

A plain language summary of the CheckMate 649 study: nivolumab in combination with chemotherapy compared to chemotherapy alone for untreated advanced or metastatic cancer of the stomach or esophagus

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Summary

What is this summary about?

This is a summary of the 1-year results of a clinical research study known as CheckMate 649 published in *The Lancet* in June 2021. The 2-year results on the participants' health and overall quality of life from the same study are in a second publication in *Nature* in March 2022. Until recently, chemotherapy was the only first treatment option for people with advanced or metastatic gastroesophageal adenocarcinoma who had not been treated before. Patients receiving chemotherapy lived on average for less than 1 year. Nivolumab is an immunotherapy that works by activating a person's immune system to fight back against cancer cells. The goal of CheckMate 649 was to find out if the combination of nivolumab and chemotherapy would help patients with advanced or metastatic gastroesophageal adenocarcinoma live longer and without their cancer getting worse.

What were the results?

Results from the final analysis are reported here. Of 1581 people who took part in the study, 789 received nivolumab and chemotherapy and 792 received chemotherapy. Researchers found that, on average, participants who received nivolumab and chemotherapy lived longer overall than those who received chemotherapy alone. The length of time participants lived without their cancer getting worse was also longer on average with nivolumab and chemotherapy than chemotherapy treatment alone. However, more participants in the nivolumab and chemotherapy group had side effects than those in the chemotherapy group. The three most common side effects in both types of treatment were nausea (urge to vomit), diarrhea and peripheral neuropathy. Participants who received nivolumab and chemotherapy had a lower risk of their cancer symptoms worsening and reported that they were 'less bothered' from side effects of treatment than those receiving chemotherapy alone.

What do the results mean?

The nivolumab and chemotherapy combination is considered a new standard treatment option and is approved in several countries as a treatment for adults who have not been treated before for their advanced or metastatic gastroesophageal cancer based on results from CheckMate 649.

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

- **Nivolumab:** nih-VOL-yoo-mab
- **Adenocarcinoma:** A-deh-noh-KAR-sih-NOH-muh
- **Esophagus:** ee-SAH-fuh-gus
- **Gastroesophageal:** GAS-troh-ee-SAH-fuh-JEE-ul

Glossary

PD-L1: Programmed death ligand 1

CPS: Combined positive score

Immunotherapy: Treatment that works by activating a patient's immune system to fight back against cancer cells

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

The original article, "First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial", was published in *The Lancet* (Janjigian YY, *et al. Lancet* 398, 27–40 [2021]):

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00797-2/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00797-2/fulltext)

You can read the accepted version of the full article for free at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8436782/>

Additional results with longer length of follow-up of participants from CheckMate 649, including results from other parts of the study, were published in *Nature* (Shitara K, *et al. Nature* 603, 942–948 [2022]). You can read the full article for free at:

<https://doi.org/10.1038/s41586-022-04508-4>

Who is this article for?

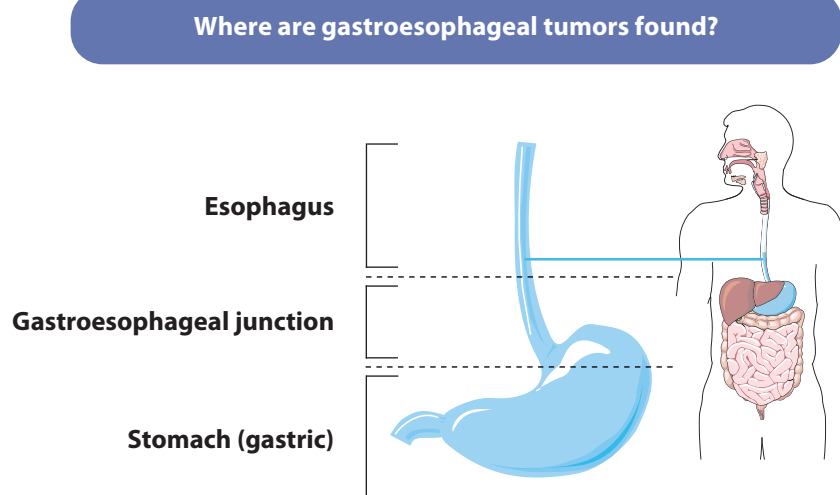
This summary was written by the authors of the original article for people who want to learn about the results of the CheckMate 649 study.

Who sponsored this study?

This study was sponsored by Bristol Myers Squibb, in collaboration with Ono Pharmaceutical.

What is metastatic or advanced gastric, gastroesophageal junction and esophageal adenocarcinoma?

- Gastric cancer is cancer of the stomach
- Esophageal cancer is cancer of the esophagus, which is the tube that passes from the mouth to the stomach
- Gastroesophageal junction cancer is cancer of the place where the esophagus is connected to the stomach



Participants in CheckMate 649 had a type of cancer called adenocarcinoma. This is a type of cancer found in the lining of the stomach, the esophagus or the gastroesophageal junction. Esophageal adenocarcinoma is often found in the lower one-third portion of the esophagus. Adenocarcinoma is the most common type of cancer that affects the stomach and gastroesophageal junction. It is also the second most common type of cancer of the esophagus. Participants had tumors that were not removable by surgery and had invaded nearby tissue or lymph nodes (also known as locally advanced) or had spread out from the stomach or esophagus to distant parts of the body (also known as metastatic).

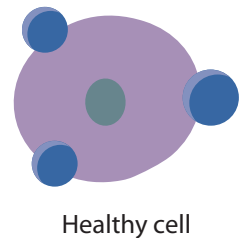
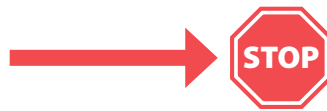
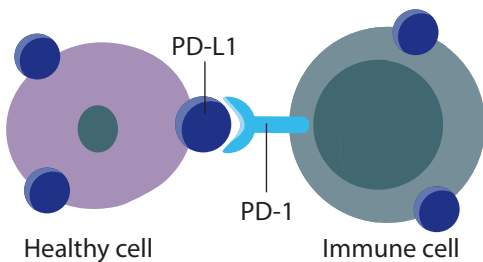
How does nivolumab work?

Nivolumab is a type of immunotherapy that works by helping the body's immune system recognize and kill cancer cells.

Healthy cells have proteins called immune checkpoints on their surface, like programmed death ligand 1 (PD-L1).

Immune cells have an additional checkpoint on their surface called programmed death-1 (PD-1) that recognizes and sometimes attaches to PD-L1.

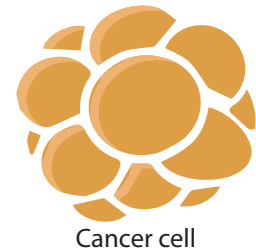
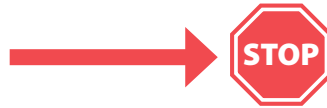
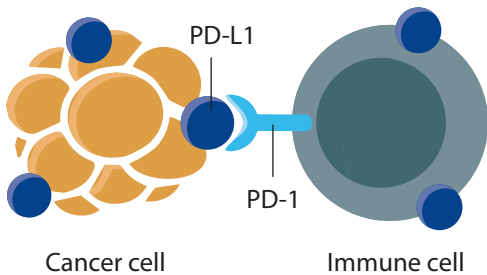
This attachment of PD-1 to PD-L1 stops the immune system from killing the healthy cells.



But many types of cancer cells also have PD-L1 on their surface.

When PD-1 on the immune cell attaches to PD-L1 on a cancer cell, the immune cell does not get activated.

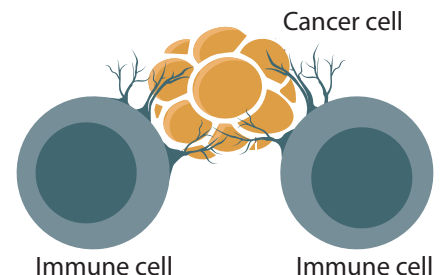
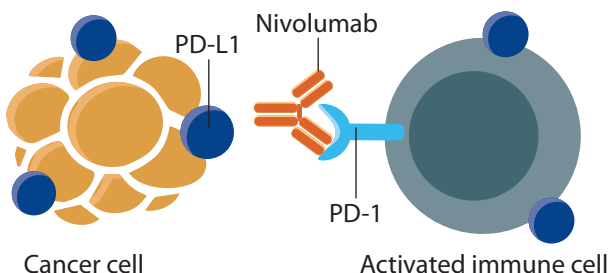
The attachment of PD-1 to PD-L1 also helps cancer cells avoid destruction by immune cells.



Immune checkpoint inhibitors are drugs that block checkpoint proteins like PD-1 on immune cells and stop them from attaching to cancer cells. Nivolumab is an immune checkpoint inhibitor.

Nivolumab attaches to PD-1 on the immune cells before they are able to attach to PD-L1 on the cancer cells.

Blocking PD-1 from attaching to PD-L1 helps the immune cells get activated. They can now recognize and kill the cancer cells.



What are biomarkers?

Biomarkers are measurable characteristics of your body. These can be images from X-rays, laboratory values of molecules in the blood or tissue or a score based on a combination of factors. Biomarkers are signs of a normal process in the body or of a condition or disease. In cancer, these markers can tell doctors about the specific kind of cancer and the stage of a tumor. They can also help determine how well a patient may respond to a treatment for their cancer. The CheckMate 649 study looked at the following biomarkers, which are considered important biomarkers by doctors based on previous studies in gastroesophageal adenocarcinoma:

- **PD-L1 combined positive score (PD-L1 CPS):** this tells how much PD-L1 protein is present on tumor cells and immune cells near the tumor. Reports indicate that higher PD-L1 CPS values may be associated with how well an immune checkpoint inhibitor could work in people with gastroesophageal adenocarcinoma. Therefore, doctors may look at the PD-L1 CPS value when choosing immune checkpoint inhibitors like nivolumab. In CheckMate 649, researchers looked at participants who had PD-L1 CPS value of 5 or higher to see how well nivolumab and chemotherapy worked over chemotherapy alone
- **Human epidermal growth factor receptor 2 (HER2):** this is a protein found on tumor cells of some people with gastroesophageal cancer, and the resulting tumor is called HER2 positive
 - Treatment options are different for people whose tumors are not HER2 positive compared with those whose are HER2 positive
 - Chemotherapy is the standard treatment option for people whose tumors are not HER2 positive
 - The CheckMate 649 study looked at people who **were not** known to have HER2-positive tumors
- **Microsatellite instability-high (MSI-H):** when cells divide, new cells with new DNA are made. This new DNA sometimes contains errors. Some cancer cells are unable to correct these errors, leading to permanent changes. Certain types of changes are found in repeated stretches of DNA called microsatellites. If a lot of these changes are detected in microsatellites of cancer cells, it is called microsatellite instability-high cancer. These types of cancer cells often respond well to immune checkpoint inhibitors like nivolumab

Why was the CheckMate 649 study conducted?

For decades, chemotherapy has been the standard treatment for people with advanced or metastatic, HER2-negative gastroesophageal cancer who have not been treated for this type of cancer before. However, half of the people who receive chemotherapy as their first treatment for this cancer live for less than 1 year. New treatments are needed that can help people with cancer live longer.

Before CheckMate 649, nivolumab given on its own was shown to be effective in people with metastatic gastroesophageal cancer who had received prior treatment. People on nivolumab lived longer overall when compared to placebo. A placebo looks the same and is given the same way as the study drug but contains no active medication.

What is chemotherapy?

Chemotherapy is a type of treatment that stops the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Researchers studying the anticancer effects of chemotherapy gave mice chemotherapy together with an immune checkpoint inhibitor similar to nivolumab. The combination killed more cancer cells than chemotherapy alone, possibly due to an improved effect of the immune checkpoint inhibitor on the immune system. The researchers then asked if a combination of nivolumab and chemotherapy would be a better treatment for cancer than chemotherapy alone. The main purpose of CheckMate 649 was to study if the nivolumab and chemotherapy combination worked in a large number of people with gastroesophageal cancer who had not had treatment before and if it was safe compared with standard chemotherapy.

What did the CheckMate 649 study look at?

To see if the treatment worked, researchers looked at the results from participants in two ways based on their PD-L1 CPS value:

- Only participants who had a PD-L1 CPS value of 5 or higher
- All participants (no matter what their PD-L1 CPS values were)

Having two groups helped researchers decide if the participant's PD-L1 CPS value impacted how they responded to the nivolumab and chemotherapy treatment.

Researchers asked the following two main questions:

- ? How long did participants who had PD-L1 CPS of 5 or higher live overall?
- ? How long did participants who had PD-L1 CPS of 5 or higher live before their cancer got worse?

These two questions were also asked for all study participants, no matter what their PD-L1 CPS values were.

Researchers also asked the following questions:

- ? Did the participants' tumors shrink in size or disappear?
- ? How long did the participants' tumors shrink or disappear before growing again?
- ? What were the side effects from treatment?
- ? How did participants feel about their health and quality of life before, during, and after treatment?

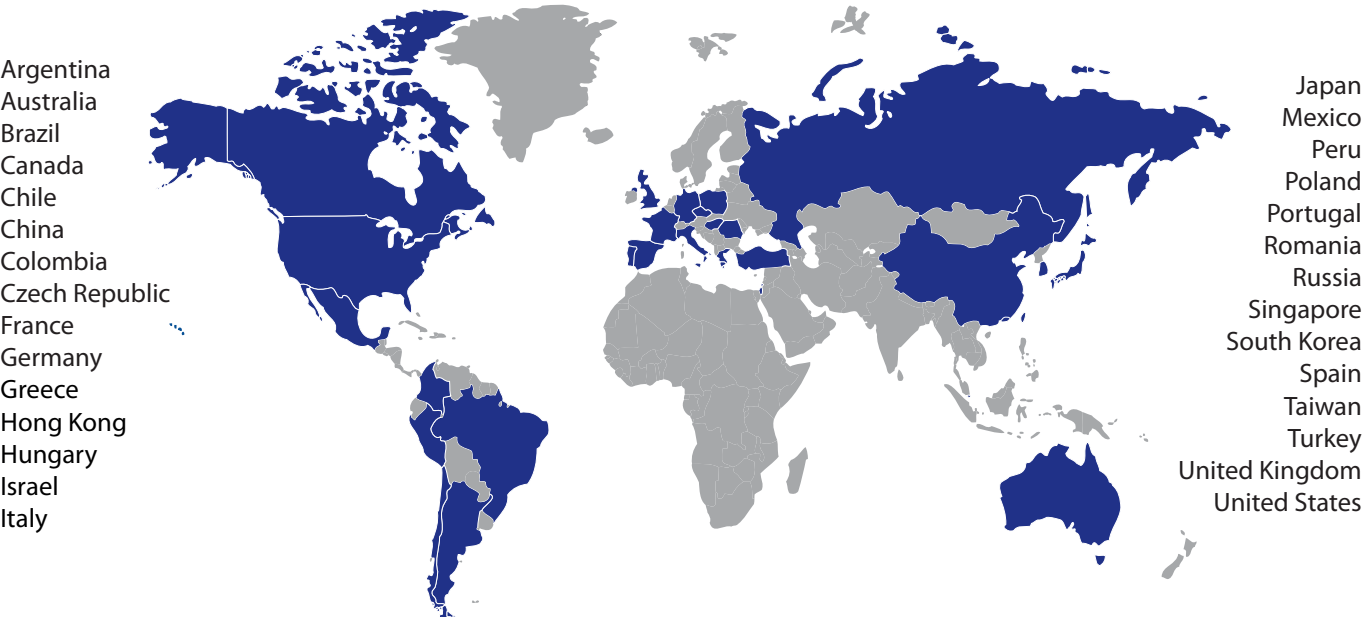
Who took part in the CheckMate 649 study?

In total, 1581 people took part in the study:

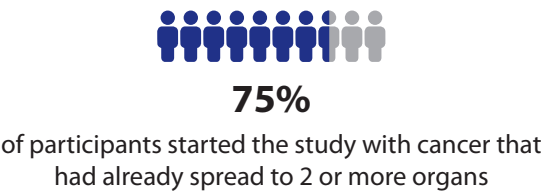
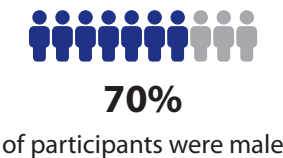
- All of them had gastroesophageal cancer that was advanced or metastatic and could not be removed by having surgery
- All of them had tumors that could be identified using a computed tomography scan, also called a CT scan, or by magnetic resonance imaging (MRI). These scans look inside the body without the need for surgery
- All of them were fully active or able to carry out light daily activities
- None of them had any treatment for their advanced or metastatic cancer before
- None of them had known HER2-positive tumors

Where did the study take place?

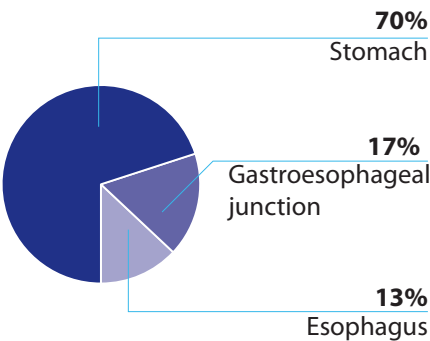
This study took place at hospitals in **29 countries** across the world:



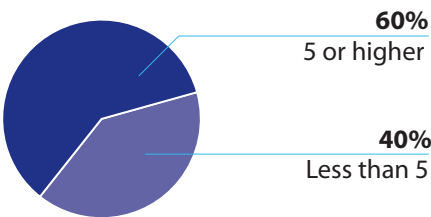
Key characteristics of participants at the start of the study



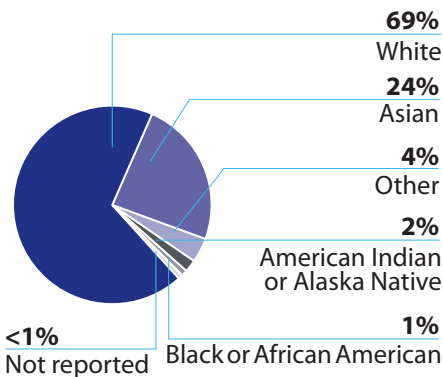
Location of tumors



PD-L1 CPS value

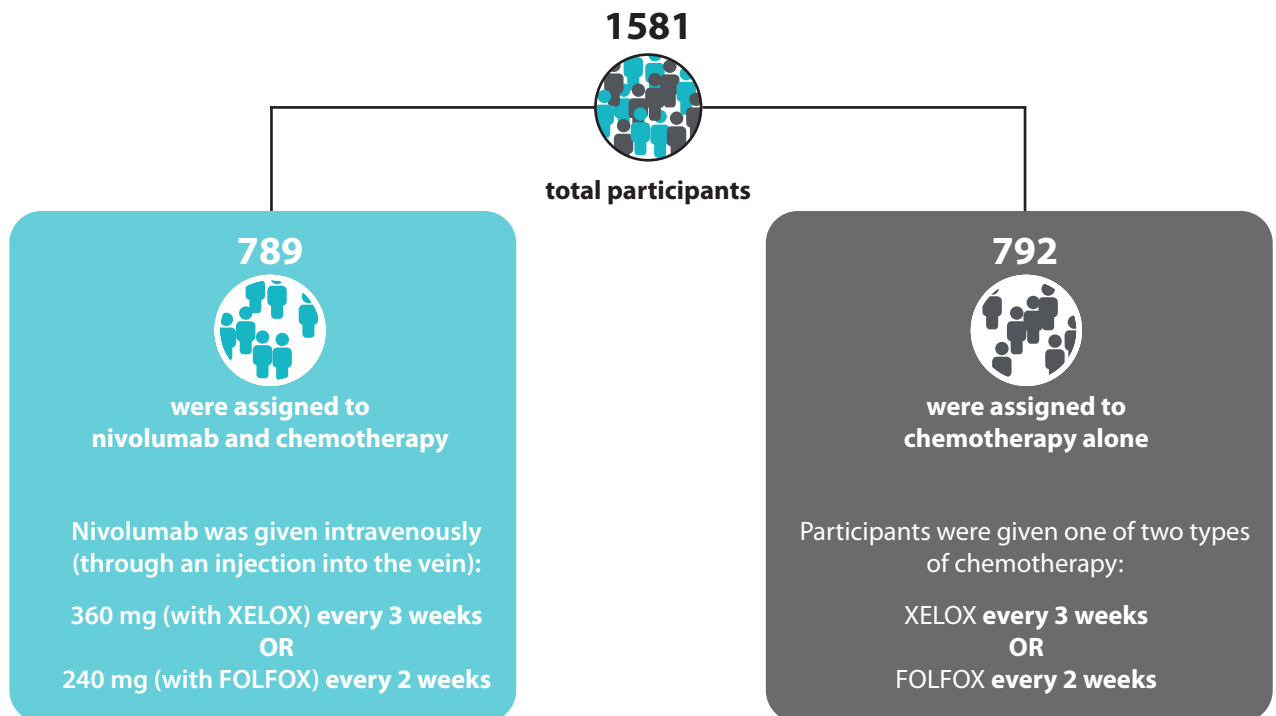


Diversity



How was the CheckMate 649 study done?

- This was an open-label study, which means both the doctor and the participant knew what drug or treatment was being given
- The part of the CheckMate 649 study that looked at participants receiving nivolumab and chemotherapy or chemotherapy alone began on 27 March 2017, and enrolled people until 24 April 2019
- Participants with metastatic gastroesophageal cancer were enrolled and assigned by chance (also called randomized) to two separate groups



XELOX is a combination of capecitabine (oral [taken by mouth]) and oxaliplatin (intravenous).
FOLFOX is a combination of leucovorin, fluorouracil, and oxaliplatin (all intravenous).

XELOX and FOLFOX were considered standards of care and the decision regarding which regimen was chosen was made by the participant and their doctor.

- If either nivolumab or any part of the chemotherapy treatment were stopped, participants could continue to receive the other parts of the treatment
- Participants kept getting treatment until their disease got worse, they had side effects that caused them to discontinue their treatment, they did not want to be in the study anymore, or the study ended
- Nivolumab was given for a maximum of 2 years. Chemotherapy was given per local standards
- CheckMate 649 also looked at the immunotherapy-only combination of nivolumab with ipilimumab, another type of immune checkpoint inhibitor, in a separate set of 409 participants; the results from that part of the study are not described here

What were the main findings of the CheckMate 649 study?

1 How long did the participants live?

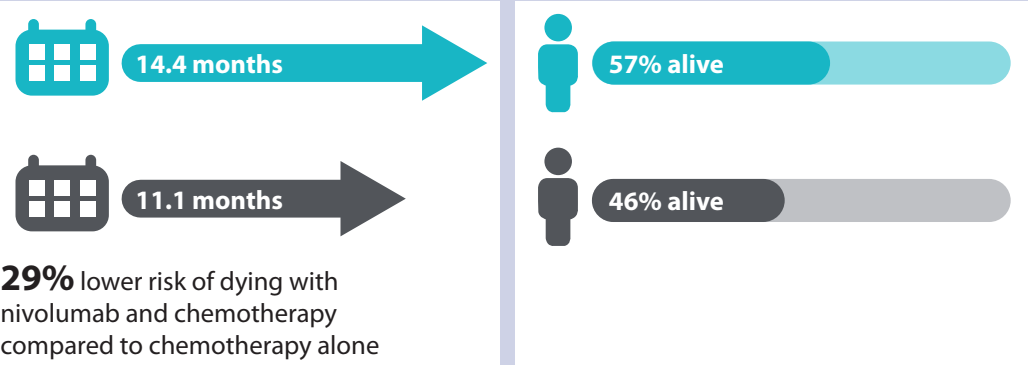
On average, participants who received the nivolumab and chemotherapy combination lived longer overall compared with participants who received chemotherapy alone. This is called overall survival. This result was seen in participants who had PD-L1 CPS of 5 or higher and in all participants

Median overall survival
(number of months half of the participants lived overall; some participants may have lived for a longer or shorter amount of time)

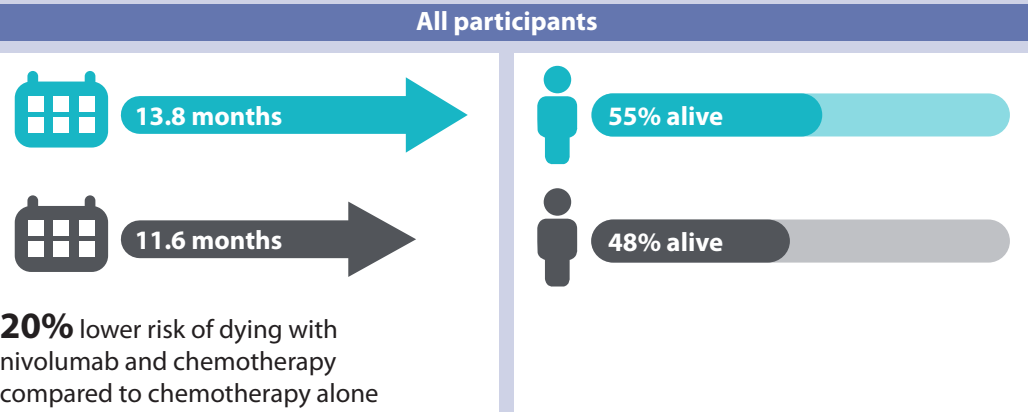
Participants who were alive at 1 year

Participants who had PD-L1 CPS of 5 or higher

- Nivolumab and chemotherapy (473 participants)
- Chemotherapy (482 participants)



- Nivolumab and chemotherapy (789 participants)
- Chemotherapy (792 participants)



More participants who received nivolumab and chemotherapy were alive at 1 year compared with participants who received chemotherapy alone

The risk of dying was even lower (by 63%-67%) in participants who had **MSI-H tumors** and received nivolumab and chemotherapy (23 participants) compared with participants who received chemotherapy alone (21 participants). However, this subanalysis did not have sufficient number of participants (44 in total, 3% of all participants) to fully determine the benefit of nivolumab and chemotherapy in participants with MSI-H tumors

2

How long did the participants live before their cancer got worse?

On average, participants who received the nivolumab and chemotherapy combination lived longer without their cancer getting worse or spreading compared with participants who received chemotherapy alone. This is called progression-free survival. This result was seen in participants who had PD-L1 CPS of 5 or higher and in all participants

Median progression-free survival
(number of months half of the participants lived without their cancer getting worse; some participants may have lived for a longer or shorter amount of time without their cancer getting worse)

Participants who were alive at 1 year without their cancer getting worse

Participants who had PD-L1 CPS of 5 or higher

Nivolumab and chemotherapy
(473 participants)



7.7 months

Chemotherapy
(482 participants)



6.0 months

32% lower risk of cancer getting worse or dying with nivolumab and chemotherapy compared to chemotherapy alone



36%

alive without their cancer getting worse



22%

alive without their cancer getting worse

All participants

Nivolumab and chemotherapy
(789 participants)



7.7 months

Chemotherapy
(792 participants)



6.9 months

23% lower risk of cancer getting worse or dying with nivolumab and chemotherapy compared to chemotherapy alone



33%

alive without their cancer getting worse



23%

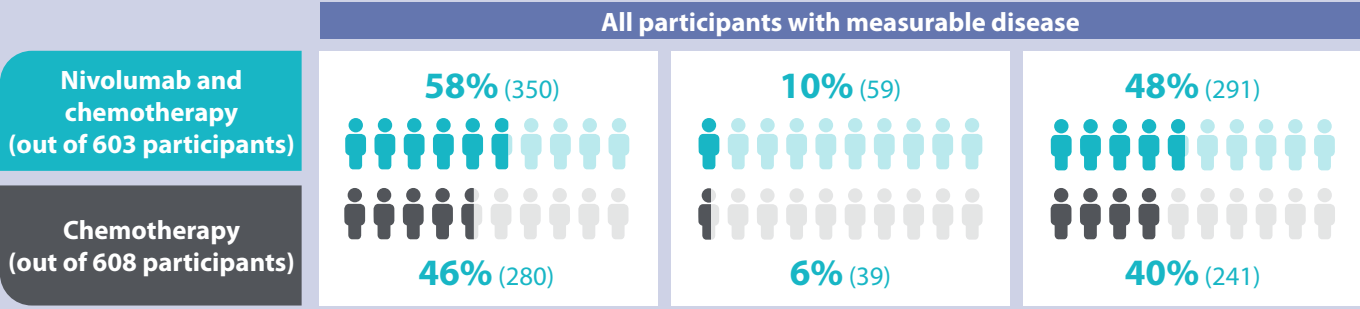
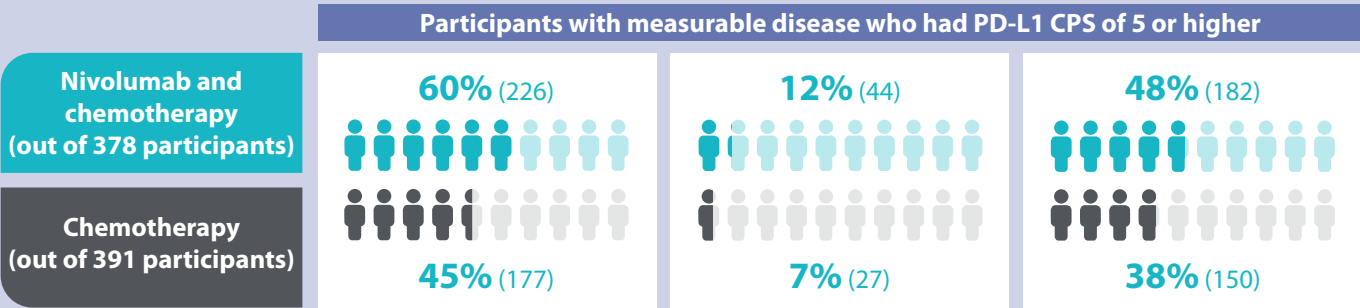
alive without their cancer getting worse

More participants who received nivolumab and chemotherapy were alive at 1 year without their cancer getting worse compared with participants who received chemotherapy alone

3 How many participants had their tumors get smaller?

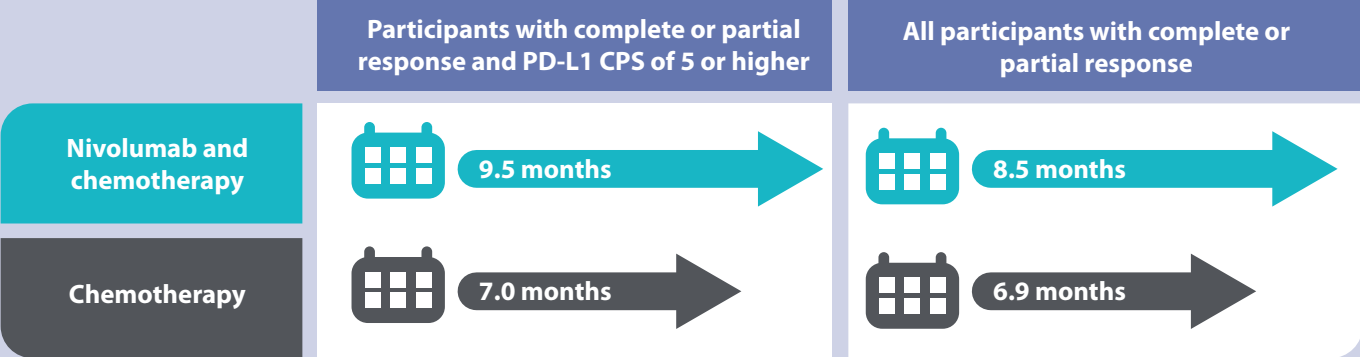
Researchers looked at change in tumor size in participants who had tumors that could be measured using a CT scan or by MRI (also known as measurable disease). More participants who received nivolumab and chemotherapy had cancer that shrank or disappeared compared with those who received chemotherapy alone

Objective response rate (percentage of participants whose cancer shrank by 30% or more or disappeared after treatment)	Complete response (tumors completely disappeared)	Partial response (tumors shrank by 30% or more)
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On average, the length of time tumors remained shrunk or disappeared completely was longer in participants who responded to nivolumab and chemotherapy compared with those who responded to chemotherapy alone

Median duration of response
(number of months half of the participants with a complete or partial response continued to have tumors that shrunk or disappeared)



What were the side effects in the CheckMate 649 study?

When doctors decide which drugs to use, they look at the side effects that are related to treatment. This helps them determine the risks associated with the treatment and if the benefits outweigh the risks.

These side effects may be **mild**, **moderate** or **severe**:

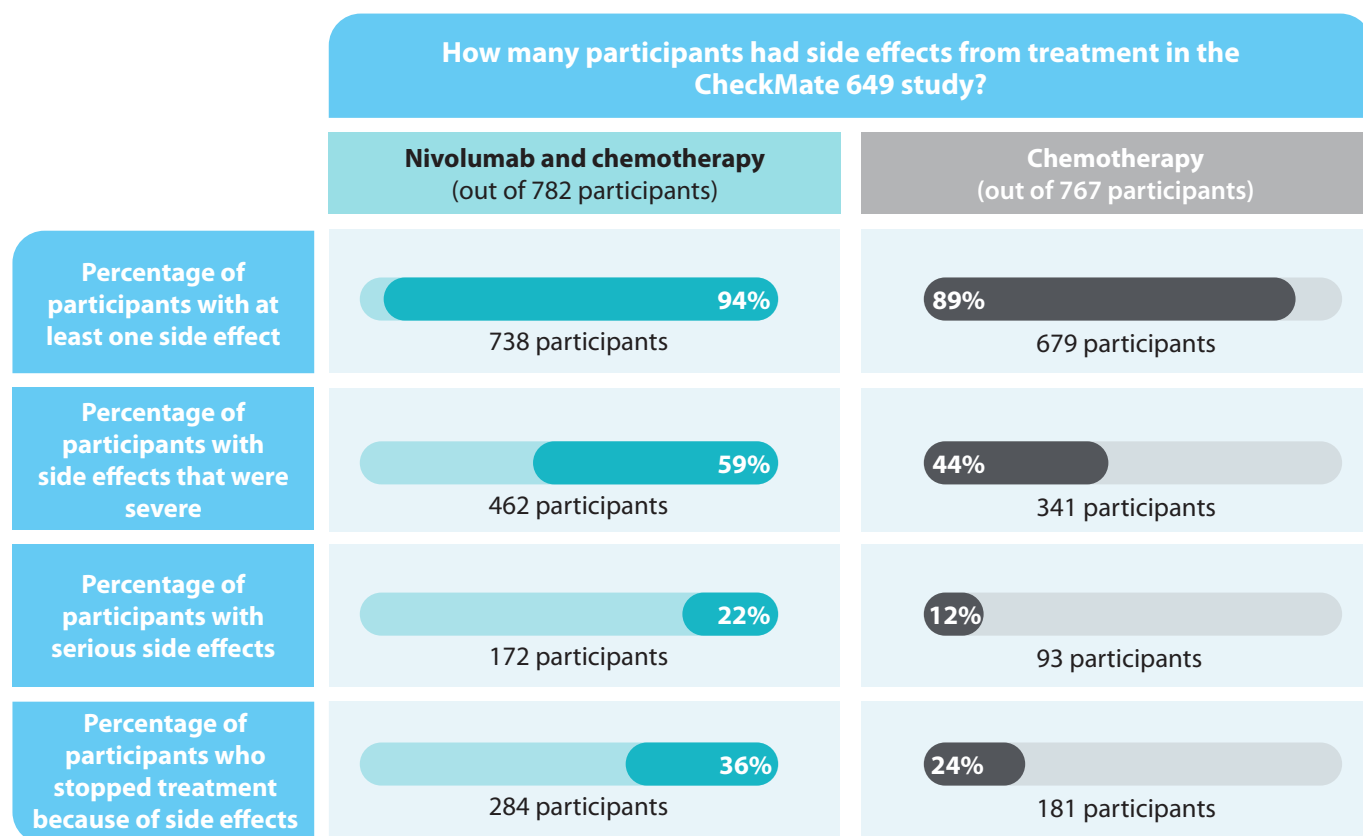
Mild	Moderate	Severe
Brief side effects that do not affect daily activities or need to be treated	Side effects that may affect daily activities but are usually improved with simple therapies	Side effects that affect daily activities. This type of side effect needs urgent treatment at a hospital and may have a risk of death

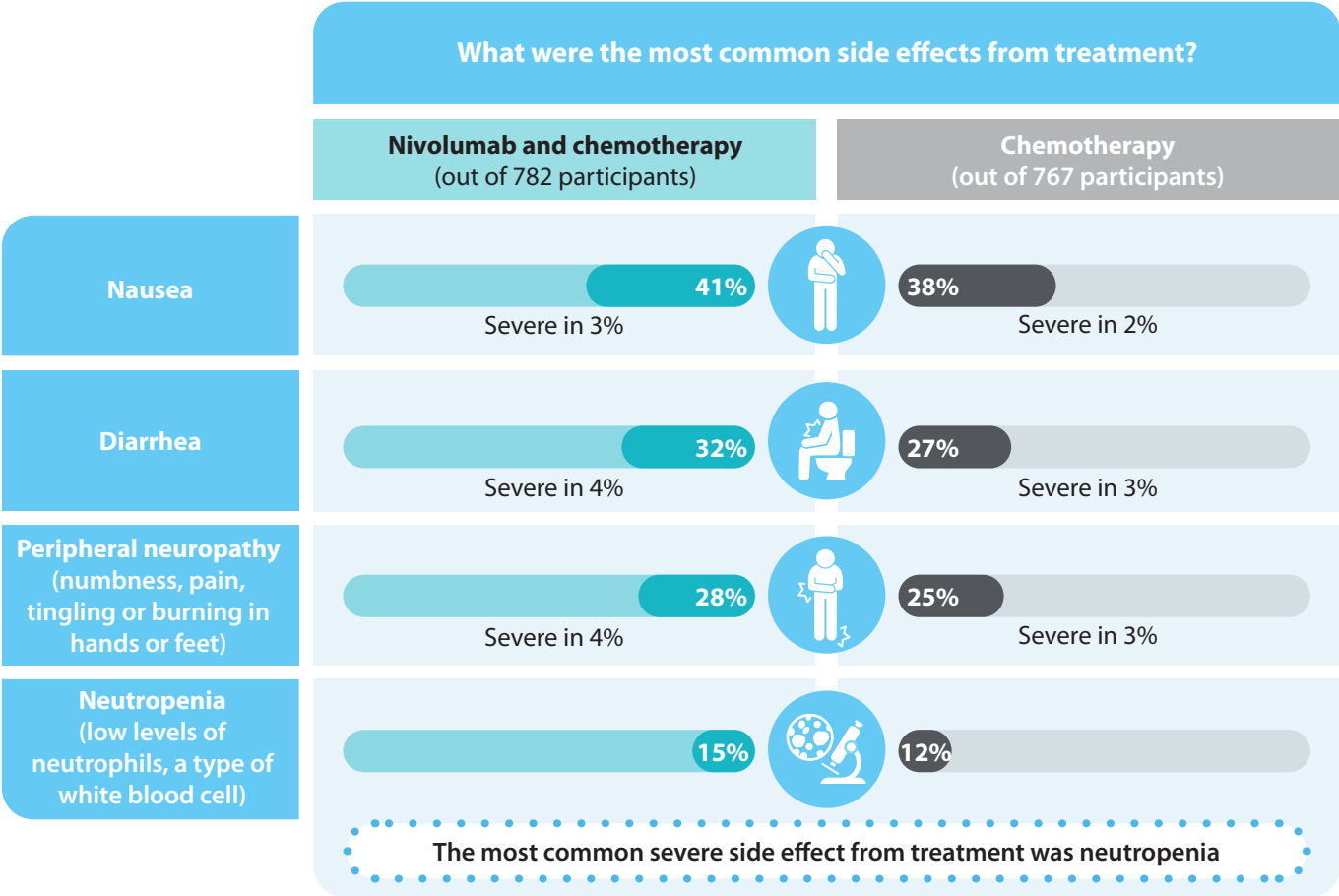
Side effects are considered serious if they are life-threatening, cause permanent damage or birth defects, result in the participant having to go to the hospital, or if they result in the participant's death.

In CheckMate 649, researchers regularly checked how the treatments were tolerated in all participants who received at least 1 dose of their assigned study treatment. Side effects were checked for up to 30 days after the last dose of study treatment, even in participants who left the study. Researchers also recorded if participants left the study because of a side effect from treatment.

- 782 participants received at least 1 dose of nivolumab and chemotherapy
- 767 participants received at least 1 dose of chemotherapy

There were 32 participants in the study (7 assigned to nivolumab and chemotherapy, 25 assigned to chemotherapy) who left the study early before they received any dose of study treatment. These participants were not asked about side effects.





Because nivolumab boosts immune cells to fight the cancer, it may also result in overactivity of the immune system. This may cause inflammatory side effects that are immune related and can affect the stomach and intestines, liver, lungs, kidney, skin or glands that secrete hormones

- These side effects may happen anytime during treatment or even after the treatment has ended
- These side effects can be controlled by treatment with immunosuppressants (a type of drug that reduces the strength of the body's immune system) or hormonal therapy
- Depending on the organ, this type of side effect happened in 3% to 34% of participants who received nivolumab and chemotherapy and in <1% to 27% of participants who received chemotherapy alone
- The majority of these cases were mild, and only 5% or fewer of these cases were severe

The side effects that the researchers saw with nivolumab and chemotherapy were similar to the known side effects of the individual treatments

How did participants feel about their treatment?

In CheckMate 649, participants filled out a questionnaire called Functional Assessment of Cancer Therapy – Gastric (FACT-Ga) every 6 weeks from randomization to say how they were feeling about their health and overall quality of life. The time it took for a participant to report worsening of their cancer symptoms or health status with nivolumab and chemotherapy and with chemotherapy alone was recorded. Worsening was determined by a clinically meaningful reduction in their score on the Gastric Cancer Subscale.

Participants who had PD-L1 CPS of 5 or higher

36% lower risk of their cancer symptoms worsening with nivolumab and chemotherapy compared to chemotherapy alone

All participants

23% lower risk of their cancer symptoms worsening with nivolumab and chemotherapy compared to chemotherapy alone

Participants were also asked to respond to the statement “I am bothered by side effects of treatment”. They had to choose from one of the following responses: “very much,” “quite a bit,” “somewhat,” “a little bit,” or “not at all.” Researchers asked this question at multiple timepoints over the course of two years. The results of this analysis were published separately in *Nature*. They found that at more timepoints, a higher percentage of participants receiving nivolumab and chemotherapy said that they were “not at all” bothered by the side effects of treatment (25–100%) than those receiving chemotherapy (21–44%).

Did any participants die because of treatment?

- 16 participants who received nivolumab and chemotherapy died because of side effects from treatment
 - Doctors thought that 7 of these deaths were from the chemotherapy part of the treatment
- 4 participants who received chemotherapy alone died because of side effects from treatment
- The number of participants who died from side effects after receiving nivolumab and chemotherapy was comparable to other clinical trials that used combinations of PD-1 inhibitors and chemotherapy for the treatment of cancer

What do the results of the CheckMate 649 study mean?



The CheckMate 649 study was important because it led to a new treatment option for patients with gastroesophageal cancer who had not been treated previously for their advanced or metastatic cancer

Researchers looked at participants who had PD-L1 CPS value of 5 or higher and all participants. They found that, compared to participants who received chemotherapy by itself, participants who received nivolumab along with chemotherapy



Lived longer on average overall



Lived longer on average without their cancer getting worse or spreading



Kept up their quality of life



Were more likely to have their tumors shrink or disappear and had a longer period of time until their cancer came back



Had side effects like those seen with other combinations of PD-1 inhibitor drugs and chemotherapy

The **nivolumab and chemotherapy combination** is approved in several countries and is considered a new standard treatment for patients with gastroesophageal cancer who have not been previously treated for their advanced or metastatic disease



What are the next steps?

The CheckMate 649 study is still ongoing so that researchers can continue to follow the participants to assess the effects of nivolumab and chemotherapy

Trial registration site

You can read more about the phase 3 CheckMate 649 study at the following registrational websites:

- <https://clinicaltrials.gov/ct2/show/NCT02872116>
- <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-001018-76>

For more information on clinical studies in general, please visit:

- <https://www.clinicaltrials.gov/ct2/about-studies/learn>
- <http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are>

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Financial & competing interests disclosure

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

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