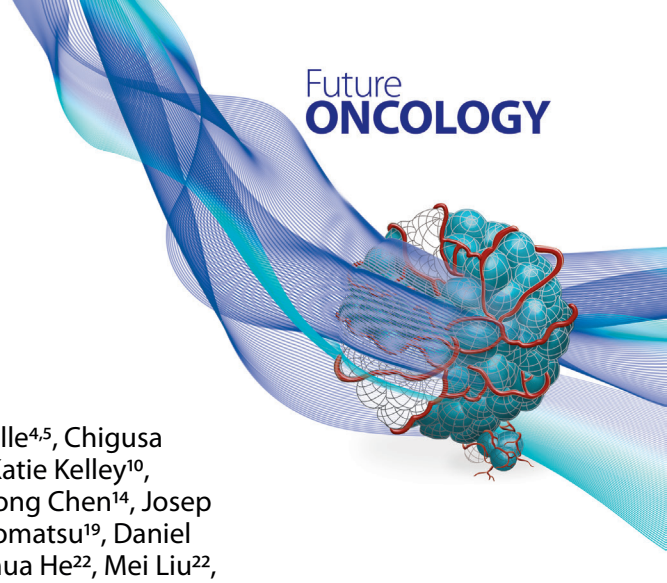
Plain Language Summary of Publication



Future ONCOLOGY

# Plain language summary of the FOENIX-CCA2 study: futibatinib for people with advanced bile duct cancer

Lipika Goyal[1], Funda Meric-Bernstam[2], Antoine Hollebecque[3], Juan W Valle[4,5], Chigusa Morizane[6], Thomas B Karasic[7], Thomas A Abrams[8], Junji Furuse[9], Robin Katie Kelley[10], Philippe A Cassier[11], Heinz-Josef Klümpen[12], Heung-Moon Chang[13], Li-Tzong Chen[14], Josep Tabernero[15], Do-Youn Oh[16], Amit Mahipal[17], Markus Moehler[18], Yoshito Komatsu[19], Daniel H Ahn[20], Robert S Epstein[21], Abdel-Baset Halim[22], Volker Wacheck[22], Yaohua He[22], Mei Liu[22], Karim A Benhadji[22] & John A Bridgewater[23], for the FOENIX-CCA2 Study Investigators

Full affiliation information can be found at the end of this plain language summary.

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

The original article discussed in this summary, called 'Futibatinib for *FGFR2*-rearranged intrahepatic cholangiocarcinoma,' was published in *The New England Journal of Medicine* in 2023. You can read the original article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa2206834

There is also a quick-take video summarizing the findings, which is available to watch for free at: https://www.nejm.org/do/10.1056/NEJMdo006868/full/

## Summary

### What is this summary about?

This summary describes the results from a **phase 2 study** called FOENIX-CCA2. The study evaluated treatment with **futibatinib** in people with a rare form of advanced **bile duct** cancer called **intrahepatic cholangiocarcinoma** (or **iCCA**), where the tumors have changes in the structure of a **gene** called ***FGFR2***. These changes include *FGFR2* **gene fusions**. Bile duct cancer often returns after surgery or cannot be treated by surgery because the tumor has spread, so it requires treatment with **chemotherapy**. People live for a **median** of 1 year after their first chemotherapy treatment and 6 months after their second treatment. This study included people whose cancer had grown/spread after one or more chemotherapy treatments. The aims of the study were to see if futibatinib could shrink the size of tumors and stop the cancer from growing/spreading and to see how long people lived when treated with futibatinib. Clinicians also looked at **side effects** from taking futibatinib and at how it affected people's quality of life.

**How to say** (download PDF and double click sound icon to play sound)...

- **Alopecia:** A-loh-PEE-shuh
- **Cholangiocarcinoma:** koh-LAN-jee-oh-KAR-sih-NOH-muh
- **FOENIX:** FEE-niks
- **Futibatinib:** FUE-ti-BA-ti-nib
- **Intrahepatic:** IN-truh-heh-PA-tik
- **Kinase:** KY-nays
- **Metastasized:** meh-TAS-tuh-sized
- **Onycholysis:** ON-ih-koh-LY-sis
- **Onychomadesis:** ON-ih-koh-ma-DEE-sis

### What were the results?

Futibatinib treatment shrank tumors in over 80% of people who received treatment. Tumors shrank by at least 30% in 42% of people. Futibatinib stopped tumors from growing/spreading for a median of 9.7 months. People who took the medicine lived for a median of 21.7 months, and 72% of people were still alive after 1 year. Side effects from taking futibatinib were like those reported for similar medicines, and clinicians considered the side effects to be manageable by adjusting the dose of futibatinib or treating the side effects. Most people reported that their quality of life stayed the same or improved during the first 9 months of taking futibatinib.

### What do the results mean?

The results support the use of futibatinib for treating people with advanced bile duct cancer. Based on the results of this study, futibatinib is now approved in the US, Europe, and Japan. Futibatinib is approved for treating adults with advanced bile duct cancer who have received previous treatment for their cancer, and whose tumors have a gene fusion or other change in the *FGFR2* gene.

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**Bile duct:** Tubes connecting the liver and gallbladder to the small intestine. These tubes transport a fluid called bile, which helps to break down and digest fats in our food.

**Chemotherapy:** A type of medicine that kills cancer cells by stopping them from growing.

***FGFR2*:** A gene that provides the instructions for making a protein (also called FGFR2, which stands for fibroblast growth factor receptor 2). There are four of these genes (*FGFR1*, *2*, *3*, and *4*). In healthy cells, the FGFR2 protein is involved in cell growth. Cancer cells that have changes in the structure of the *FGFR2* gene can have uncontrolled growth (known as tumors).

**Futibatinib:** A medicine that is used to treat adults with bile duct cancer, whose tumors have *FGFR2* gene fusions and have spread or cannot be removed by surgery. Futibatinib works by blocking the action of a protein, called FGFR kinase, that signals cancer cells to multiply. This helps slow or stop the spread of cancer cells. Futibatinib comes as a tablet that is taken by mouth.

**Gene:** A section of DNA that provides instructions for making specific proteins in a cell. These proteins then play a role in how the cell works.

**Gene fusion:** This is when parts of two different genes join together and form a hybrid gene (a fusion gene). Inside cells, DNA is coiled up in structures called chromosomes. Fusion genes, and the fusion proteins that come from them, can be made naturally in the body when part of the DNA from one chromosome moves to another chromosome. Fusion proteins produced by this change may lead to the development of some types of cancer.

**Intrahepatic cholangiocarcinoma (iCCA):** A rare type of cancer where tumors form in the bile ducts inside ('intra') the liver ('hepatic'), as opposed to the bile ducts outside the liver (extrahepatic).

**Median:** The value in the middle of a data set, when the values are placed in order.

**Phase 2 study:** A study that tests whether a new treatment works for a certain type of cancer or other disease (for example, whether it shrinks a tumor or improves blood test results). Phase 2 clinical trials may also provide more information about the safety of the new treatment and how the treatment affects the body. Also called a phase II clinical trial.

**Side effects:** Unintended effects that are thought to be caused by taking the medicine.

## 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. The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence and not on the results of a single study.

## Who should read this summary?

This plain language summary may be helpful for people with iCCA, their caregivers and families, patient advocates, and healthcare professionals. This summary may also be helpful to those who are interested in learning about advances in the treatment options available for advanced bile duct cancers.


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## Who sponsored this study and summary?

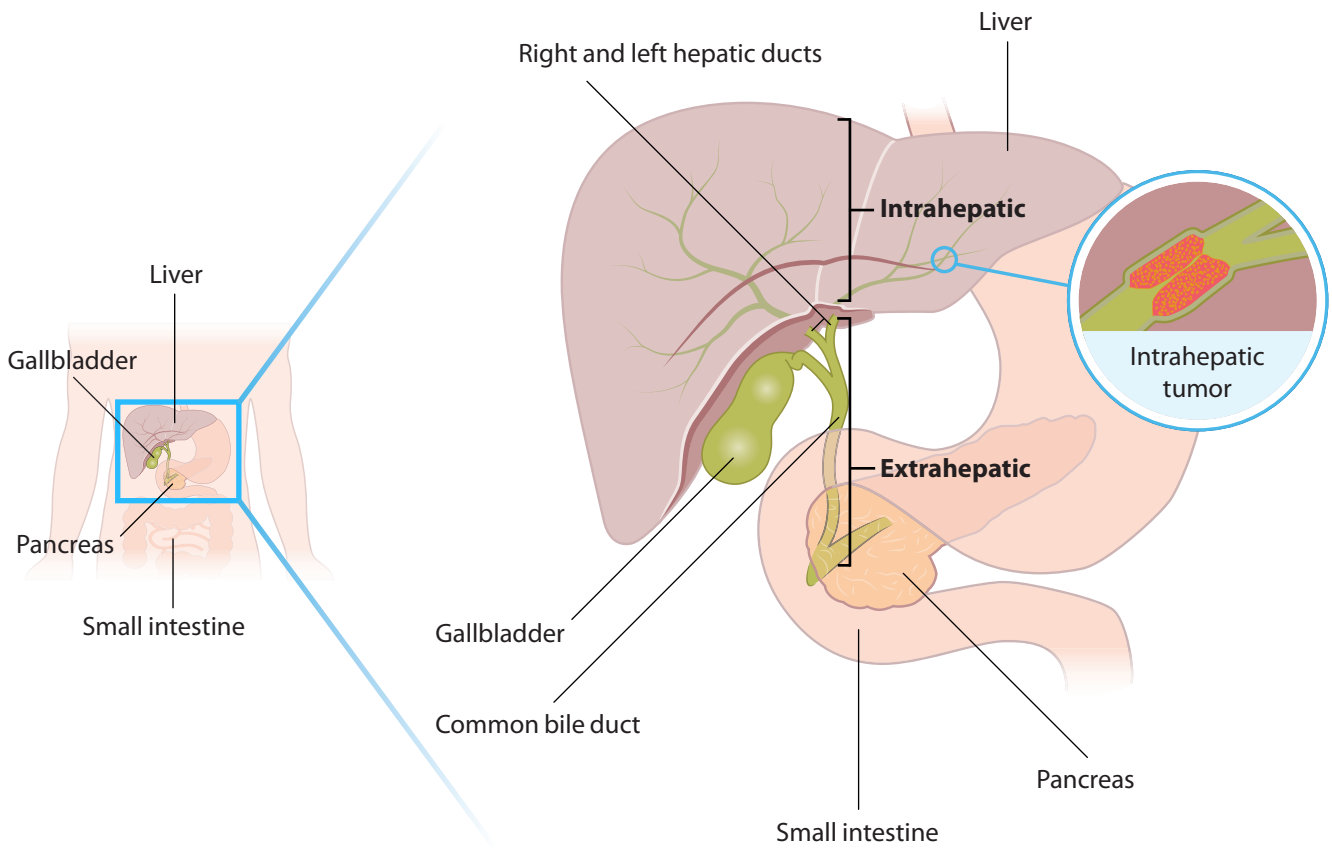
The pharmaceutical company Taiho Pharmaceutical Co., Ltd. and subsidiaries, funded and were responsible for conducting this study. The **sponsor** for this plain language summary was Taiho Oncology, Inc.

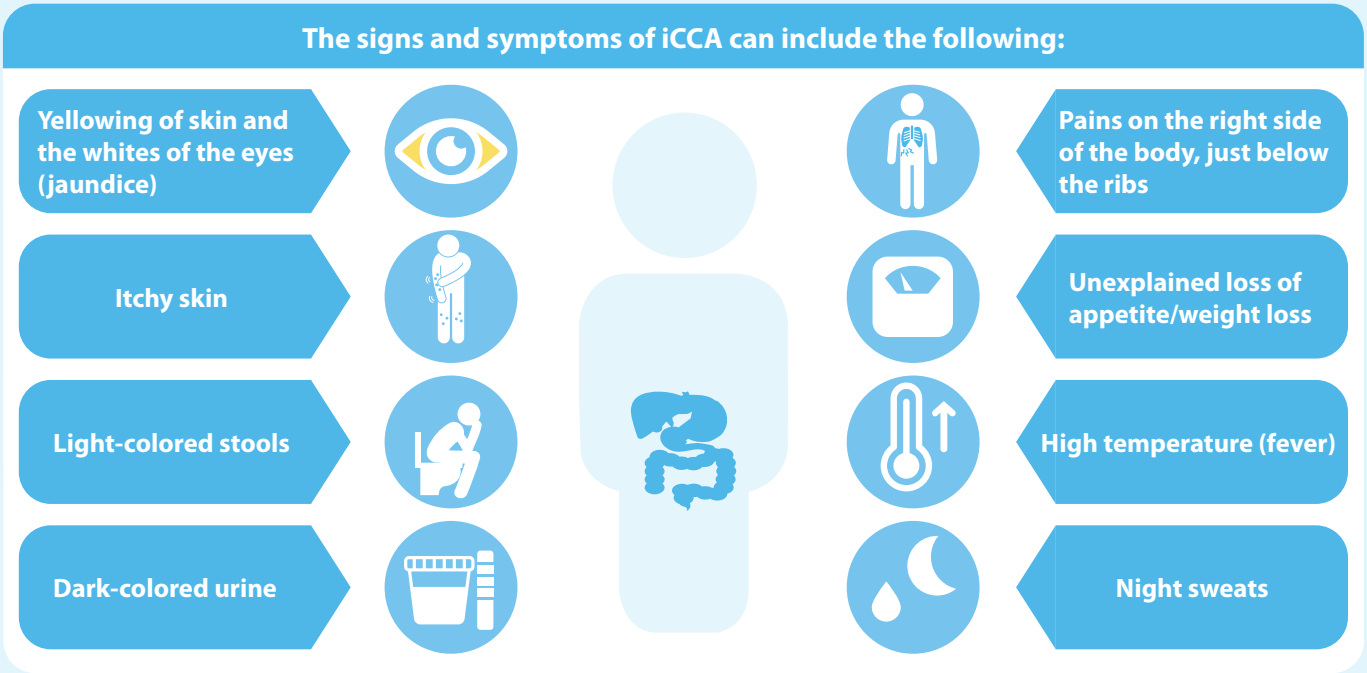
**Sponsor:** A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

## What is iCCA and how is it treated?

iCCA (intrahepatic cholangiocarcinoma) is a rare and aggressive type of cancer that starts in the bile ducts inside the liver.

- Bile ducts are part of the digestive system.
- Bile is a fluid that is made in the liver and stored in the gallbladder.
- Bile ducts connect the liver and gallbladder to the small intestine.
- Bile travels through the bile ducts and enters the small intestine to help break down and digest fats in our food.

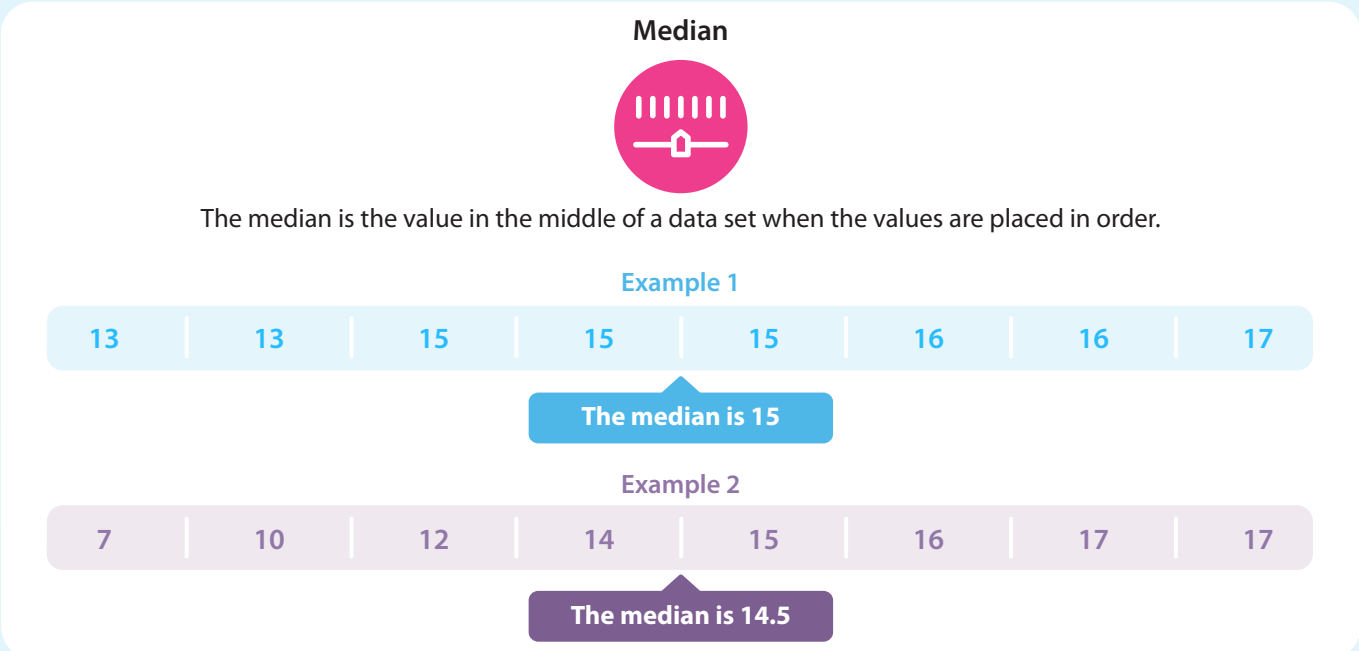





Many of the symptoms of iCCA do not appear until the person has had the disease for a long time, making iCCA difficult to diagnose. Because of this, many people are diagnosed after the cancer has already spread to other parts of the body.

If it is caught early, iCCA is usually treated with surgery to remove the tumor. However, in many people (60–70%), the cancer comes back after surgery. The standard treatment option for people whose cancer has grown/spread is chemotherapy. People who receive standard chemotherapy medicines live for a median of 1 year after their first treatment and a median of 6 months following their second treatment.

Currently, fewer than 8% of people who receive standard chemotherapy for iCCA are still alive 5 years after being diagnosed. There is a need for new treatment options for people with iCCA.





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## What happens when tumors have changes in the *FGFR2* gene?

In cancer cells that have changes in the *FGFR2* gene, too much of the FGFR2 protein is made. The FGFR2 protein is involved in cell growth, so too much of it can lead to uncontrolled cell growth (known as tumors).

### Around 10–15% of people with iCCA have tumors with changes in the *FGFR2* gene


- Genetic testing looks at a person's genes to check for any changes in the *FGFR2* gene. The test is done with a sample of tumor tissue.
- If doctors know that a person's cancer cells have changes in the *FGFR2* gene, they will be better able to choose the right treatment for that person.

Pemigatinib is a **targeted therapy** that is approved in the US and Europe for the treatment of people with iCCA whose tumors have changes in the *FGFR2* gene. A phase 2 study that evaluated pemigatinib in bile duct cancer showed that 37% of people had at least 30% tumor shrinkage. The study was called FIGHT-202 and 147 people took part, including 107 people whose cancer had changes in the *FGFR2* gene. People in the study were treated in 21-day treatment cycles. In each cycle, people took pemigatinib every day for 14 days, followed by a 7-day rest period when they did not take the medication.

**Targeted therapy:** This is a type of cancer medicine that works by finding and attaching to a specific target structure inside cancer cells. It can help stop the cells from growing, dividing, and spreading.

## What is futibatinib?

Futibatinib is a type of targeted therapy that aims to stop the growth and spread of tumors that have changes in *FGFR* genes. Futibatinib works by attaching to (or targeting) the abnormal FGFR proteins in the cancer cell. This reduces the signals that tell the cancer cell to grow and multiply, which helps to slow or stop the spread of cancer cells.

Futibatinib works differently to pemigatinib. Futibatinib attaches to a different part of the abnormal FGFR protein compared with medicines like pemigatinib. Futibatinib binds very tightly to the FGFR protein (an irreversible bond), and therefore tends to stay attached. Pemigatinib also binds tightly to the FGFR protein but can detach from it (a reversible bond).

In laboratory experiments, futibatinib has been shown to overcome some of the **mutations** that are known to cause the failure of other medicines. The benefit that futibatinib has shown in treating people with bile duct cancer is partly attributed to its very tight bond to the FGFR protein and its ability to overcome these mutations.

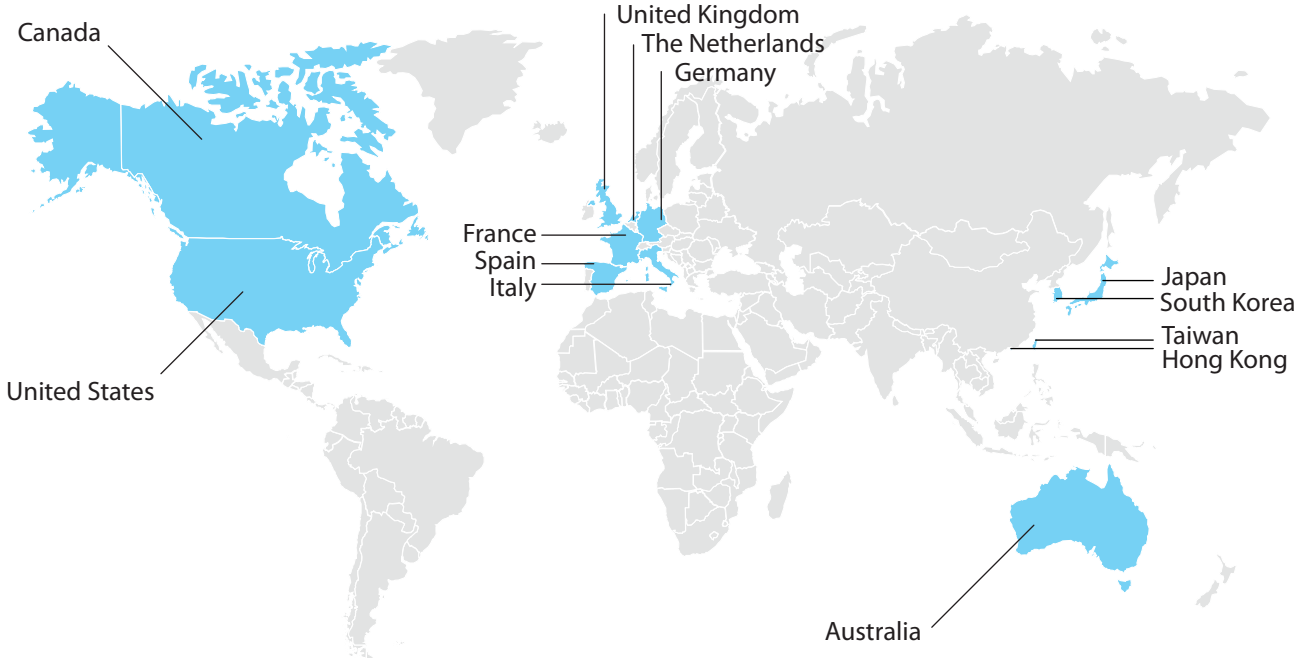
**Mutations:** Changes to the genetic instructions inside a cell, which may lead to the production of proteins with abnormal shapes or structures.

## What was the FOENIX-CCA2 study designed to look at?

FOENIX-CCA2 was a clinical trial that was designed to see if futibatinib could shrink people's tumors, stop their tumors from getting any bigger, or stop the cancer from spreading. The researchers also looked at how long people lived when treated with futibatinib, the types of side effects, and how the treatment affected people's quality of life.

## Where did the study take place?

People from all over the world were included in the FOENIX-CCA2 study.



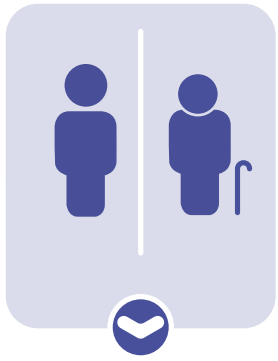

## Who took part in the study?

To take part in the study, people needed to:

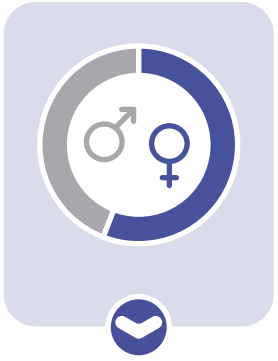
- Be aged 18 years or older;
- Have iCCA that was not suitable for surgery or had spread (or **metastasized**) to nearby tissues or other areas of the body;
- Have tumors with *FGFR2* gene fusions;
- Have received one or more previous **systemic treatments** for iCCA;
- Have an **Eastern Cooperative Oncology Group (ECOG) performance score** of 0 or 1.


Of 783 people who were screened between 16 April 2018 and 29 November 2019, 103 people with iCCA whose tumors had *FGFR2* gene fusions were enrolled in the study and took five futibatinib tablets (a total of 20 mg) every day. People continued to receive futibatinib until their disease worsened or they had unmanageable side effects.

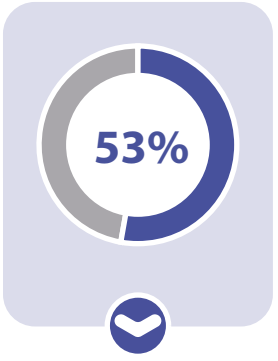
## People who took part in the FOENIX-CCA2 study



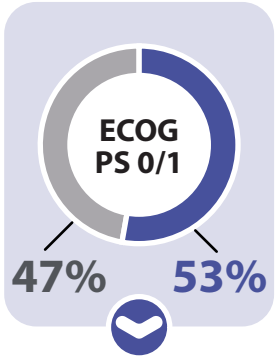
People in the study were aged between **22** and **79** years



**56%** were female and **44%** were male




**53%** had received 2 or more previous systemic treatments




ECOG performance score was **0** in **47%** and **1** in **53%** of people

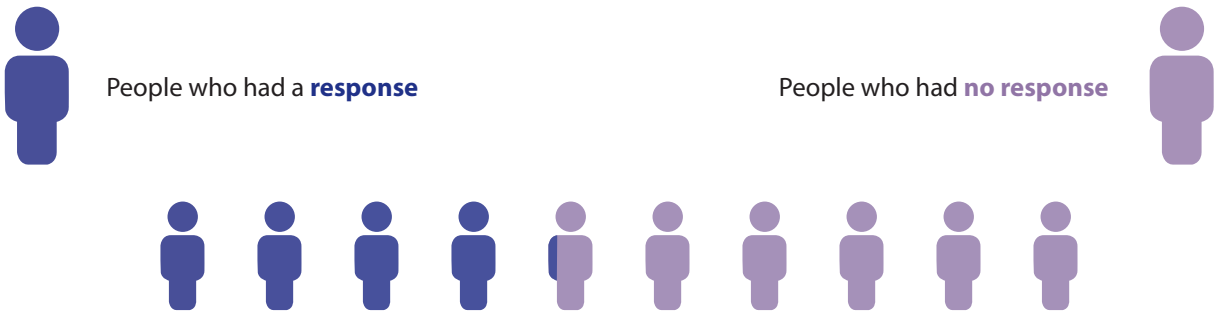
**ECOG performance score:** A tool used by doctors to look at how the disease impacts a person's daily living ability. A score of 0 means that the person is fully active and able to carry out the same activities as before their disease, and a score of 1 means that the person is restricted in physically strenuous activity but able to carry out light work.

**Metastasized:** This is when cancer cells spread from one part of the body to another. When cancer cells metastasize and form new (secondary) tumors, the cells in the metastatic tumor are like those in the original (primary) tumor.

**Systemic treatment:** A type of treatment that travels through the bloodstream to target cancer cells throughout the body.

## What did the results show?

### Of 103 people who received futibatinib in the FOENIX-CCA2 trial, 42% had a response to the treatment



After taking futibatinib, these people's tumors shrank by at least 30% and stopped growing/spreading for a median of 9.7 months (the shortest time was 7.6 months, and the longest time was 17.0 months).

**Responses** were seen in people who were 65 years of age or older and in people who had received one or multiple previous systemic treatments.

Among those who had a response to futibatinib treatment, the response lasted at least 6 months in 72% of people and at least 12 months in 14% of people.

Overall, 83% of people who took futibatinib had either a response to treatment or had stable disease, meaning their tumor neither increased nor decreased in size.

People who were treated with futibatinib lived for a median of **9.0 months** without their cancer progressing

**72%** of people treated with futibatinib were still alive after **12 months**

Overall, people treated with futibatinib lived for a median of **21.7 months**

**Response:** A person was considered to have a response when their tumor shrank by at least 30% or disappeared after treatment.

## What were the most common side effects of futibatinib?

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Of **side effects** relating to fingernails, 16% of people had a disease or deformity of the nail, 16% had detachment of fingernails starting from the tip of the nail (onycholysis), 14% had detachment of fingernails starting from the base of the nail (onychomadesis), and 14% had changes in the color of their nails.

The side effect of **high phosphate levels** was successfully managed by using medicines that lower phosphate levels, by temporarily stopping futibatinib therapy, or by switching to a lower dose of futibatinib.

2% of people had to stop taking futibatinib because of side effects. Futibatinib therapy did not cause any deaths during the study.

**High phosphate levels:** This often does not cause symptoms by itself. Doctors can do a blood test to check blood phosphate levels. When there is extra phosphate in the blood, it can cause calcium to be removed from bones or other parts of the body, leading to low calcium levels. As a result, people may experience weak bones, muscle cramps, bone and joint pain, itchy skin, or a rash.

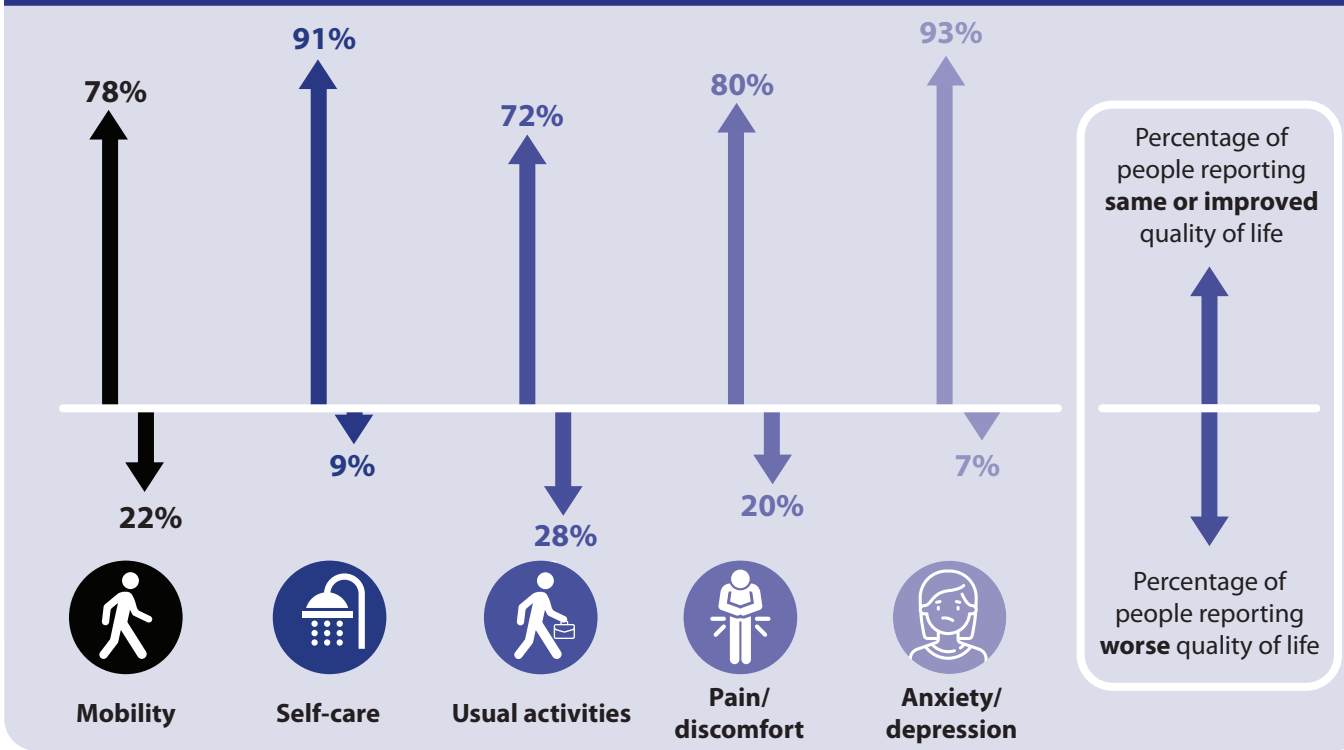
**Side effects:** Unintended effects that are thought to be caused by taking the medicine.

## How did futibatinib therapy affect people's quality of life?

89% of people who took futibatinib completed questionnaires about how the treatment affected their daily life across different areas. In one of these questionnaires, people were asked to describe their health by ticking one of three boxes for each of the following areas:

- Mobility: no problems in walking about, some problems in walking about, or being confined to bed.
- Self-care: no problems, some problems, or inability to wash or dress.
- Usual activities: no problems, some problems, or inability to perform activities related to work, studying, housework, family, or leisure.
- Pain/discomfort: no presence or presence of moderate or extreme pain or discomfort.
- Anxiety/depression: no presence or presence of moderate or extreme anxiety or depression.

**Most people reported that their quality of life was the same or improved during the first 9 months of futibatinib therapy**



## What do the results of this study mean?

The FOENIX-CCA2 study involved people with advanced iCCA whose tumors had changes in the *FGFR2* gene and who had received 1 or more previous systemic treatments

The tumors of most people who took futibatinib either shrank by at least 30% or stayed the same, and the response lasted for several months

The side effects from taking futibatinib were similar to those reported for other related medicines. Researchers considered most side effects to be manageable

Futibatinib is now approved in the US, Europe, and Japan for the treatment of adults with advanced cholangiocarcinoma whose cancer has been treated and whose tumors have an *FGFR2* gene fusion or other change in the structure of the *FGFR2* gene

## Where can I find more information?

The original article discussed in this summary, called 'Futibatinib for *FGFR2*-rearranged intrahepatic cholangiocarcinoma,' was published in *The New England Journal of Medicine* in 2023. You can read the original article for free at: https://www.nejm.org/doi/full/10.1056/NEJMoa2206834

The full citation for the article is:

- Goyal L, Meric-Bernstam F, Hollebecque A, *et al.* Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma. *N Engl J Med.* 2023;388(3):228-239. doi:10.1056/NEJMoa2206834

There is also a quick-take video summarizing the findings, which is available to watch for free at: https://www.nejm.org/do/10.1056/NEJMdo006868/full/

The full name of the FOENIX-CCA2 study is 'Phase 2 Study of TAS-120 in Patients With Advanced Solid Tumors Harboring *FGF/FGFR* Aberrations' (NCT02052778).

To find out more about the FOENIX-CCA2 study, please visit: https://clinicaltrials.gov/study/NCT02052778

The start date of the FOENIX-CCA2 study was 21 July 2014 and the end date was 29 May 2021.

A further study of futibatinib in bile duct cancer is ongoing:

- 'Phase 2 Study of Futibatinib 20 mg and 16 mg in Patients With Advanced Cholangiocarcinoma With *FGFR2* Fusions or Rearrangements (FOENIX-CCA4)' (NCT05727176). To find out more about the FOENIX-CCA4 study, please visit: https://clinicaltrials.gov/study/NCT05727176

Patient advocacy groups:

- The Cholangiocarcinoma Foundation (CCF)
  https://cholangiocarcinoma.org/
  A global, nonprofit organization dedicated to improving the quality of life for people with bile duct cancer.
- The Global Cholangiocarcinoma Alliance (GCA)
  https://www.globalccaalliance.com/
  A patient advocacy group dedicated to raising awareness of bile duct cancer.

Further reading:

If you are interested in reading about the phase 1 study results that led to the phase 2 FOENIX-CCA2 study, the original articles can be found at the following links:

- 'Futibatinib, an Irreversible FGFR1-4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF*/*FGFR* Aberrations: A Phase I Dose-Expansion Study' was published in *Cancer Discovery* in 2022. You can read the original article for free at: https://aacrjournals.org/cancerdiscovery/article/12/2/402/678504/Futibatinib-an-Irreversible-FGFR1-4-Inhibitor-in
- 'Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1-4 inhibitor in patients with advanced solid tumors' was published in *Annals of Oncology* in 2020. You can read the original article for free at: https://www.annalsofoncology.org/article/S0923-7534(20)39928-2/fulltext

More information about the phase 2 FIGHT-202 study of pemigatinib can be found at the following links:

- 'An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202' was published in *ESMO Open* in 2024. You can read the original article for free at: https://www.esmoopen.com/article/S2059-7029(24)01257-2/fulltext
- The full name of the FIGHT-202 study is 'A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including *FGFR2* Translocations Who Failed Previous Therapy' (NCT02924376). To find out more about the FIGHT-202 study, please visit: https://clinicaltrials.gov/study/NCT02924376

## Acknowledgments

In memoriam of Edith P Mitchell, who sadly passed away on 21 January 2024, and who was an author of the original article on which this summary is based. The authors thank the patients in this study and their families and the worldwide team of investigators and study site personnel for their contributions to this study. The authors also thank Jennifer L Silhavy, MSc, of Illumina, for her contribution to the analyses of circulating tumor DNA. The authors thank the Envision the Patient team, of Envision Pharma Group, for reviewing the use of patient-friendly language in this PLSP, and for organizing and providing feedback from a patient reviewer.

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## Competing interests disclosure

LG has participated in a data safety monitoring board for AstraZeneca. RKK has served on a clinical trial steering committee for AstraZeneca; and has participated in an investigator meeting and satellite symposium for Ipsen Biopharmaceuticals Inc. JT has provided educational collaboration for Imedex, Medscape Education, MJH Life Sciences, and PeerView Institute for Medical Education and Physicians Education Resource. RSE is a member of the board of directors for Fate Therapeutics, Illumina Inc., and Veracyte. A-BH, VW, YH, ML, and KAB are current or former employees of Taiho Oncology, Inc. 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.

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[1]Department of Medicine, Stanford University School of Medicine, and the Stanford Cancer Center, Palo Alto, CA, USA; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Drug Development Department, Gustave Roussy, Villejuif, France; [4]Cholangiocarcinoma Foundation, Herriman, UT, USA; [5]Division of Cancer Sciences, University of Manchester, Manchester, UK; [6]National Cancer Center Hospital, Tokyo, Japan; [7]Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [8]Mass General Cancer Center, Harvard Medical School, and Dana-Farber Cancer Institute, Boston, MA, USA; [9]Kanagawa Cancer Center, Yokohama, Japan; [10]University of California, San Francisco, San Francisco, CA, USA; [11]Centre Léon Bérard, Lyon, France; [12]Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [14]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; [15]Vall d'Hebron Hospital Campus and Vall d'Hebron Institute of Oncology, University of Vic-Central University of Catalonia, Baselga Oncologic Institute, Hospital Quiron, Barcelona, Spain; [16]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [17]Mayo Clinic, Rochester, MN, USA; [18]University Medical Center of Johannes Gutenberg University, Mainz, Germany; [19]Hokkaido University Hospital Cancer Center, Sapporo, Japan; [20]Mayo Clinic, Phoenix, AZ, USA ; [21]Epstein Health, Woodcliff Lake, NJ, USA; [22]Taiho Oncology, Inc., Princeton, NJ, USA; [23]University College London Cancer Institute, London, UK.



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