Clinical Study Results

Research Sponsor: Eisai Inc.
Drug Studied: E7080, also called lenvatinib
Short Study Title: A study to learn how lenvatinib works when given together with ifosfamide and etoposide and their safety in participants with bone cancer

Thank you!

You or your child took part in this clinical study for the study drug E7080, also called lenvatinib, given together with other drugs called ifosfamide and etoposide. All of the participants helped researchers learn more about lenvatinib, given together with ifosfamide and etoposide, and how they may help people with a type of bone cancer called osteosarcoma. Participants in this study had osteosarcoma that had not responded to or had come back since previous treatment.

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

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

If you or your child 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 March 2020.

The study included 81 participants from 44 study sites in the following countries:

Australia	Canada	Czech Republic	Finland
France	Hong Kong	Israel	Italy
Netherlands	New Zealand	Singapore	South Korea
Spain	Sweden	Switzerland	Taiwan
United Kingdom	United States		

Of the 81 participants, 78 received study drugs at least once.

The sponsor of the study reviewed the data collected up to June 2022 and created a report of the primary results. This is a summary of that report.

Why was the research needed?

Researchers were looking for a different way to treat children and young adults who have osteosarcoma.

The standard treatments for people with osteosarcoma include surgery, chemotherapy such as ifosfamide and etoposide, and other treatments that may help shrink tumors. But these treatments may not help all people with osteosarcoma, especially in the later stages of their cancer.

Researchers thought that lenvatinib, if given with ifosfamide and etoposide, may help participants with osteosarcoma. Lenvatinib works by targeting and blocking specific proteins that help cancer cells survive and grow.

The researchers in this study wanted to find out how lenvatinib, given together with ifosfamide and etoposide, works in people with osteosarcoma. 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:

- Did participants who received lenvatinib plus ifosfamide and etoposide live longer without their osteosarcoma getting worse compared with those who received only ifosfamide and etoposide?
- What adverse reactions did participants who received lenvatinib, ifosfamide, and etoposide have? An adverse reaction is a medical problem that may be caused by the study drug.

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

What kind of study was this?

To answer these main questions, researchers asked for the help of participants aged 2 to 24 years and who had osteosarcoma that had not responded to or had come back since previous treatment.

Of these participants, 57% were male, and 43% were female.

The participants in this study were divided into 2 groups:

- **Group A**: Participants in this group received lenvatinib plus ifosfamide and etoposide.
- **Group B**: Participants in this group received only ifosfamide and etoposide. They also had the option to receive lenvatinib plus ifosfamide and etoposide for a maximum of 5 cycles.

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

The study drugs were given in repeating 21-day time periods called treatment cycles.

Lenvatinib capsules were taken by mouth once every day. A suspension of lenvatinib was prepared for participants who could not swallow capsules. A suspension is a liquid with solid particles of the study drug mixed into it.

Both ifosfamide and etoposide were given through a needle into a vein, also called intravenous or IV infusion. Both ifosfamide and etoposide were given for 3 days in 21-day treatment cycles for a maximum of 5 cycles.

The amount of lenvatinib, ifosfamide, and etoposide given was measured in milligrams (mg) and based on participant's body surface area measured in meters squared (m^2).

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

78
participants
received study drugs

The amount of study drugs participants received was based on their individual **height** and **weight**.

A treatment cycle lasted **21 days**. Participants continued to receive study drugs until they had an intolerable medical problem

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:

- Confirmed that participants had osteosarcoma that had not responded to treatment or had come back since previous treatment
- Took blood and urine samples for analyses
- Checked each participant's heart health
- Took scans of each participant's body to assess their tumors

During the Treatment period, the participants received their assigned dose of study drugs in 21-day treatment cycles.

Throughout the study, the study doctors or staff:

- Took scans of each participant's 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

Each participant could continue receiving the study drugs until:

- Their cancer got worse
- They had intolerable medical problems
- They chose to leave the study
- The sponsor chose to end the study

About 30 days after their last dose, all participants returned to the study site.

The participants:

- Had their blood and urine samples taken
- Were asked if they had any medical problems and if they were taking any other medicines
- Were followed up to check on their health every 12 weeks for up to 2 years

The figure below shows how the study was done.

How did this study work?

Before the study started

The study doctors or staff:

- Checked each participant's health to make sure they could join the study
- Confirmed all participants had osteosarcoma
- Took blood and urine samples
- Took scans to assess their tumor

During treatment period

All 78 participants received an assigned dose of study drugs in **21-day** treatment cycles**.**

The study doctors or staff:

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

After treatment period

All participants returned to study sites **30 days** after receiving their last dose of study drugs.

The study doctors or staff asked participants if they had medical problems and followed up on their health every 12 weeks for up to 2 years.

What were the results of the study?

This is a summary of the main results of this study up to June 2022. The results each person had individually may 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.

Did participants who received lenvatinib plus ifosfamide and etoposide live longer without their osteosarcoma getting worse compared with those who received only ifosfamide and etoposide?

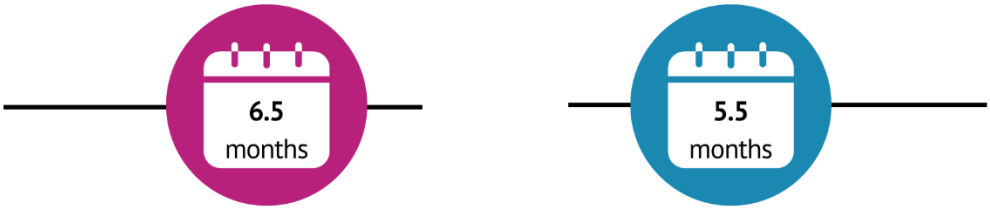
To answer this question, researchers looked at the results of participants who were assigned to receive study drug.

Researchers counted the time from the date participants were assigned study drug up to the date participants' tumors got worse or the participant died. This is called progression-free survival or PFS. Researchers then compared the midpoint PFS of participants in Group A to that of participants in Group B.

Midpoint PFS means half of participants had longer PFS and half had shorter PFS.

The chart below shows the midpoint PFS from participants in Group A and Group B.

The midpoint PFS from participants in Group A and Group B after taking study treatment



Group A

Participants who received lenvatinib, ifosfamide, and etoposide had a midpoint PFS of **6.5 months**.

Group B

Participants who received only ifosfamide and etoposide had a midpoint PFS of **5.5 months**.

The difference in the results between 2 groups was too small for the researchers to tell whether lenvatinib, ifosfamide, and etoposide worked better than ifosfamide and etoposide without lenvatinib in helping participants go longer without their osteosarcoma getting worse.

What medical problems did participants have?

Medical problems that happen in clinical studies are called “adverse events.” An adverse event that the study doctors thought was caused by the study drug is called an “adverse reaction.” An adverse reaction 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 reactions that happened during this study. 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 drug causes a medical problem.

Results in this section were from participants who received at least 1 dose of any study drug.

How many participants had adverse reactions?

In this study, 76 out of 78 participants (97%) had adverse reactions.

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

Adverse Reactions in this Study

	Out of 39 participants in Group A	Out of 39 participants in Group B
How many participants had adverse reactions?	38 (97%)	38 (97%)
How many participants had serious adverse reactions?	23 (59%)	12 (31%)
How many participants stopped receiving study drug(s) because of adverse reactions?	10 (26%)	3 (8%)

What were the most common adverse reactions?

The most common adverse reactions were:

- Low levels of red blood cells
- Low platelet count (platelets are components of blood that help it to clot)
- Underactive thyroid gland

The table below shows the adverse reactions that happened in 15% or more of participants overall. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions in this Study

	Out of 39 participants in Group A	Out of 39 participants in Group B
Low levels of red blood cells	26 (67%)	23 (59%)
Low platelet count	20 (51%)	16 (41%)
Underactive thyroid gland	34 (87%)	0
Feeling sick	19 (49%)	14 (36%)
Decreased neutrophil (type of white blood cell) count	14 (36%)	13 (33%)
Excess protein in the urine	20 (51%)	4 (10%)
Vomiting	14 (36%)	10 (26%)
Low levels of neutrophils with fever	14 (36%)	9 (23%)
Low levels of neutrophils	9 (23%)	8 (21%)
Swelling of mouth and lips	10 (26%)	6 (15%)
Tiredness	7 (18%)	8 (21%)
High blood pressure	15 (39%)	0
Low white blood cell count	3 (8%)	12 (31%)
Fever	7 (18%)	5 (13%)

What were the most common serious adverse reactions?

In this study, 35 out of 78 participants (45%) had serious adverse reactions.

In this study, 1 participant in Group A died due to a serious adverse reaction.

The table below shows the serious adverse reactions that happened in 4% or more of participants overall. There were other serious adverse reactions, but these happened in fewer participants.

Most Common Serious Adverse Reactions in this Study

	Out of 39 participants in Group A	Out of 39 participants in Group B
Low levels of neutrophils with fever	14 (36%)	7 (18%)
Collapsed lungs	5 (13%)	0
Fever	4 (10%)	1 (3%)
Low platelet count	3 (8%)	0
Reversible brain condition caused by ifosfamide	3 (8%)	0

How has this study helped participants and researchers?

In this study, researchers learned more about how lenvatinib, when given with ifosfamide and etoposide, may have helped people with osteosarcoma.

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 children 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.clinicaltrialsregister.eu - Once you are on the website, click "**Home and Search**", then type **2019-003696-19** in the search box and click "**Search**."
- https://www.clinicaltrials.gov - Once you are on the website, type **NCT04154189** into the search box and click "**Search**."

Full study title: A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)

Protocol number: E7080-G000-230

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.

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Certara Synchrogenix Headquarters 100 Overlook Center, Suite 101, Princeton, NJ 08540
https://www.certara.com • 1-415-237-8272