Clinical Study Results

Research Sponsor: Eisai Inc.
Drug Studied: E7080, also called lenvatinib
Short Study Title: A study to learn how lenvatinib works and its safety in participants with solid tumors or osteosarcoma

Thank you!

You or your child took part in this clinical study for the study drug E7080, also called lenvatinib. All of the participants helped researchers learn more about lenvatinib to help people with solid tumors, throat cancer, or a type of bone cancer called osteosarcoma that has not responded to or has come back since previous treatment. Cancer is a term for diseases in which the cells in the body divide uncontrollably. A tumor is when this uncontrolled growth forms an abnormal mass of tissue. This is also called a solid tumor. Solid tumors can form in many parts of the body. One of which is sarcoma. A sarcoma is a tumor that begins in the connective tissues, such as bones, muscles, or fats. A cancer that starts in the bone is called osteosarcoma. People with osteosarcoma often experience pain and swelling in their bones or joints, making it hard for them to move.

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 the results of the study.

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 December 2014.

The study included 117 participants from 19 study sites in France, Germany, Italy, Spain, the United Kingdom, and the United States.

Of the 117 participants, 97 received study treatment at least once.

The sponsor of the study reviewed the main results collected up to October 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 a solid tumor, throat cancer, or osteosarcoma that has not responded to or has come back since previous treatment. The standard treatments for solid tumor, throat cancer, and osteosarcoma include surgery, radiation, and chemotherapy, such as ifosfamide (also called IFOS) and etoposide (also called ETOP). Researchers thought that lenvatinib alone or when given with IFOS and ETOP could help improve symptoms of solid tumors, throat cancer, or osteosarcoma.

The researchers in this study wanted to find out the highest dose of lenvatinib (also called the recommended dose) when given alone and when given with IFOS and ETOP. Lenvatinib works by targeting and blocking specific proteins that help cancer cells survive and grow. The researchers wanted to know if the recommended dose of lenvatinib when given alone or with IFOS and ETOP could help improve the symptoms of solid tumors, throat cancer, or osteosarcoma. They also wanted to find out if people had any medical problems during the study.

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

- What was the highest dose of lenvatinib when given alone to children or adolescents with solid tumors?
- Did the recommended dose of lenvatinib when given alone help improve the symptoms of osteosarcoma?
- What was the highest dose of lenvatinib when given with IFOS and ETOP to participants with osteosarcoma?
- Did the recommended doses of lenvatinib, IFOS, and ETOP help improve the symptoms of osteosarcoma?
- What adverse reactions did participants receiving lenvatinib 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 works. 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 participants aged 3 to 25 years. Of these participants, 56% were male, and 44% were female. They all had either a solid tumor, throat cancer, or osteosarcoma that had not responded to or had come back since previous treatment.

The participants in the study were divided into 3 groups.

Group 1

Participants in Group 1 included children and adolescents with solid tumor.

Groups 2A and 2B

Participants in Groups 2A and 2B included children, adolescents, and young adults with throat cancer or osteosarcoma that was coming back and not responding to treatment.

Groups 3A and 3B

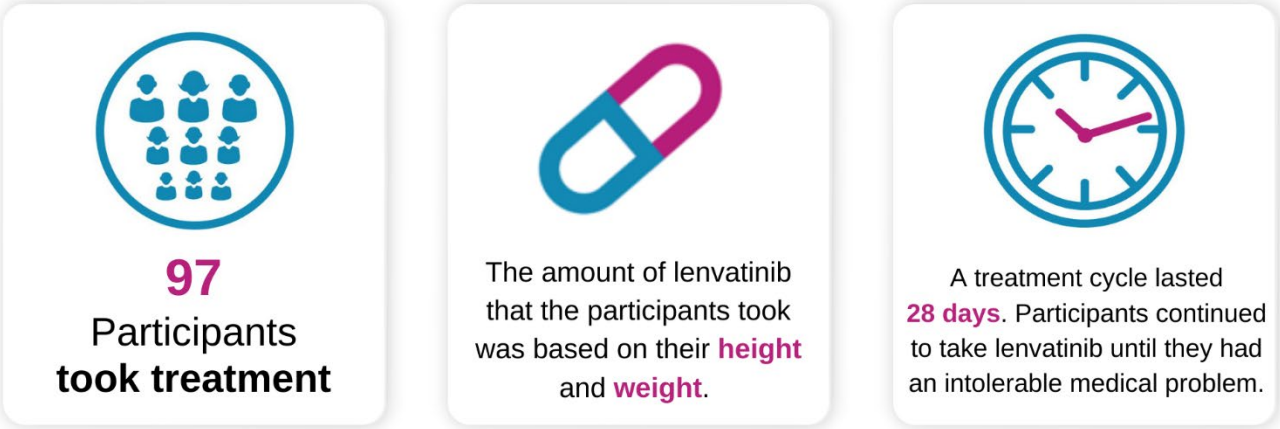
Participants in Groups 3A and 3B included children, adolescents, and young adults with osteosarcoma that was coming back and not responding to treatment.

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

All participants took lenvatinib as a capsule or as a liquid with solid particles in it, also known as a suspension, by mouth once daily. Some participants in the study had lenvatinib together with IFOS and ETOP. Both IFOS and ETOP were given through a needle into a vein, also called intravenous or IV infusion.

- The amount of lenvatinib, IFOS, and ETOP was measured in milligrams (mg) and based on the participants' body surface area measured in meters squared (m^2).
- Researchers used different doses of lenvatinib to find out which were safest when it was given alone or together with IFOS and ETOP.
- Participants in Groups 1, 2A, and 2B took lenvatinib alone while participants in Groups 3A and 3B took lenvatinib together with IFOS and ETOP.
- The study treatment was given in repeating 28-day time periods called treatment cycles.

The figure below shows how treatment was given.



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 the participants had solid tumor, throat cancer, or osteosarcoma that was coming back and not responding to previous treatment
- asked what medications they were taking
- took blood, urine, and stool samples
- checked each participant's heart health using an electrocardiogram

During the Treatment period, the participants took their assigned dose of lenvatinib by mouth once every day. Some participants also received IFOS and ETOP by IV infusion once every day for 3 days in a row in each 28-day time period (treatment cycle) for a maximum of 5 treatment cycles. After completing IFOS and ETOP, the participant could continue receiving lenvatinib alone.

Throughout the study, the study doctors or staff:

- continued to check participants' health
- took blood, urine, and stool samples
- asked participants if they had any medical problems and what medicines they were taking

Each participant could continue receiving the study drug until:

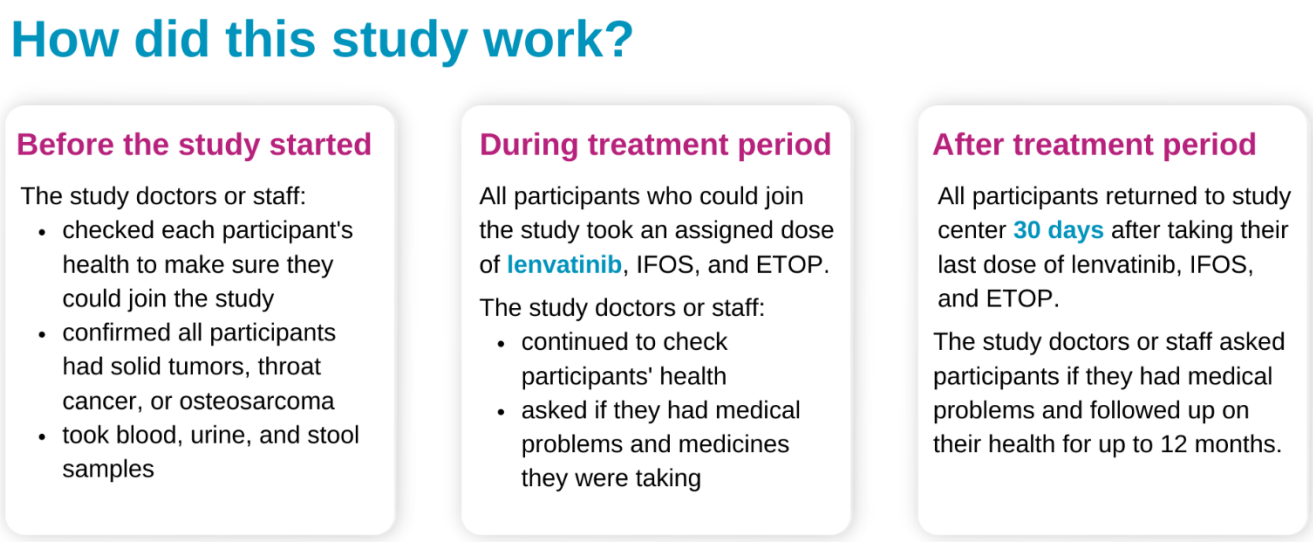
- their solid tumor or osteosarcoma got worse;
- they had intolerable medical problems;
- they decided not to participate in the study; or
- the sponsor ended the study

Thirty days after their last dose, all participants who stopped taking lenvatinib returned to the study site.

The participants:

- had their blood and urine samples taken
- were asked if they had any medical problems and what medicines they were taking
- were followed up to check their health every 3 months for up to 12 months

The figure below shows how the study was done.



What were the results of the study?

This is a summary of the main results of this study up to October 2022. The results each person had might be different and are not in this summary. But the results each person had have been combined and so 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 that any medical problems due to the study drug can be treated or managed effectively. Other studies may provide new information or different results. Always talk to a doctor before making any treatment decisions.

The researchers planned to include children, adolescents, and young adults with thyroid cancer in this study. But as of October 2022, only 1 adolescent with thyroid cancer took part in this study. The results of this 1 adolescent were not included in this summary to protect their privacy.

What was the highest dose of lenvatinib when given alone to children or adolescents with solid tumors?

To answer this question, researchers looked at the results of the children and adolescents in Group 1 of the study who took different doses of lenvatinib alone.

The study doctors checked if the children and adolescents had medical problems that would prevent an increase in the dose of lenvatinib. These medical problems are called dose-limiting toxicities, or DLTs.

Researchers then looked at the highest dose that each child and adolescent took before they had a DLT.

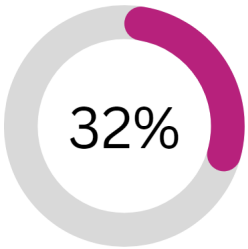
The researchers learned that medical problems due to lenvatinib at a dose of **14 mg/m²** once daily could generally be treated or managed effectively. Researchers decided to use this dose in other groups in the study.

Did the recommended dose of lenvatinib when given alone help improve the symptoms of osteosarcoma?

To answer this question, researchers looked at the results of the participants in Group 2 of the study who took 14 mg/m^2 of lenvatinib alone.

The study doctors checked how many participants were alive without their disease getting worse. This is called progression-free survival, or PFS. Researchers reviewed the PFS results of the participants after the participants' health had been followed for 4 months, or sooner if a participant stopped study treatment earlier. This is called the PFS-rate at 4 months (PFS-4).

They also compared the PFS-4 result to other drugs that were used or have been studied for osteosarcoma that has come back after treatment or did not respond to treatment. They did this to check the chances that the effect of lenvatinib was greater than what they expected would happen in the study. If the effect of lenvatinib was greater than what the researchers expected, this was called significant.



Researchers found out that
9 out of 28 participants (32%) were alive without worsening of osteosarcoma after following up on their health for 4 months or sooner.
The researchers also found this result not significant.

What was the highest dose of lenvatinib when given with IFOS and ETOP to participants with osteosarcoma?

To answer this question, researchers looked at the results of the participants in Group 3A of the study who got different doses of lenvatinib, IFOS, and ETOP.

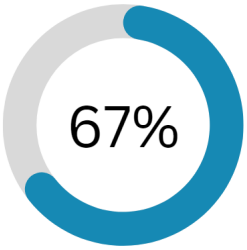
The researchers looked at the highest manageable doses of lenvatinib, IFOS, and ETOP.

The researchers learned that medical problems due to lenvatinib, IFOS, or ETOP at doses mentioned above could generally be treated or managed effectively.
Researchers decided to use these doses in Group 3B in the study.

Did the recommended doses of lenvatinib, IFOS, and ETOP help improve the symptoms of osteosarcoma?

To answer this question, researchers looked at the results of the participants in Group 3B of the study who got the recommended doses of lenvatinib, IFOS, and ETOP.

Researchers reviewed the PFS-4 results of participants in Group 3B. They also checked if the PFS-4 results were significant.



Researchers found out that **10 out of 15 participants (67%)** were alive without worsening of osteosarcoma after following up on their health for 4 months or sooner.
The researchers also found this result significant.

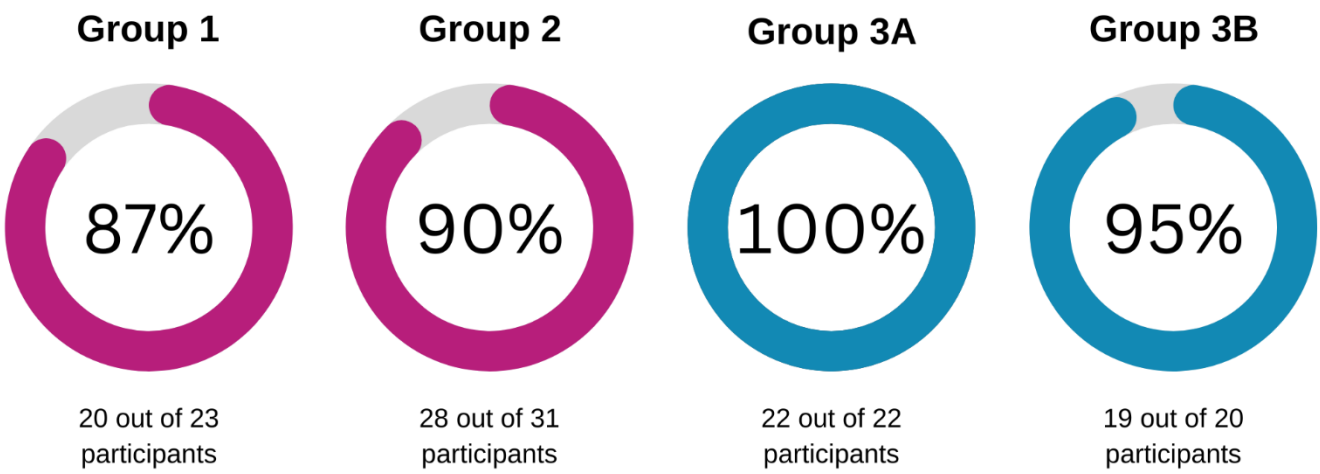
What medical problems did participants have?

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, 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 study drug causes a medical problem.

How many participants had adverse reactions?

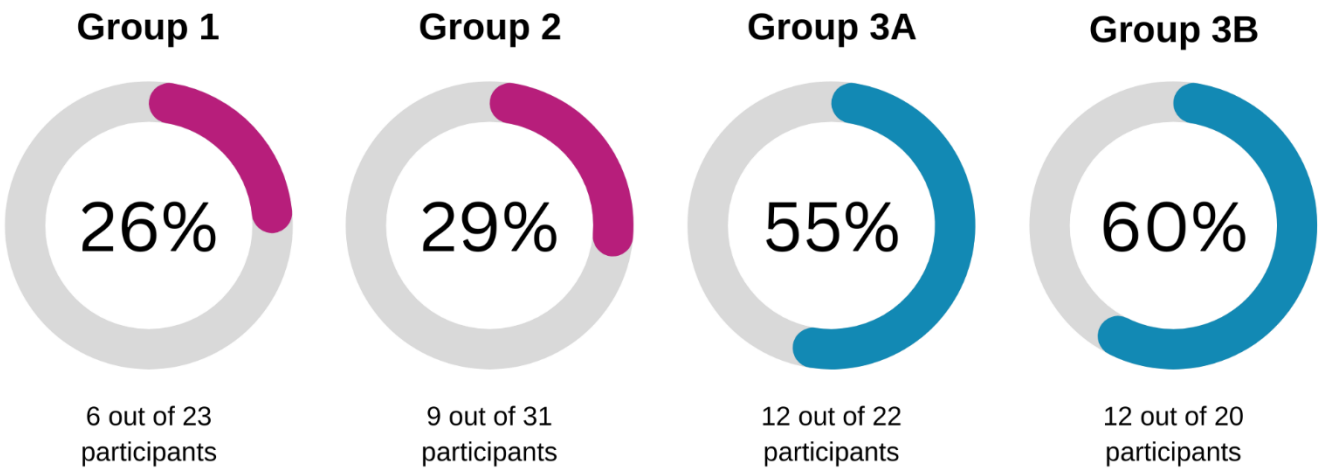
The chart below shows how many participants in each group had adverse reactions during the study.



In this study, all adverse reactions that caused the participants to stop taking lenvatinib happened in no more than 1 participant each in any group.

What were the most common serious adverse reactions?

The chart below shows how many participants in each group had serious adverse reactions during the study.



No participants in this study died due to serious adverse reactions.

In Groups 1 and 2, all serious adverse reactions happened in 1 participant each, except for:

- high blood pressure
- collapsed lung

In Groups 3A and 3B, the most common serious adverse reactions were:

- low levels of neutrophils with fever
- collapsed lung
- decreased level of white blood cells

The table below shows the serious adverse reactions that happened in 2 participants or more in Groups 3A and 3B. There were other serious adverse reactions, but these happened in fewer participants.

Most Common Serious Adverse Reactions in This Study				
	Out of 23 participants in Group 1	Out of 31 participants in Group 2	Out of 22 participants in Group 3A	Out of 20 participants in Group 3B
Low levels of neutrophils with fever	0	0	8 (36%)	2 (10%)
Collapsed lung	0	2 (6%)	4 (18%)	1 (5%)
Decreased level of white blood cells	0	0	0	5 (25%)
Vomiting	1 (4%)	0	2 (9%)	2 (10%)
Decreased level of platelets	0	1 (3%)	0	4 (20%)
Decreased level of neutrophils	0	0	0	4 (20%)
Nosebleed	0	0	2 (9%)	1 (5%)
High blood pressure	2 (9%)	1 (3%)	0	0
Low levels of red blood cells	0	0	0	2 (10%)
Dehydration	0	0	0	2 (10%)

What were the most common adverse reactions?

In this study, 89 out of 96 participants (93%) had an adverse reaction.

In Groups 1 and 2, the most common adverse reactions were:

- underactive thyroid gland
- decreased appetite
- diarrhea
- high blood pressure

In Groups 3A and 3B, the most common adverse reactions were:

- low levels of red blood cells
- nausea
- vomiting

The table below shows the adverse reactions that happened in 30% or more of participants in any group. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions in This Study				
	Out of 23 participants in Group 1	Out of 31 participants in Group 2	Out of 22 participants in Group 3A	Out of 20 participants in Group 3B
Underactive thyroid gland	12 (52%)	13 (42%)	11 (50%)	6 (30%)
Nausea	6 (26%)	8 (26%)	15 (68%)	13 (65%)
Diarrhea	11 (48%)	8 (26%)	10 (45%)	12 (60%)
Vomiting	10 (43%)	7 (23%)	11 (50%)	12 (60%)
Low levels of red blood cells	1 (4%)	2 (6%)	16 (73%)	15 (75%)
Decreased appetite	9 (39%)	13 (42%)	6 (27%)	5 (25%)
Excess protein in the urine	6 (26%)	7 (23%)	7 (32%)	8 (40%)
High blood pressure	9 (39%)	10 (32%)	5 (23%)	3 (15%)
Pain in the abdomen	5 (22%)	5 (16%)	11 (50%)	6 (30%)
Loss of weight	8 (35%)	6 (19%)	8 (36%)	4 (20%)
Tiredness	7 (30%)	8 (26%)	6 (27%)	3 (15%)
Low levels of neutrophils	0	0	12 (55%)	8 (40%)
Decreased level of white blood cells	0	0	7 (32%)	12 (60%)
Weakness	3 (13%)	8 (26%)	1 (5%)	7 (35%)
Decreased level of platelets	1 (4%)	1 (3%)	5 (23%)	11 (55%)
Low levels of platelets	0	3 (10%)	9 (41%)	5 (25%)
Nosebleed	2 (9%)	2 (6%)	9 (41%)	4 (20%)
Inflammation of the lining of the mouth	1 (4%)	3 (10%)	8 (36%)	4 (20%)
Constipation	2 (9%)	3 (10%)	7 (32%)	2 (10%)
Decreased level of neutrophils	0	0	3 (14%)	9 (45%)
Low levels of neutrophils with fever	0	0	8 (36%)	2 (10%)

How has this study helped patients and researchers?

In this study, researchers learned more about how lenvatinib may have helped people with solid tumors, throat cancer, or 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 are 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:

- http://www.clinicaltrialsregister.eu - Once you are on the website, click "**Home and Search**", then type **2013-005534-38** in the search box and click "**Search**".
- http://www.clinicaltrials.gov - Once you are on the website, type **NCT02432274** into the search box and click "**Search**".

Full study title: Phase 1/2 Study of Lenvatinib in Children and Adolescents With Refractory or Relapsed Solid Malignancies and Young Adults with Osteosarcoma

Protocol number: E7080-G000-207

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.

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.

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