Plain Language Summary of Publication

Future ONCOLOGY

A plain language summary of the results from the phase 2b HERIZON-BTC-01 study of zanidatamab in participants with HER2-amplified biliary tract cancer

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

The original article titled 'Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study,' published in the journal *The Lancet Oncology*, can be accessed through their website at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00242-5/fulltext.

This article is not available for free access by the journal.

Summary

What is this summary about?

Researchers wanted to study whether the research drug zanidatamab could help people with a type of cancer called **biliary tract cancer**. In some people, biliary tract cancer cells make extra copies of a gene called HER2 (also called ERBB2). This is known as being HER2-amplified.

Zanidatamab is an antibody designed to destroy cancer cells that have higher-than-normal HER2 protein or gene levels. Zanidatamab is currently under research and is not yet approved for any diseases. Participants in this **phase 2b** clinical study had tumors that were HER2-amplified and at the **advanced or metastatic stage**. Participants also had cancer which had become worse after previous **chemotherapy** or had **side effects** that were too bad to continue chemotherapy. They also had to meet other requirements to be enrolled. Researchers measured the amount of HER2 protein in the tumor samples of the participants who were enrolled. There were 80 participants with tumors that were both **HER2 amplified** and had higher-than-normal HER2 protein amounts (considered to be '**HER2-positive**'). There were 7 participants with tumors that were HER2-amplified, but had little-to-no levels of the HER2 protein (considered to be '**HER2-low**'). All participants in the study were treated with zanidatamab and no other cancer treatments once every 2 weeks.

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

- **Biliary:** bi-lee-ur-ee
- **Biopsy:** bai-op-see
- **Cholangiocarcinoma:** kuh-lan-jee-uh-kaar-suh-now-muh
- **Extrahepatic:** ex-tra-he-pah-tic
- **Gallbladder:** gaal-bla-der
- **Gemcitabine:** jem-sai-tuh-been
- **HER2:** hur-too
- **Immunohistochemistry:** im-mune-no-his-toe-kem-ist-ree
- ***In situ* hybridization :** in-sit-yoo-hi-brid-eye-zay-shun
- **Intrahepatic:** in-truh-he-pah- tic
- **Intravenously:** in-truh-vee-nuhs-lee
- **Zanidatamab:** zani-datuh-mahb

Biliary tract cancer: A type of cancer found in the bile tubes inside and outside of the liver or in the gallbladder, where bile is stored.

Phase 2b: An early testing phase before the regulatory authorities allow a treatment to be prescribed by doctors.

Advanced or metastatic stage: The cancer has spread to other parts of the body and the tumors cannot be removed by surgery.

Chemotherapy: A drug treatment commonly used to kill cancer cells in the body.

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What are the key takeaways?

In the HER2-positive group, 33 of 80 (41%) participants had their tumors shrink by 30% or more of their original size. In half of these participants, their tumors did not grow for 13 months or longer. No participant in the HER2-low group had their tumors shrink by 30% or more.

In total, 63 of 87 participants (72%) had at least one side effect believed to be related to zanidatamab treatment. Most side effects were mild or moderate in severity. No participant died from complications related to zanidatamab. Diarrhea was one of the more common side effects and was experienced by 32 of 87 participants (37%). Side effects related to receiving zanidatamab through the vein, such as chills, fever, or high blood pressure, were experienced by 29 of 87 participants (33%).

Side effects: Reactions to a drug or treatment that is beyond its desired effect. Side effects can be harmful.

HER2-amplified: The tumor has extra copies of the HER2 gene.

HER2-positive: The tumor has extra copies of the HER2 gene and HER2 protein.

HER2-low: The tumor has extra copies of the HER2 gene, but little-to-no levels of HER2 protein.

What are the conclusions reported by the researchers?

The results of this study support the potential for zanidatamab as a new therapy for people with HER2-positive biliary tract cancer after they had already received chemotherapy. More research is occurring to support these results.

Who sponsored the study?

Funding and the drug for this study were provided by the following pharmaceutical companies: Zymeworks, Jazz Pharmaceuticals, and BeiGene.

Sponsor: A company or organization that oversees and pays for a clinical research study. They also collect and analyze the information that was generated during the study.

Who is this article for?

This summary was developed for anyone who would like to learn about the results of the HERIZON-BTC-01 study, which tested zanidatamab treatment in participants with HER2-amplified biliary tract cancer.

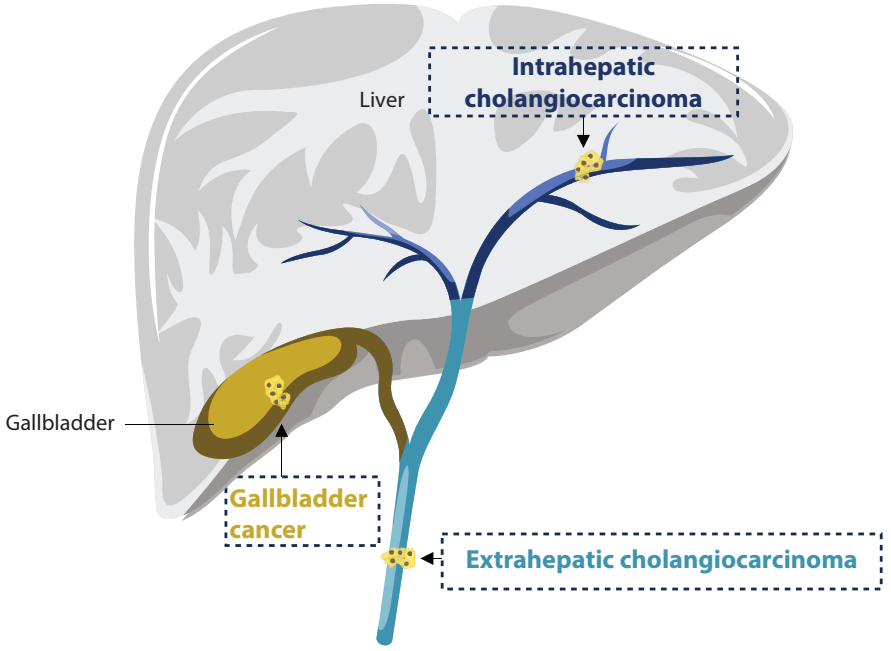
What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. Zanidatamab is not approved to treat the condition under study that is discussed in this summary. This summary reports the results of a planned interim analysis of the study. This means that the study has not yet been completed. This study described is still ongoing, therefore the final outcomes of this study may differ from the outcomes described in this summary. The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence not on the results of a single study.

What is biliary tract cancer?

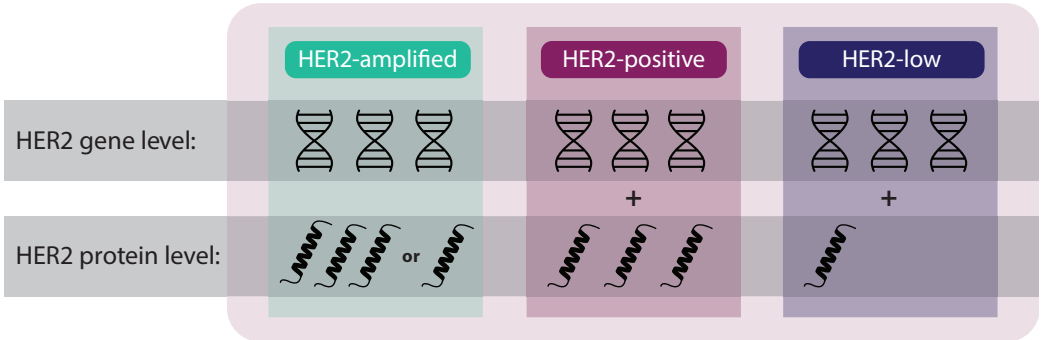
The liver is a large organ in the right side of the body, located below the ribs. It makes a yellow-green liquid called bile that helps to digest fatty food. The biliary tract is a system of tubes that drains bile into the gallbladder, where bile is stored. After meals, the gallbladder squeezes the bile into the gut. When cancer forms anywhere in the biliary tract, it is generally called biliary tract cancer. People are typically diagnosed with a specific type of biliary tract cancer, depending on the location of the cancer within the biliary tract.

Biliary tract cancers might form inside the liver (called 'intrahepatic cholangiocarcinoma'), outside the liver (called 'extrahepatic cholangiocarcinoma'), and in the gallbladder (called 'gallbladder cancer'). The biliary tract cancers outlined in black boxes are the cancers that are included in the HERIZON-BTC-01 study.



Adapted with permission from Moeini A, Haber PK, Sia D. Cell of origin in biliary tract cancers and clinical implications. *JHEP Rep*. doi:10.1016/j.jhepr.2021.100226 (2021)

Some biliary tract cancers (also called tumors) make extra copies of the HER2 gene (this is known as HER2-amplified cancer). Genes are tiny blueprints that tumor cells use to make proteins. Proteins are living chemicals that form the building blocks of life. All participants in this study had tumors that were HER2-amplified. When cells are HER2-amplified, they can also make too much HER2 protein (this is sometimes known as HER2-positive cancer). These tumors grow bigger and faster than tumors with normal amounts of the HER2 protein. Some biliary tract cancers that are HER2-amplified can have little-to-no amounts of the HER2 protein (this is sometimes known as HER2-low cancer).



More icons in the gene row indicate higher levels of the HER2 gene and more icons in the protein row indicate higher levels of the HER2 protein.

What is zanidatamab and how does it work?

Antibodies are chemical messengers that are made by the body to find germs to stop infection. Researchers have adapted these antibodies to find cancer cells. Treatment with antibodies leads to these cancer cells dying or being removed. Zanidatamab is a research treatment that is an antibody designed to find cancer cells that have HER2 protein on the surface of their cells or are HER2-amplified.
Once in the body, zanidatamab:

- Sticks to 2 different HER2 proteins at the same time and then form clumps around the cancer cells. This causes the tumor cells to destroy those HER2 proteins.
- Stops the HER2 proteins from sending 'grow' messages from the cancer cell, limiting cancer growth and survival.
- Recruits the participant's own defense system (the immune system) to destroy the cancer cells.

Who took part in the HERIZON-BTC-01 clinical study?

Participants were enrolled in the study between September 2020 and March 2022. The study is ongoing. The results reported in this summary come from an analysis completed in October 2022.

Participants did not receive any other cancer treatments with zanidatamab. The study is not accepting new participants, however, participants who have joined will continue to receive zanidatamab until:

- Their cancer worsens.
- They withdraw consent (decide to leave the study for any reason).
- The doctor decides to stop treatment for any reason.
- They miss follow-up appointments.
- Death.

A total of 87 participants from 32 clinical study sites across Canada, Chile, China, France, Italy, the Republic of Korea, Spain, the United Kingdom, and the United States participated in this study. For participants to join the clinical study, they needed to meet the following criteria:

- They needed to give their written informed consent.
- They needed to be 18 years old or older.
- They had HER2-amplified cancer of the biliary tract.
- Their biliary tract cancer could not be removed by surgery.
- The cancer either got worse after completing previous chemotherapy or participants had side effects that were too bad to continue chemotherapy.

Participants could not take part in the study if they had:

- A biliary tract cancer where the HER2 gene was not amplified.
- Previous therapy targeted towards HER2.
- Cancer of the brain or around the covering of the brain or spine.

Why was this study needed?

Unfortunately, biliary tract cancer is often discovered after the cancer has spread to other parts of the body. Only a small proportion of biliary tract cancers are HER2-amplified. Some chemotherapy treatment is available. However, researchers urgently need to find out if the antibody therapy zanidatamab could be a treatment option for participants with HER2-amplified biliary tract cancer. They also asked:

- How many participants had their tumors shrink after receiving zanidatamab?
- How long did it take for the participant's biliary tract cancer to get better or worse?
- How long do participants live after starting treatment?
- How many participants had side effects and what kind of side effects happened?

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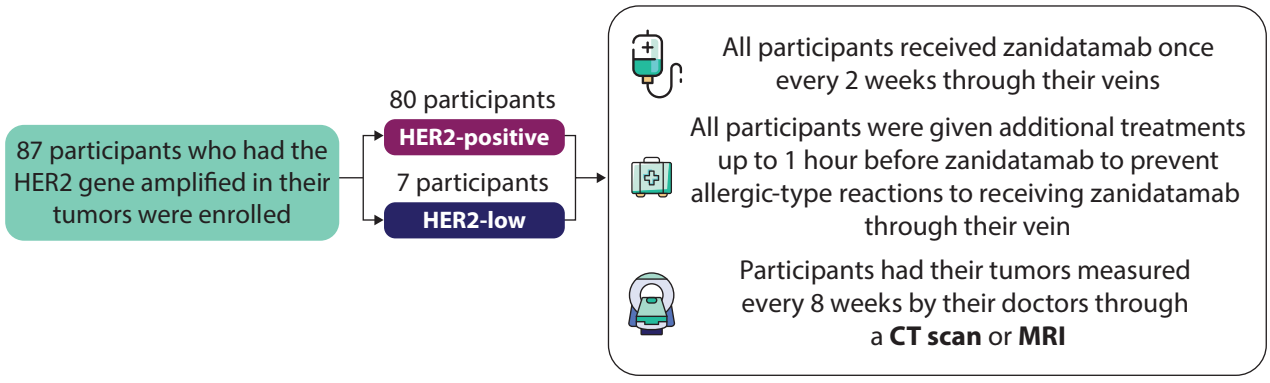
What happened during the study?

Participants with biliary tract cancer had small samples of their tumor removed (this is called a biopsy).

- Researchers first tested the tumor samples to find out whether the tumors were HER2-amplified.
  - If the tumors had extra copies of the HER2 gene, participants were enrolled in the study as long as they met the other eligibility criteria.
- Researchers then tested the tumor samples to see how much HER2 protein there was.
  - Participants with tumors that had higher-than-normal levels of the HER2 protein, in addition to having extra copies of the HER2 gene, were considered to be 'HER2-positive'. There were 80 participants with these HER2-positive tumors who were enrolled in the study.
  - Participants with tumors that only had extra copies of the HER2 gene but low or normal levels of the HER2 protein were considered to be 'HER2-low' in this study. There were 7 participants with these HER2-low tumors who were enrolled in the study.

Efficacy results were looked at separately for participants with HER2-positive and HER2-low tumors to see if zanidatamab shrank tumors in either group. Safety results were looked at for all participants, regardless of whether they had HER2-positive or HER2-low tumors.

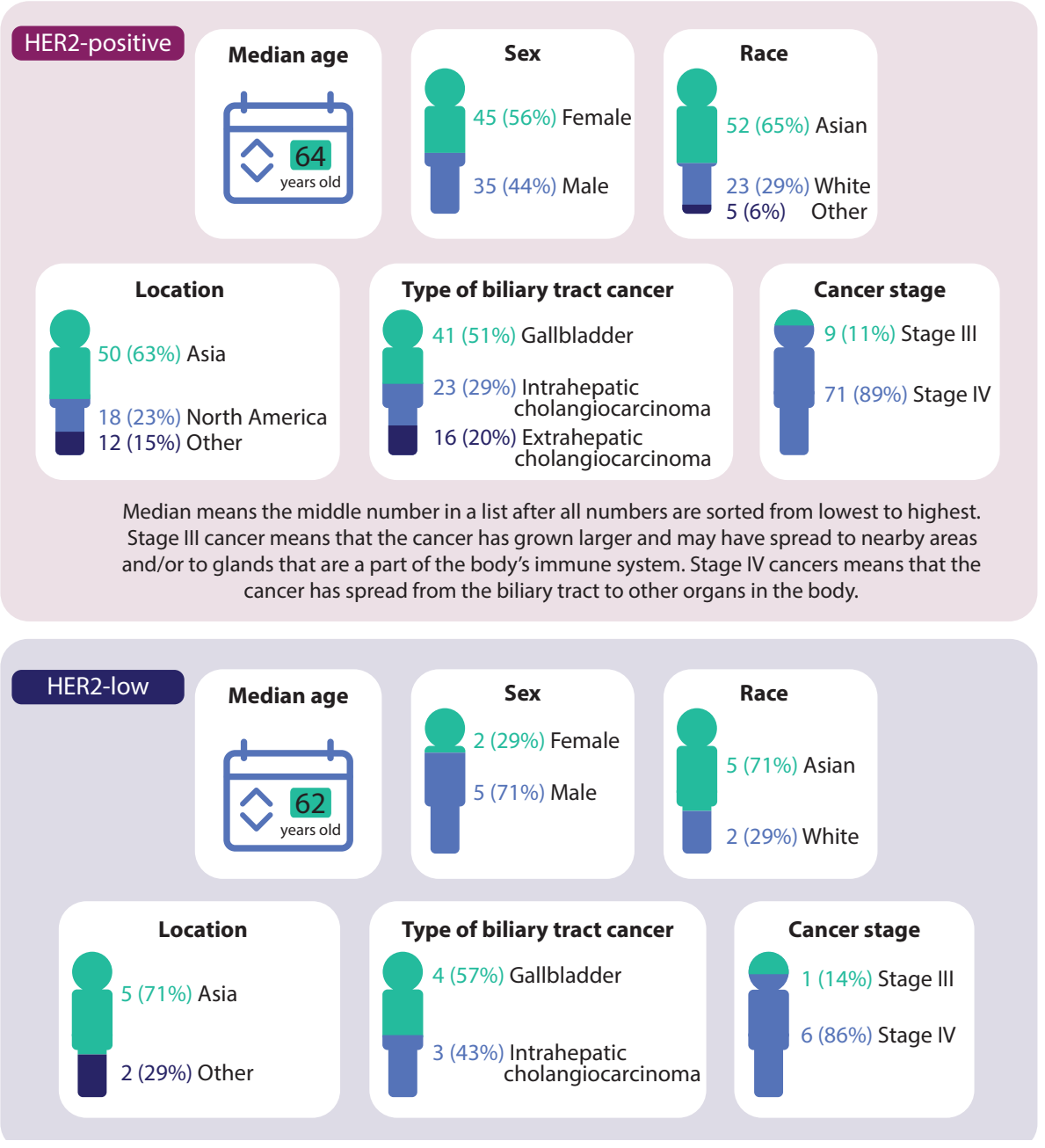
Efficacy: The ability of a treatment to prevent tumors from growing.



CT scan: A scan that takes many x-ray images that allow doctors to see inside of the body.
MRI: A scan that uses a strong magnetic field and radiowaves to create detailed images of bones, blood vessels, and soft tissues inside of the body.

Participants did not receive any other cancer treatments with zanidatamab. The additional treatments included steroids given through the vein, antihistamines taken by the mouth or through the vein, or acetaminophen taken by the mouth.

What were the characteristics of the participants in the study?



The results reported in this summary come from an analysis completed in October 2022

- When the data were analyzed, 18 out of 87 participants (21%) were still receiving zanidatamab. In total, 23 participants (26%) stopped zanidatamab treatment, but continued to visit their doctors for medical checks.
  - The remaining 46 participants stopped zanidatamab treatment because they withdrew their consent (they decided to leave the study for any reason) or they died.

All participants in the study:

Median length of treatment	Median number of visits participants had to receive zanidatamab through their veins	Median time participant was observed in the study
5.1 months	6.0	12.4 months

Median means the middle number in a list after all the numbers are sorted from lowest to highest.

Did tumors shrink with zanidatamab treatment?

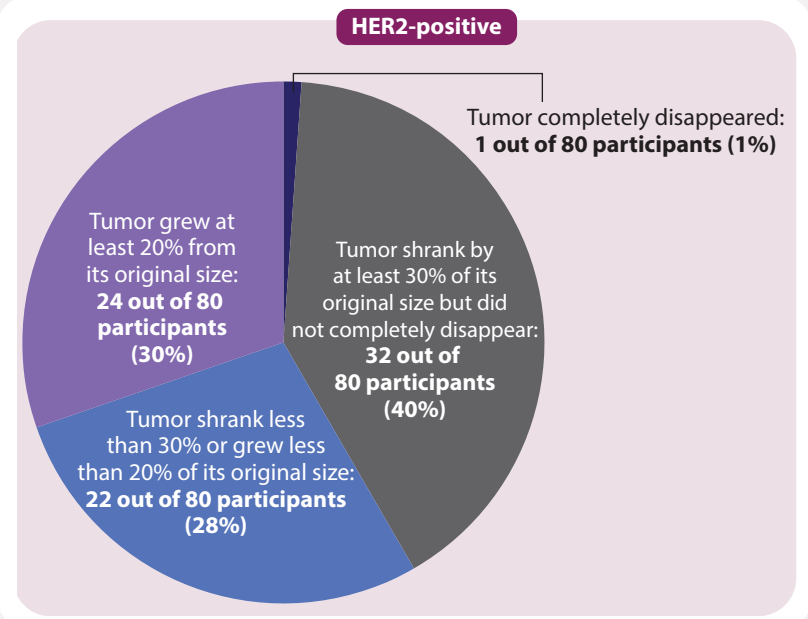
The results presented were evaluated by a **central laboratory** for consistency, but the results were similar when evaluated by each participant's **treating physician**.

Central laboratory: A laboratory that processes all samples from clinical study participants for consistency.

Treating physician: The doctor who is treating a participant.

In the HER2-positive group:

- 54 out of 80 participants (68%) had their tumors shrink by any amount.
  - 33 out of 54 participants (41%) had their tumors shrink by at least 30% of their original size.
    - 1 of these participants (1%) had their tumor completely disappear.
    - 25 of these participants (76%) had their tumors shrink by at least 30% by the time they visited their doctor for the first time after starting zanidatamab treatment.
    - In half of these participants whose tumors shrank by at least 30%, their tumors did not get bigger for 13 months or longer.
  - 22 out of 80 participants (28%) had that their tumors shrink less than 30% of their original size or grow less than 20% of their original size.
  - 24 out of 80 participants (30%) had their tumors grow at least 20% from their original size.
- In the HER2-low group, no one had tumors that shrank by at least 30% from their original size after receiving zanidatamab.



How long did participants live without their cancer getting worse?

In the HER2-positive group, half of the participants lived 5.5 months or longer without their cancer worsening. In the HER2-low group, half of the participants lived 1.9 months or longer without their cancer worsening.

What was the overall safety of zanidatamab?

Side effects occurred in 84 out of 87 participants (97%) regardless of whether the side effect was considered to be related to zanidatamab treatment.

63 out of 87 participants (72%) had at least one side effect that was believed to be related to zanidatamab treatment based on the treating physician's judgment.

Serious side effects related to zanidatamab occurred in 7 out of 87 participants (8%).

Side effects were considered serious if they:

- Were life-threatening.
- Caused the participants to go to the hospital for care.
- Disrupted the participant's normal life.
- Resulted in death.

There were 2 participants who experienced side effects related to zanidatamab that led to stopping treatment.

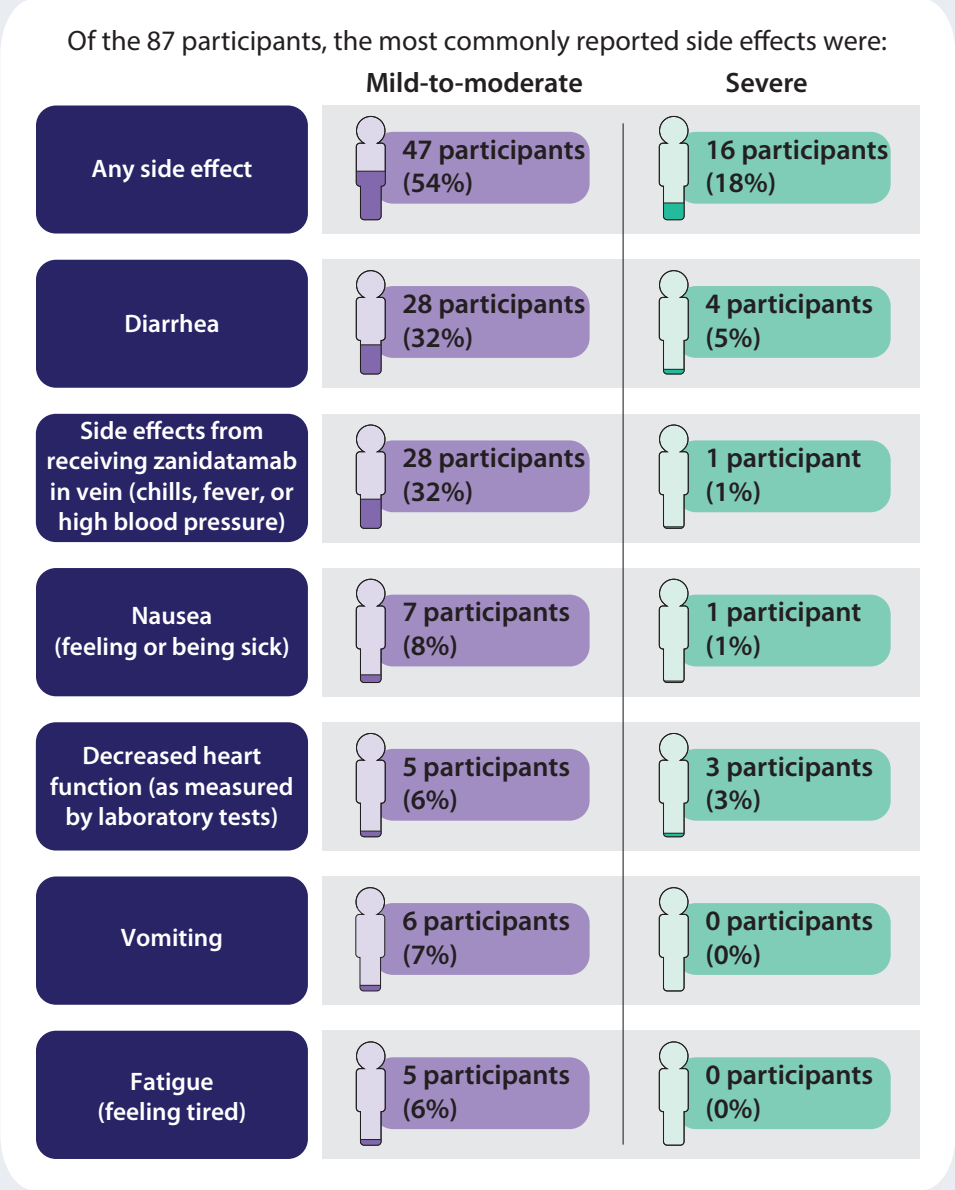
- One of these participants stopped zanidatamab due to decreased heart function and the other participant due to lung inflammation.

In total, 37 participants died due to their cancer worsening or side effects the treating doctor did not consider to be related to zanidatamab.

- 5 of these 37 participants died within 30 days of their last treatment dose and were no longer receiving zanidatamab during this 30-day period.
    - Three of these deaths were due to the participants' cancer worsening whereas the other 2 deaths were due to complications the treating doctor did not consider to be related to zanidatamab.

What were the side effects that participants receiving zanidatamab experienced?

Side effects were categorized as either mild-to-moderate or severe to life-threatening and the most common side effects related to zanidatamab treatment are shown in the graphic below:



No life-threatening side effects or deaths due to side effects were reported.

Diarrhea was one of the most common side effects reported and was experienced by 32 out of 87 participants (37%).

- Most participants were treated for diarrhea at home, and at the time of the analysis, were no longer experiencing diarrhea.
- Approximately half of participants had their diarrhea last for 2 days or less.

Side effects from receiving zanidatamab through the vein, such as chills, fever, or high blood pressure, were also commonly reported and experienced by 29 out of 87 participants (33%).

- At the time of this analysis, all participants were no longer experiencing these side effects.

What do the results mean?

HERIZON-BTC-01 is the largest clinical study performed, to our knowledge, for people with HER2-amplified biliary tract cancer. The results of this study support the potential for zanidatamab as a new targeted therapy for people with HER2-positive biliary tract cancer following previous standard chemotherapy, therefore expanding treatment options.

Where can readers find more information on HERIZON-BTC-01?

The full citation of the original article, titled 'Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study,' is Harding JJ, et al. *Lancet Oncol.* 2023;24(7):772-782.
The first participant was enrolled in the study (signed informed consent) on September 15, 2020, and received their first treatment on October 1, 2020. The results presented in this plain language summary report are the results between September 2020 and March 2022.
This original article was published in the journal *The Lancet Oncology* and can be accessed through their website at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00242-5/fulltext. This article is not available for free access by the journal.
More information on the HERIZON-BTC-01 study is also available on ClinicalTrials.gov (https://clinicaltrials.gov/study/NCT04466891).

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Competing interests disclosure

JJ Harding has consulted or been an advisory board member for Adaptimmune, AstraZeneca, Bristol Myers Squibb, Eisai, Elevar, Exelixis, Genoscience, Hepion, Imvax, Merck, Medivir, QED, Tyra, and Zymeworks. DY Oh has been an advisory board member for Arcus Biosciences, ASLAN, AstraZeneca, Basilea, Bayer, BeiGene, Bristol Myers Squibb/Celgene, Genentech/Roche, Halozyme, IQVIA, Merck Serono, Novartis, Taiho, Turning Point, Yuhan, and Zymeworks. HJ Choi has consulted for AstraZeneca and Roche. JW Kim has consulted for AstraZeneca, BeiGene, Beyond Bio, Bristol Myers Squibb/

Celgene, Eisai, GC Cell, Merck Sharp & Dohme, ONO, Sanofi-Aventis, Servier, and TCUBEit. HC Sun has consulted for TopAlliance. T Macarulla has an advisory role at Ability Pharmaceuticals SL, AstraZeneca, Basilea Pharma, Baxter, BioLineRX Ltd., Bristol Myers Squibb/Celgene, Eisai, Incyte, and Ipsen Bioscience Inc.; and has received speaker's fees from Janssen and Lilly. J Bridgewater has consulted for Bristol Myers Squibb, Incyte, Servier, and Taiho. H Wasan is an advisory board member and/or invited speaker at Amgen, Bayer, Bristol Myers Squibb/Celgene, BTG, Erytech Pharma, Incyte, Merck KGaA, Pfizer, Pierre Fabre, Roche/Genentech/FM, Seagen, Servier, SIRTEX Medical, and Zymeworks; has consultancies at Bayer, Bristol Myers Squibb/Celgene, Incyte, NICE/BSI expert, Oncosil, and Pierre Fabre; and is a member of the Global Trials steering committee at ARCAD (Pancreas Academic), Merck KGaA, Pfizer/Array, SIRTEX Medical, and Zymeworks. M Ducreux has been an advisory board member for Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Daiichi Sankyo, Merck Serono, Merck Sharp & Dohme, Pierre Fabre, Roche, and Servier; has been a speaker in symposia for Bayer, Daiichi Sankyo, Merck Serono, Merck Sharp & Dohme, Pierre Fabre, Roche, and Servier; and participated in independent data monitoring committees for Pancan and Roche. M Ducreux's spouse is the head of the oncology business unit at Sandoz France. S Pant has consulted for AskGene Pharma, Boehringer Ingelheim, Ipsen, Janssen, Novartis, and Zymeworks. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

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