Clinical Study Results

Research Sponsor: Eisai Inc.
Drug Studied: Lenvatinib, also called E7080
Short Study Title: A study to learn how lenvatinib and pembrolizumab work together and their safety in participants with a liver cancer called hepatocellular carcinoma

Thank you!

You took part in this clinical study for the study drug called E7080, also called lenvatinib, given together with another drug called pembrolizumab. You and all of the participants helped researchers learn more about lenvatinib, given together with pembrolizumab, and how it may help people with a type of liver cancer called hepatocellular carcinoma. Cancer is a term for diseases in which the cells in the body divide uncontrollably and spread to other parts of the body.

Eisai, a Japanese pharmaceutical company and the sponsor of this study, thanks all participants for their contribution. Eisai is committed to improving health through continuing research in areas of unmet need and sharing with you the results of the study you participated in.

Eisai prepared this summary with a medical and regulatory writing organization called Certara Synchrogenix.

If you participated in the study and have questions about the results, please speak with the doctor or staff at your study site.

What has happened since the study started?

The study started in February 2017.

The study included 163 participants from 24 study centers in France, Italy, Japan, the Russian Federation, Spain, the United Kingdom, and the United States. Out of 163 participants, 104 received at least 1 dose of study treatment.

The sponsor of the study reviewed the data collected until November 2022 and created a report of the results. This is a summary of that report.

Why was the research needed?

Researchers were looking for a different way to treat people who have liver cancer. The standard treatments for people with liver cancer include surgery and other treatments that help decrease the size of the tumors. But these treatments may not help all people with liver cancer, especially in the later stages of their cancer. Researchers therefore wanted to learn about new treatments that might help some of these people.

Lenvatinib stops tumors from growing by blocking signals that tell cancer cells to grow. It also stops cancer cells from forming new blood vessels that they need to keep growing. Pembrolizumab helps to decrease the size of the tumors by helping the immune system identify and target cancer cells.

The researchers in this study wanted to find out if lenvatinib and pembrolizumab work when given together to participants with liver cancer. They also wanted to find out if participants had any medical problems during the study.

The main questions the researchers wanted to answer in this study were:

- How effective was lenvatinib, when given together with pembrolizumab, at decreasing the size of the tumors of participants with liver cancer?
- For those participants with liver cancer who responded to study treatment, how long did their response last?
- What adverse events did participants receiving lenvatinib and pembrolizumab have? An adverse event is a medical problem that may or may not be caused by the study drug.

It is important to know that this study was designed to get the accurate answers to the questions listed above. There were other questions the researchers wanted to answer to learn more about how lenvatinib and pembrolizumab work together. But these were not the main questions the study was designed to answer.

What kind of study was this?

To answer these questions, researchers asked for the help of men and women aged at least 18 years. The participants in the study were 47 to 86 years old. Of these participants, 81% were male, and 19% were female.

The study had 2 parts:

- **Part 1**: Researchers wanted to learn about the safety of 2 different doses of lenvatinib when taken with pembrolizumab.
- **Part 2**: Researchers wanted to learn how lenvatinib and pembrolizumab work together to decrease the size of the tumors of participants with liver cancer. They also wanted to learn how long the participants continued to respond to study treatment.

All participants in this study had liver cancer that could not be removed by surgery.

People could not take part in the study if they had liver cancer that affected 50% or more of the liver, had liver cancer that affected the bile duct (tube that carries bile), and received lenvatinib before.

This study was "open-label". This means that the participants, the study doctors and staff, and the sponsor knew which study treatment the participants received.

Study treatment was given in 21-day time periods called treatment cycles. The amount of lenvatinib and pembrolizumab received was measured in milligrams (mg) and based on the participant's body weight. Participants with a body weight of less than 60 kg received a starting dose of lenvatinib at 8 mg per day. Participants with a body weight of 60 kg or more received a starting dose of lenvatinib at 12 mg per day. All participants received a 200 mg dose of pembrolizumab every 3 weeks.

Lenvatinib capsules were taken by mouth. Pembrolizumab was given through a needle into the vein, also called intravenous or IV.

- **Part 1**: Each participant received the first dose of lenvatinib and pembrolizumab for 1 treatment cycle (21 days). Participants who completed the first cycle were allowed to move to Part 2.
- **Part 2**: Participants continued to take the same dose of lenvatinib and pembrolizumab until any of the following occurred:
    - Their cancer got worse
    - They had toxicities that made them leave the study
    - They chose to leave the study or withdrew their consent
    - The sponsor chose to end the study

The figure below shows how treatment was given in your study.

What happened during the study?

Before the study started, the study doctors did a full check-up to make sure each participant could join the study.

The study doctors or staff also did the following:

- Performed physical examination and checked which medications each participant had been taking before they joined the study
- Checked each participant's heart health
- Took blood and urine samples for analyses
- Took scans of each participant's brain, bone, and body to assess their tumors

During treatment in Parts 1 and 2, the study doctors or staff did the following:

- Took scans of each participant's body, brain, and bone, as needed, to assess their tumors
- Took blood and urine samples for analyses
- Checked what other medicines each participant was taking
- Checked what adverse events each participant was experiencing

Within 30 days after their last dose, all participants returned to the study center.

The participants had the following:

- Physical examination
- Their heart health checked
- Provided blood and urine samples for analyses
- Were asked about adverse reactions and medicines they were taking

Study doctors or staff continued to check the participants' health every 12 weeks up to 2 years after the last participant joined Part 2 of the study or until participants withdrew their consent.

The figure below shows how the study was done.

How did this study work?

Before the study started

To make sure each participant could join the study, the study doctors or staff:

- Confirmed all participants had liver cancer
- Checked each participant's heart health
- Took blood and urine samples
- Took imaging scans to assess each participant's tumor

During treatment period

All participants who could join the study took an assigned dose of study treatment.

The study doctors or staff:

- Continued to check participant's health
- Asked if participants had medical problems and what medicines participants were taking

After their last dose

All participants returned to the study center within **30 days** after taking their last dose of study treatment.

The study doctors or staff performed final check-ups and collected blood and urine samples and continued to check participant's health every 12 weeks.

What were the results of the study?

This is a summary of the main results. The results each person had might be different and are not in this summary. But the results each person had are part of the summary of results. A full list of the questions researchers wanted to answer can be found on the websites listed at the end of this summary. If a full report of the study results is available, it can also be found on these websites.

Researchers look at the results of many studies to decide which treatment options may work best and may be well tolerated. Other studies may provide new information or different results. Always talk to a doctor before making any treatment decisions.

Results in this section are from 100 participants who received liver cancer treatment for the first time.

How effective was lenvatinib, when given together with pembrolizumab, at decreasing the size of the tumors of participants with liver cancer?

To answer this question, the researchers looked at the imaging scan results from participants with liver cancer. Researchers then checked the tumor of each participant to see if it decreased in size or completely disappeared after receiving study treatment.

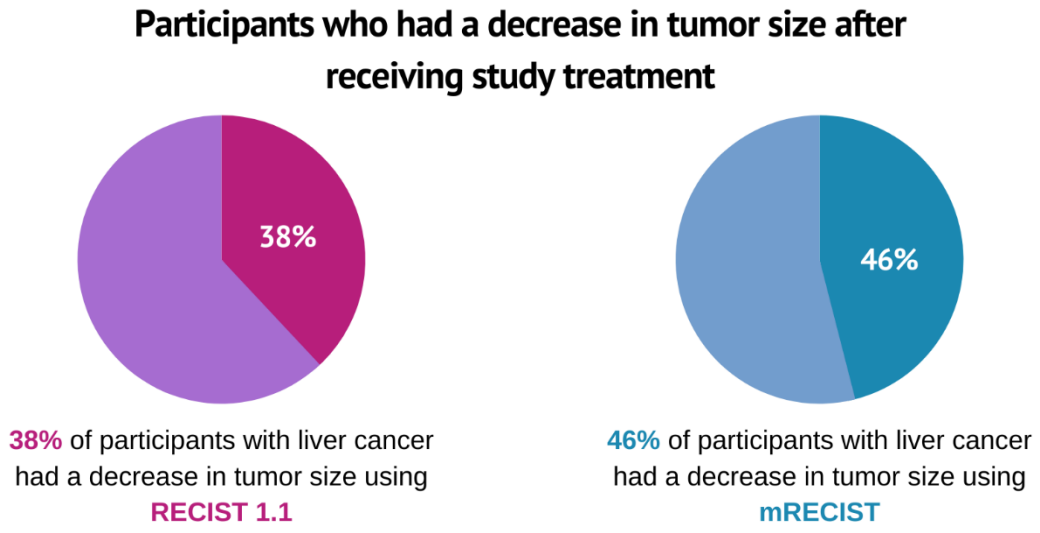
Researchers also used the following guidelines to assess if the participant's tumor decreased in size or not:

- Response Evaluation Criteria in Solid Tumors (also called RECIST 1.1)
- Modified RECIST for liver cancer (also called mRECIST)

Overall, researchers found the following:

- 38 out of 100 participants (38%) with liver cancer had a decrease in tumor size using RECIST 1.1
- 46 out of 100 participants (46%) with liver cancer had a decrease in tumor size using mRECIST

The chart below shows the proportion of participants who had a decrease in tumor size.



For those participants with liver cancer who responded to study treatment, how long did their response last?

To answer this question, the researchers looked at the results from participants with liver cancer who had responded to study treatment.

Of the participants whose tumors had decreased in size, the midpoint time their tumors continued to respond to study treatment was 17 months using mRECIST. This means that half of the tumors that responded to study treatment responded for more than 17 months, and the other half responded for less than 17 months.

The midpoint time of participants' tumors that continued to respond to study treatment using RECIST 1.1 could not be computed because of the small number of participants whose tumor got worse.

What medical problems did participants have?

Medical problems that happen in clinical studies are called “adverse events”. An adverse event is called “serious” when it is life-threatening, causes lasting problems, or the participant needs to be admitted to a hospital.

This section is a summary of the adverse events that happened during this study. These medical problems may or may not be caused by the study drug. The websites listed at the end of this summary may have more information about the medical problems that happened in this study. A lot of research is needed to know whether a study drug causes a medical problem.

Results in this section are from 100 participants who received liver cancer treatment for the first time.

How many participants had adverse events?

In this study, 99 participants (99%) had adverse events.

The table below shows how many participants had adverse events in this study.

Adverse Events in the Study

	Out of 100 participants of the study
How many participants had adverse events?	99 (99%)
How many participants had serious adverse events?	74 (74%)
How many participants stopped receiving either lenvatinib or pembrolizumab because of adverse events?	47 (47%)

What were the most common serious adverse events?

In this study, 74 participants (74%) had serious adverse events. Out of these 74 participants, 43 had serious adverse events the study doctors thought were caused by study treatment. The most common serious adverse events were the following:

- Increased level of bilirubin (breakdown product of red blood cells)
- Brain damage caused by liver problems
- Fever

The table below shows the serious adverse events that happened in more than 2 participants of the study. There were other serious adverse events, but these happened in fewer participants. These other serious adverse events are listed in the full report.

Serious Adverse Events in the Study

	Out of 100 participants of the study
Increased level of bilirubin	9 (9%)
Brain damage caused by liver problems	6 (6%)
Fever	5 (5%)
Pain in abdomen	4 (4%)
Infection of the lungs	4 (4%)
Heart condition caused by a blocked blood supply	3 (3%)
Heart attack	3 (3%)
Scarring of the liver	3 (3%)
Infection of the parts of the body that collect and pass out urine	3 (3%)
Fall	3 (3%)
Increased level of AST[a]	3 (3%)

Abbreviations: AST = aspartate aminotransferase

[a]AST is an enzyme in the liver that doctors use to check the health of the liver. Increase in levels of AST could mean there is a problem with the liver function.

Eighteen participants (18%) died due to a serious adverse event in the study. Out of the 18 participants who died, 3 had serious adverse events related to study treatment.

What were the most common adverse events?

The most common adverse events in this study were the following:

- Diarrhea
- High blood pressure
- Decreased appetite

The table below shows the adverse events that happened in 25% of participants or more of the study. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in the Study

	Out of 100 participants of the study
Diarrhea	60 (60%)
High blood pressure	47 (47%)
Decreased appetite	39 (39%)
Tiredness	38 (38%)
Decreased weight	35 (35%)
Underactive thyroid gland	33 (33%)
Increased level of AST[a]	32 (32%)
Low levels of red blood cells	30 (30%)
Excess protein in the urine	30 (30%)
Weakness	27 (27%)

Abbreviations: AST = aspartate aminotransferase

[a]AST is an enzyme in the liver that doctors use to check the health of the liver. Increase in levels of ALT could mean there is a problem with the liver function.

How many participants had adverse events the study doctors thought were caused by study treatment?

In this study, 96 participants (96%) had adverse events the study doctors thought were caused by study treatment. The most common adverse events the study doctors thought were caused by study treatment were the following:

- Diarrhea
- High blood pressure
- Tiredness

How has this study helped patients and researchers?

In this study, researchers learned more about how lenvatinib when given together with pembrolizumab, may have helped people with liver cancer.

Researchers look at the results of many studies to decide which treatment options may work best and are well tolerated. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with lenvatinib are ongoing.

Where can I learn more about the study?

You can find more information about this study on the websites listed below. If a full report of the study results is available, it can also be found here:

- https://www.clinicaltrials.gov - Once you are on the website, type **NCT03006926** into the search box and click "**Search**".

Full study title: An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects With Hepatocellular Carcinoma

Protocol number: E7080-J081-116

Eisai, the sponsor of this study, has headquarters in Tokyo, Japan, and regional headquarters in Nutley, New Jersey, USA and Hatfield, Hertfordshire, UK. The phone number for general information is 44-845-676-1400 (UK) and 1-888-274-2378 (USA).

Thank you

Eisai would like to thank you for your time and interest in participating in this clinical study. Your participation has provided a valuable contribution to research and improvement in health care.

Eisai Co., Ltd. is a global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our human health care (hhc) philosophy. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites, and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products in multiple therapeutic areas with high unmet medical needs, including Oncology and Neurology. For more information, please visit https://www.eisai.com.

Certara Synchrogenix is a worldwide medical and regulatory writing organization and is not involved in recruiting participants or in conducting clinical studies.
Certara Synchrogenix Headquarters 100 Overlook Center, Suite 101, Princeton, NJ 08540
https://www.certara.com • 1-415-237-8272