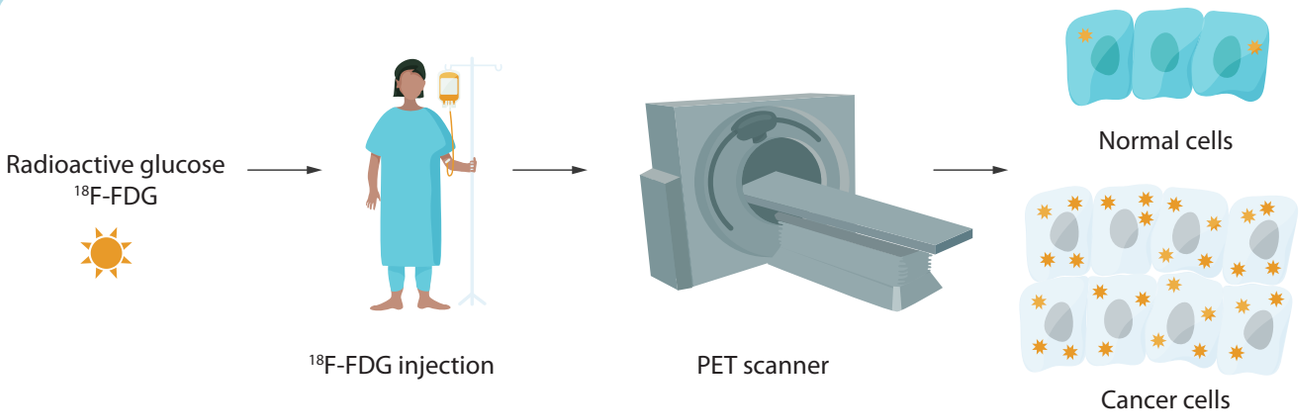
A type of scan to determine how far the cancer has spread and how well it is responding to treatment.

How does an FDG-PET scan work?

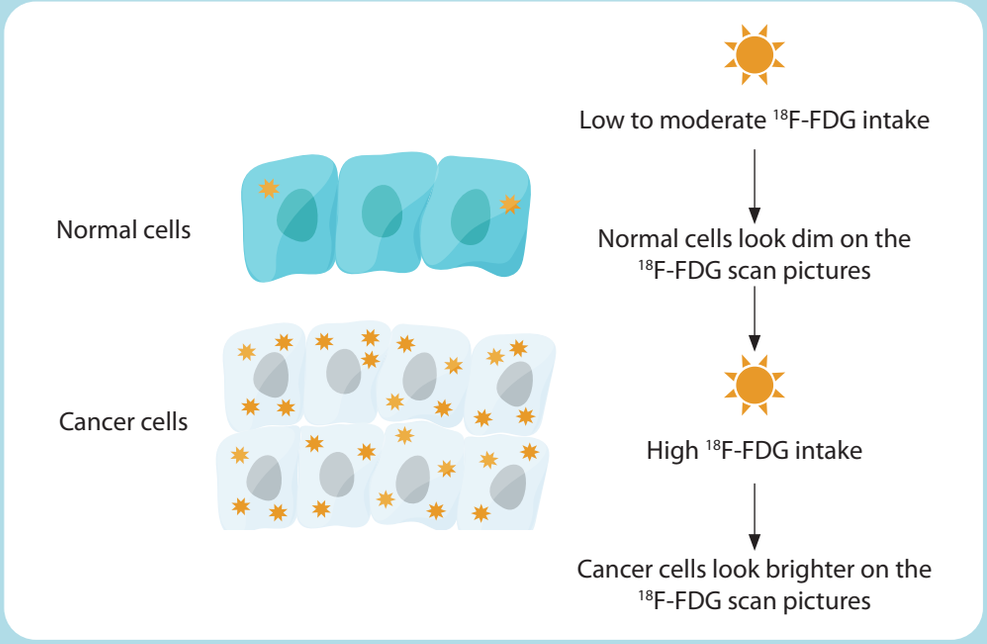
When ^{18}F is combined with FDG it generates the radioactive glucose ^{18}F-FDG.



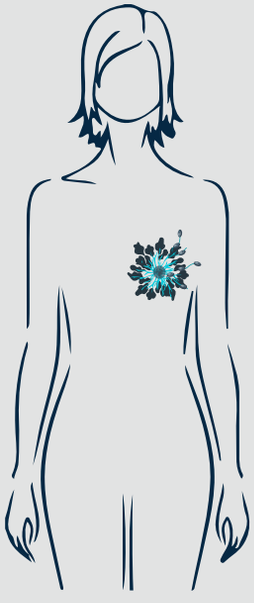
^{18}F-FDG is injected into the vein and a PET scanner take a picture of where the glucose is being used in the body.



Cancer cells which divide excessively will show up brighter in the picture because they take up more glucose as main source of energy than normal cells do. Thus, the composed word ^{18}F-FDG-PET means that a PET scanner utilizes the radioactive glucose ^{18}F-FDG to detect malignant cells with high glucose intake.



Why did the PHERGain study take place?



Substantial development in the research of HER2-targeted agents have significantly improved the prognosis of patients with HER2-positive breast cancer that has not spread beyond the breast or the axillary lymph nodes.

Trastuzumab and pertuzumab work to stop, prevent, or slow the growth of HER2-positive breast tumors by specifically blocking the activity of HER2. Trastuzumab and pertuzumab plus chemotherapy are already approved for use in patients with HER2-positive breast cancer that has not spread beyond the breast or the nearby lymph nodes (early-stage disease) and that have spread from the breast to other parts of the body (metastatic disease). Chemotherapy is a treatment that kills cancer cells or stops them from dividing. A subgroup of patients with HER2-positive breast cancer can be sufficiently treated with 'right-sizing therapy', such as minimizing the intensity and extent of chemotherapy regimens'.

In the study, participants took a treatment before having their tumors removed by surgery consisting of either chemotherapy (docetaxel and carboplatin) plus trastuzumab and pertuzumab (group A) or trastuzumab and pertuzumab alone (in combination with hormone therapy if tumor was HR-positive; group B).

The disappearance of all invasive cancer in the breast and axillary lymph nodes (also known as pathological complete response) is considered a robust, simple and well-studied marker for improved long-term survival outcomes.

Chemotherapy-free regimen with trastuzumab and pertuzumab before surgery has resulted in remarkable pathological complete response rates (around 20–36%), providing further rationale for future treatments for patients with HER2-positive, operable breast cancer.

Several studies demonstrated that early metabolic evaluation using ^{18}F-FDG-PET might identify HER2-positive tumors with high anti-HER2 sensitivity and an increased likelihood of achieving a pathological complete response to HER2 blockade before surgery.

What was the purpose of the PHERGain study?

1. The first objective of the PHERGain study was to see how many participants with HER2-positive breast cancer that could be treated with surgery (known as operable breast cancer) receiving trastuzumab and pertuzumab alone (in combination with hormone therapy if tumor was HR-positive) would see a disappearance of all invasive cancer in the breast and axillary lymph nodes after 8 cycles of treatment. This was assessed by seeing which participants achieved an early metabolic response using ^{18}F-FDG-PET scans.

2. The second objective was to see how many participants assigned to group B would remain alive and free of invasive cancer at 3 years of treatment (known as 3-year invasive disease-free survival), after having their tumors completely removed by surgery.

3. Other objectives included the most common adverse events (side effects) and health-related quality of life that participants have during treatment.

For a full list of the aims that the researchers wanted to answer in this study, please refer to the websites listed at the end of this summary.

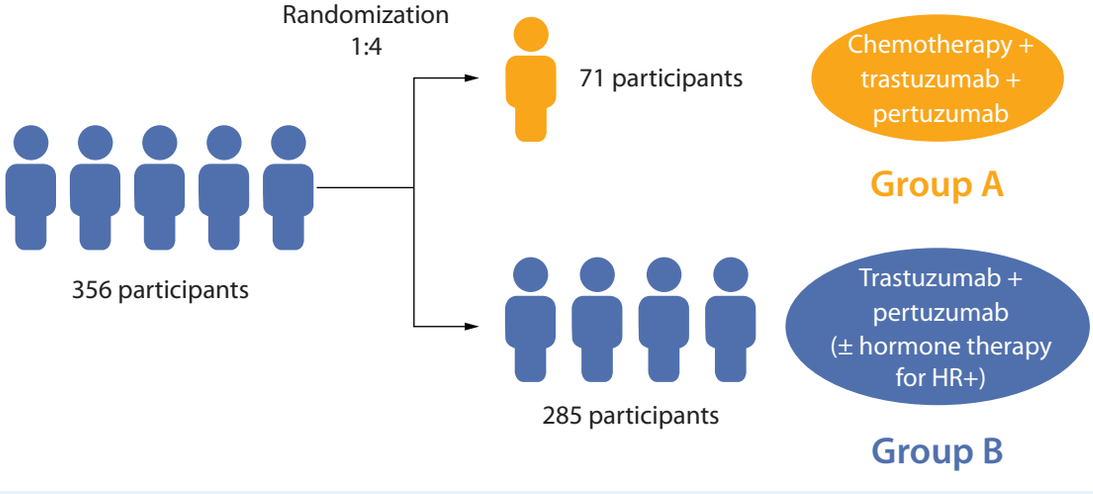
What happened during study?

Participants were assigned by chance (also known as randomization process) in a 1:4 ratio to:

Group A receiving chemotherapy (docetaxel and carboplatin) plus trastuzumab and pertuzumab

or

Group B receiving trastuzumab and pertuzumab alone (plus hormone therapy if tumor was HR-positive):

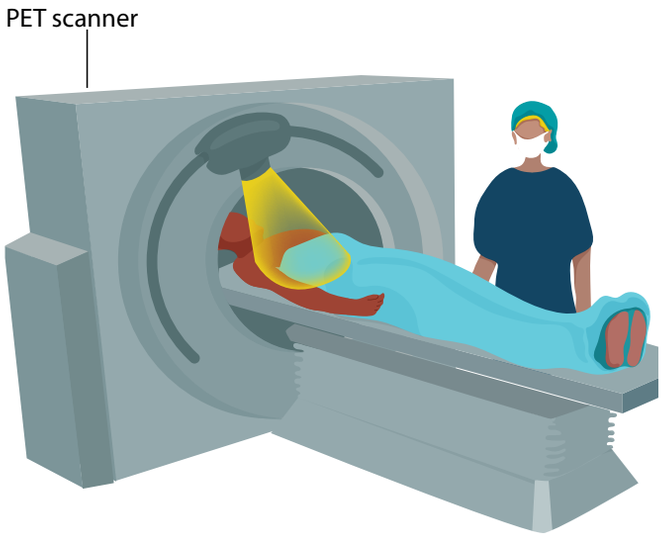


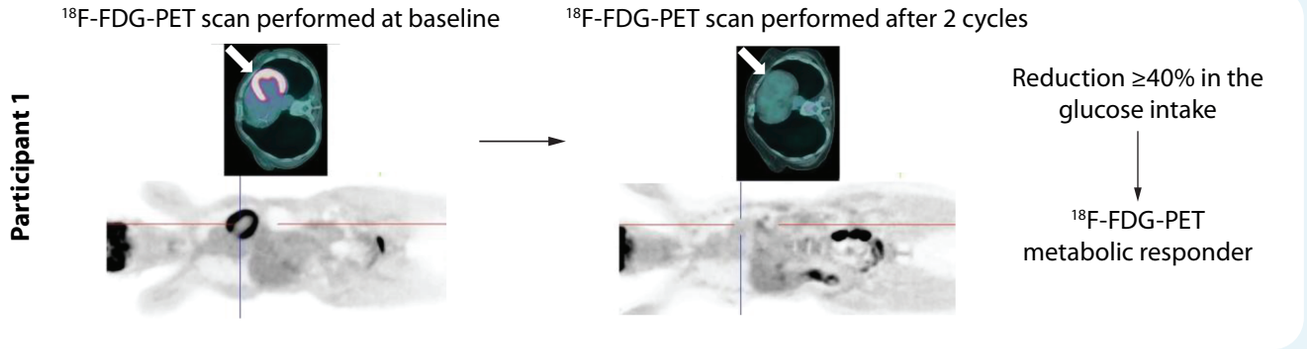
If participants who received trastuzumab and pertuzumab alone (group B) had HR-positive tumor, they received additional hormone therapy that slows or stops the growth of hormone-sensitive tumors. Hormone therapies are the standard treatments for HR-positive breast cancers and the addition of chemotherapy to hormone therapy is solely marginally beneficial. That is why participants in group A with HR-positive tumors did not receive additional hormone therapy to chemotherapy, trastuzumab and pertuzumab.

Both the participant and their doctor knew which treatment they were taking.

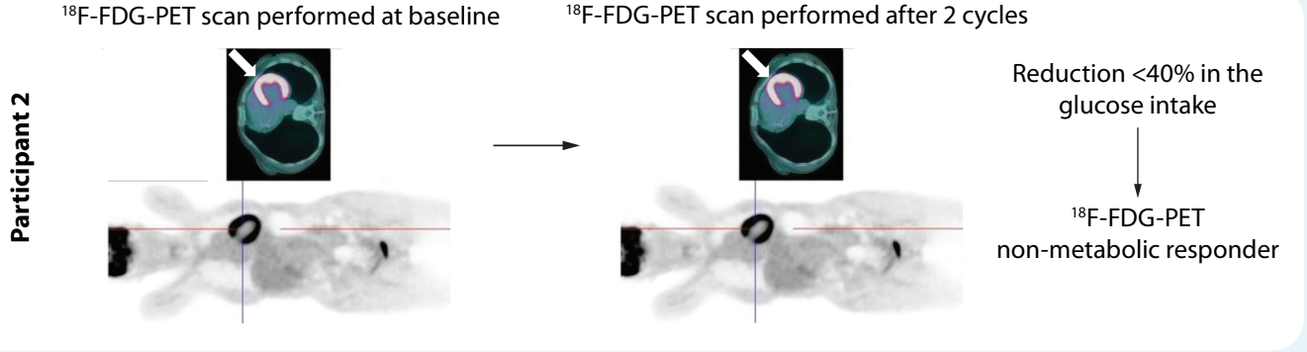
The rate of glucose intake in tumor cells of all patients included in the study was monitored by ^{18}F-FDG-PET scan before starting treatment and after 2 treatment cycles.

If tumor cells showed a reduction of at least 40% in the glucose intake after 2 cycles of treatment, participants were considered as **'^{18}F-FDG-PET metabolic responders'**. These participants continued to receive the same treatment without chemotherapy for 6 further cycles.





In comparison, all other participants that did not show a reduction of at least 40% in the glucose intake were deemed **'^{18}F-FDG-PET non-metabolic responders'**. These participants switched to 6 cycles of chemotherapy plus trastuzumab and pertuzumab.



Participants assigned to group A completed 6 cycles of treatment regardless of ^{18}F-FDG-PET results.
All participants had definitive surgery after completing the assigned treatment.
Additional cancer treatment was administered after surgery to lower the risk that the cancer will come back.

1 year

Participants from both therapy groups received post-surgery treatment with trastuzumab and pertuzumab to complete 1 year, in combination with hormone therapy and radiation therapy according to HR status and institutional practices, unless the cancer came back, or the participant decided to stop treatment for other reasons.

Participants assigned to group B who did not have a disappearance of all invasive cancer in the breast and axillary lymph nodes at surgery received an additional 6 cycles of chemotherapy plus trastuzumab and pertuzumab, then 4 cycles of trastuzumab and pertuzumab.

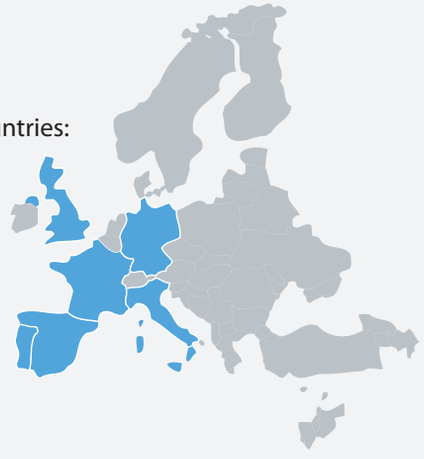
Who participated in the study?

26 June 2017 → 24 April 2019

376 participants

45 hospitals

Seven European countries:
- Germany
- Italy
- France
- Belgium
- Spain
- Portugal
- United Kingdom



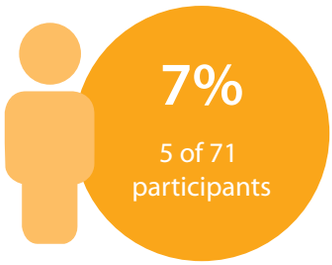
The characteristics of participants included in each treatment group were similar:

- were aged 42–59 years and the median age was 50 years
- around half the participants were postmenopausal
- approximately two-thirds of participants had stage II breast cancer
- in around half of the participants axillary lymph nodes contained cancer
- approximately two-thirds of participants had HR-positive status, meaning their tumor had on the cell membrane receptors of estrogen and/or progesterone
- All participants had HER2-positive breast cancer, and approximately 80% of those had high expression of HER2 (score 3+)

Percentage of participants who discontinued the study before surgery:

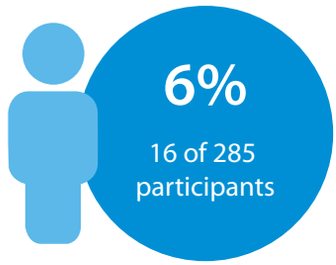
Reasons for discontinuing:

Group A



- 3 participants experienced serious side effects
- 2 participants withdrew the informed consent form

Group B



- 7 participants had a worsening of disease that spreads in other parts of the body
- 5 participants withdrew the informed consent form
- 2 participants had a protocol violation
- 1 participant for investigator's decision
- 1 participant experienced serious side effects

What were the overall results of the study?

Almost **38%** of ^{18}F-FDG-PET metabolic responders in group B achieved a total disappearance of invasive cancer in the breast and axillary lymph nodes.

This appears to be higher than the percentages reported in previous studies evaluating the same treatment.

Group A

58%

had higher disappearance of all invasive cancer in the breast and axillary lymph nodes

Group B

35%

had higher disappearance of all invasive cancer in the breast and axillary lymph nodes

Participants with HR-negative tumors in group A, but not in group B, achieved higher pathological complete response rates than those with HR-positive tumors.

The pathological complete response rate was higher in participants with a high expression of HER2 (score 3+) than in those with a moderate expression (score 2+) both in group A and group B.

What were the most common adverse events?

The doctors kept track of the adverse events that the participants had during the study. An adverse event is any side effect that participants have during a study. An adverse event is considered serious when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the treatments in the study. A lot of research is needed to know whether a treatment causes an adverse event.

The results below include information for the 68 participants in group A and 283 participants in group B who had received at least one dose of treatment.

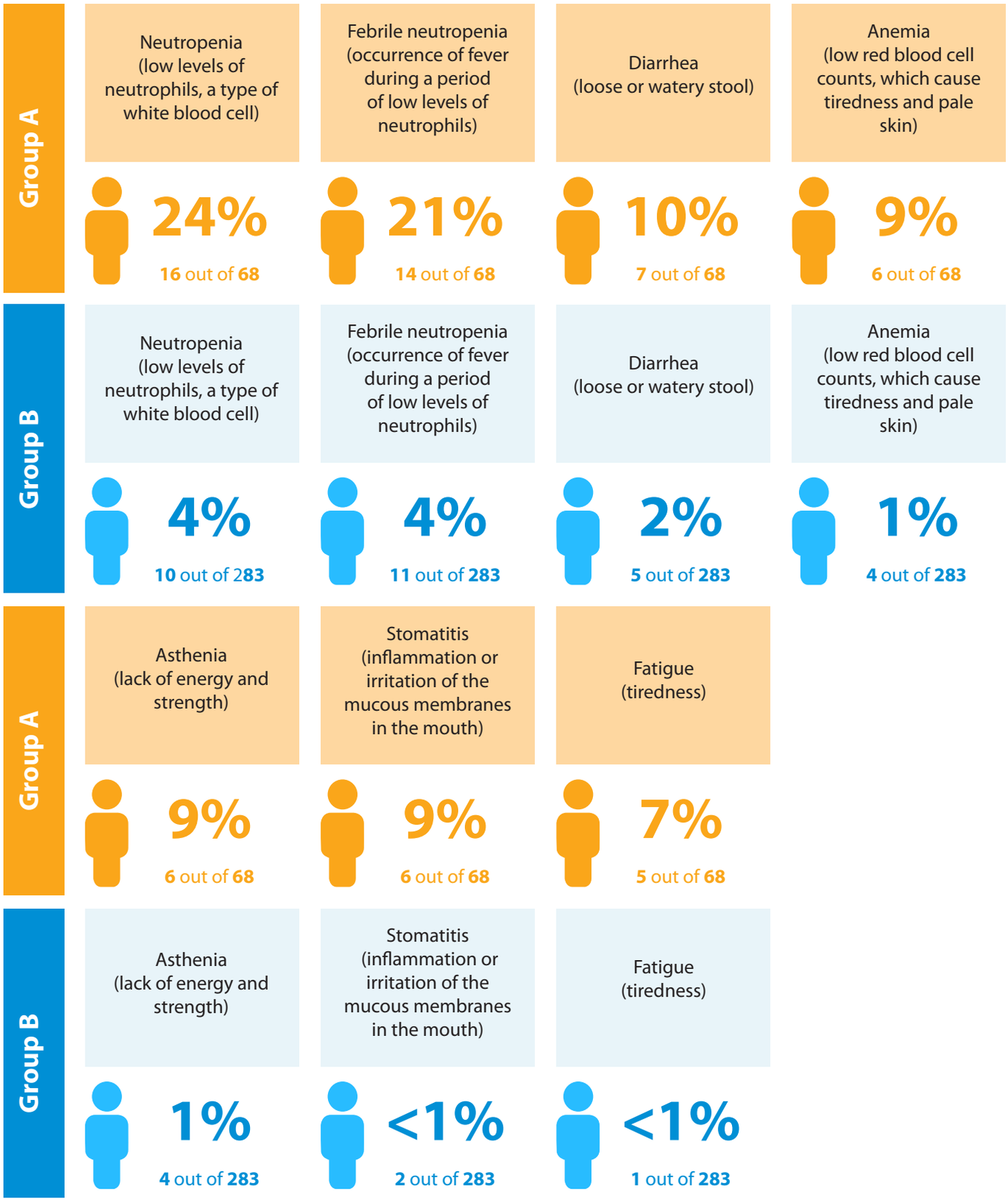
Group A

How many participants experienced serious adverse events?	Percentage of participants with grade 3–4 (moderate–severe) adverse events:	Percentage of participants who received a reduced amount of treatment during the study due to adverse events:	Percentage of participants with treatment stopped due to the adverse events severity:
29%	**59%**	**40%**	**4%**
20 out of **68**	**40** out of **68**	**27** out of **68**	**3** out of **68**

Group B

How many participants experienced serious adverse events?	Percentage of participants with grade 3–4 (moderate–severe) adverse events:	Percentage of participants who received a reduced amount of treatment during the study due to adverse events:	Percentage of participants with treatment stopped due to the adverse events severity:
5%	**12%**	**7%**	**<1%**
13 out of **283**	**34** out of **283**	**21** out of **283**	**1** out of **283**

What were the most common grade 3–4 (moderate–severe) adverse events?



No new cardiac adverse events were observed.
No deaths (overall and treatment-related deaths) were reported.
We also measured the participant-reported quality of life, which can be defined as the patient's ability to enjoy normal life activities through the evaluation of physical, psychological, social and spiritual parameters. The study showed that participants assigned to group B experienced a lower decline in the overall quality of life than participants assigned to group A (35.5% versus 65.0%, respectively).

What do the results of this study mean?

- The study results showed that ^{18}F-FDG-PET could represent a useful tool to identify patients with HER2-positive breast cancer who could be treated before surgery with trastuzumab and pertuzumab without chemotherapy.
- Higher levels of HER2 protein seem to be a reliable marker for predicting those patients who are likely to benefit from regimen with trastuzumab and pertuzumab without chemotherapy.
- As expected, treatment that did not include chemotherapy was associated with fewer side effects and substantial improvement in health-related quality of life, representing a main goal for participants treated with curative intent.
- In previous studies investigating the efficacy of HER2-targeting agents without chemotherapy in early-stage disease, post-surgery treatment was administered at the physician's discretion and most of these participants received chemotherapy. However, in the PHERGain study, up to a third of participants will not receive chemotherapy at any time.
- Evaluating the rate of participants who survive without any signs or symptoms of cancer at 3 years from surgery (also called as 3-year invasive disease-free survival) is crucial to understand whether participants who avoid chemotherapy have a similar outcome to participants receiving chemotherapy plus trastuzumab and pertuzumab.

The PHERGain clinical study is still ongoing and more results are expected to be released in 2023.

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

You can read the original article published in the journal *The Lancet Oncology* at:
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00122-4/fulltext

Who sponsored this study?

This study was sponsored by F Hoffmann-La Roche.

Where can I find more information?

The full title of the original publication in *The Lancet Oncology* is: "Chemotherapy de-escalation using an ^{18}F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial"
You can read the original article at (by paying a fee as the article is not open-access): https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00122-4/fulltext
You can read more about the PHERGain clinical study on the following websites:

- ClinicalTrials.gov: www.clinicaltrials.gov/ct2/show/NCT03161353
- The European Union Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002676-27/GB

Educational resources

Learn about the European Society for Medical Oncology (ESMO) clinical practice guidelines for the treatment of breast cancer. These guidelines assist physicians in determining the best treatment for their patients. Read the guidelines for patients at:

- https://www.esmo.org/for-patients/patient-guides/breast-cancer

Financial & competing interests disclosure

Full author disclosure information can be found in the original article.

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