Clinical Study Results

Research Sponsor: Eisai Co., Ltd.

Drugs Studied: Lenvatinib, also called E7080
Nivolumab, also called ONO-4538

Short Study Title: A study to learn how lenvatinib and nivolumab work together and about their safety in participants with liver cancer

Thank you!

You took part in this clinical study for the study drug called lenvatinib, also called E7080, given together with another drug called nivolumab. You and all of the participants helped researchers learn more about lenvatinib, given together with nivolumab, and how it may help people with liver cancer. 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 January 2018 and ended in December 2022.

The study included 39 participants from 7 study centers in Japan. Out of 39 participants, 30 received at least 1 dose of study treatment.

The sponsor of the study reviewed the data collected 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 with 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.

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. Nivolumab is an antibody (a protein that helps the body fight foreign matter) that works to fight tumor cells.

The researchers in this study wanted to find out if lenvatinib and nivolumab 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:

- What were the dose-limiting toxicities (or DLTs) that happened in participants who received lenvatinib and nivolumab in the study? DLTs are medical problems related to the study drug that would prevent participants from taking a higher dose.
- How safe and tolerable were lenvatinib and nivolumab in participants with liver cancer?
- What adverse events did participants receiving lenvatinib and nivolumab 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 nivolumab 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 20 years. The participants in the study were 36 to 81 years old. Of these participants, 80% were male, and 20% were female.

The study had 2 parts:

- **Part 1**: Researchers wanted to learn about the tolerability of lenvatinib when taken with nivolumab.
- **Part 2**: Researchers wanted to learn the safety of lenvatinib and nivolumab and how they work together to decrease the size of the tumors of participants with liver cancer.

All participants in Part 1 of the study had liver cancer that could not be removed by surgery or for which there was no alternative standard treatment.

All participants in Part 2 of the study had not received treatment for advanced liver cancer that could not be removed by surgery.

People could not take part in the study if they had received lenvatinib or nivolumab before.

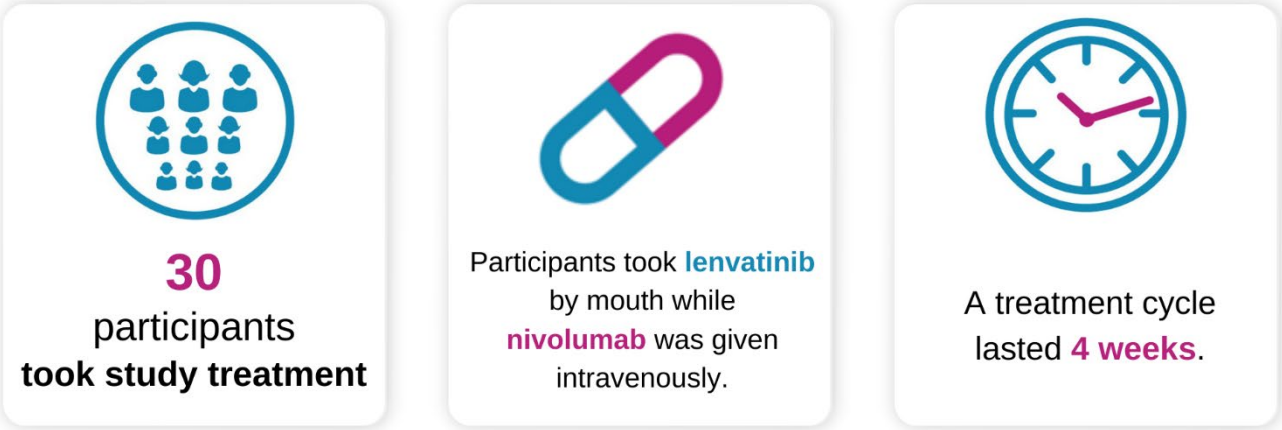
This study was "open-label". This means that the participants, the study doctors and staff, and the sponsor knew which study treatment the participants received.

Study treatment was given in 4-week time periods called treatment cycles. The amount of lenvatinib and nivolumab participants 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 240 mg dose of nivolumab every 2 weeks.

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

- **Part 1**: Each participant received a dose of lenvatinib and nivolumab for 1 treatment cycle (4 weeks). Participants who completed the first cycle were allowed to continue the treatment until any of the following occurred:
    - Their cancer got worse
    - They had toxicities that made them leave the study
    - They became pregnant
    - They chose to leave the study or withdrew their consent
    - The sponsor chose to end the study
- **Part 2**: After the confirmation of tolerability in Part 1, participants took lenvatinib and nivolumab until any of the above occurred:

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 examinations 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, bones, 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 brain, bones, and body as needed, to assess their tumors
- Took blood and urine samples for analyses
- Checked what other medicines each participant was taking
- Checked what medical problems each participant was experiencing

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

The participants:

- Had a physical examination
- Provided blood and urine samples for analyses
- Were asked about medical problems they were having 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 participants' 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 are well tolerated. Other studies may provide new information or different results. Always talk to a doctor before making any treatment decisions.

What were the DLTs that happened in participants who received lenvatinib and nivolumab in the study?

To answer this question, the researchers looked at the DLTs participants with liver cancer had during Part 1 of the study. Dose limiting toxicities are medical problems related to the study treatment that would prevent participants from taking a higher dose of study treatment.

During Part 1 of the study, none out of 6 participants had DLTs.

How safe and tolerable were lenvatinib and nivolumab in participants with liver cancer?

To answer this question, the researchers looked at the adverse events that happened in participants during the study.

Overall, researchers found out the following:

- All participants had adverse events the study doctors thought were caused by study treatment.
- Fifteen participants had serious adverse events.
- Three participants died due to an adverse event.

More information on the safety of lenvatinib and nivolumab is shown below.

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 or fatal, 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.

How many participants had adverse events?

In this study, 30 participants (100%) had adverse events.

The table below shows how many participants had adverse events during Part 1 and Part 2 of the study.

Adverse Events in the Study

	Out of 30 participants of the study
How many participants had adverse events?	30 (100%)
How many participants had serious adverse events?	15 (50%)
How many participants stopped receiving lenvatinib because of adverse events?	5 (17%)
How many participants stopped receiving nivolumab because of adverse events?	5 (17%)

What were the most common serious adverse events?

In this study, 15 participants (50%) had serious adverse events. Out of these 15 participants, 10 had serious adverse events the study doctors thought were caused by study treatment. All serious adverse events happened in 1 participant each, except for one. The serious adverse event that happened in 2 participants was brain damage caused by liver problems.

In this study, 3 participants (10%) died due to a serious adverse event of lung infection caused by a fungus called aspergillus, a tear in the blood vessel of the heart, or liver failure.

What were the most common adverse events?

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

- Diarrhea
- Hand-foot syndrome
- Changes in the sound or tone of the voice

The table below shows the adverse events that happened in 30% of participants or more during Part 1 and Part 2 of the study. There were other adverse events, but these happened in fewer participants.

Most Common Adverse Events in the Study

	Out of 30 participants of the study
Diarrhea	19 (63%)
Hand-foot syndrome	18 (60%)
Changes in the sound or tone of the voice	16 (53%)
Decreased appetite	15 (50%)
Excess protein in the urine	14 (47%)
High blood pressure	11 (37%)
Underactive thyroid	10 (33%)
Inflammation of the lining of the mouth	10 (33%)
Tiredness	9 (30%)
Feeling generally unwell	9 (30%)

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

In this study, all participants (100%) 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:

- Hand-foot syndrome
- Changes in the sound or tone of the voice
- Decreased appetite

How has this study helped patients and researchers?

In this study, researchers learned more about how lenvatinib, when given together with nivolumab, 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 in combination with nivolumab are not planned.

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 **NCT03418922** into the search box and click "**Search**".
- https://rctportal.niph.go.jp/en - Once you are on the website, type **jRCT2080223794** into the JPRN Search Portal and click "**Search**".

Full study title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Protocol number: E7080-J081-117

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), and +81 (0)3-3817-3700 (Japan).

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.

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