Clinical Study Results

Research Sponsor: Eisai Inc.
Drug Studied: E7080, also called lenvatinib
Short Study Title: A study to learn how lenvatinib and everolimus work together and their safety in participants with certain solid tumors

Thank you!

You or your child took part in this clinical study for the study drug E7080, also called lenvatinib, given together with another drug called everolimus. You, your child, and all of the participants helped researchers learn more about lenvatinib, given together with everolimus, and how it may help people with certain cancers called solid tumors.

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 November 2017.

The study included 64 participants from 24 study centers in Canada and the United States. All participants took at least 1 dose of study treatment.

The sponsor of the study reviewed the data collected up to 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 certain solid tumors. The standard treatments for people with a solid tumor include surgery and other treatments that help shrink tumors. But these treatments may not help all people with solid tumors, 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, which they need to keep growing. Everolimus helps to shrink tumors by blocking a special protein that causes cancer to grow.

The researchers in this study wanted to find out if lenvatinib, when given with everolimus, could help improve symptoms of participants with certain solid tumors.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 was the highest dose of lenvatinib with manageable side effects that can be given together with everolimus to participants with a solid tumor?
- What were the dose-limiting toxicities of lenvatinib, when given together with everolimus to participants with a solid tumor? Dose-limiting toxicities, also called DLTs, are medical problems that would prevent participants from taking a higher dose.
- How effective are the selected doses of lenvatinib and everolimus at shrinking the tumors of participants with certain solid tumors after 16 weeks of treatment?
- What adverse reactions did participants receiving lenvatinib and everolimus have? An adverse reaction is a medical problem that may be caused by the study drug.

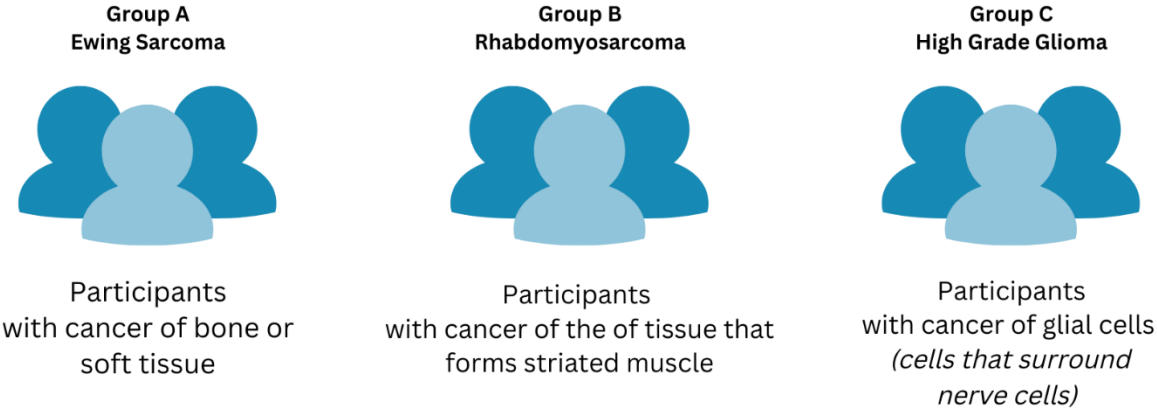
It is important to know that this study was designed to get accurate answers to the questions listed above. There were other questions the researchers wanted to answer to learn more about how lenvatinib and everolimus work together. But, these were not the main questions the study was designed to answer.

What kind of study was this?

To answer these questions, researchers asked for the help of males and females like you. The participants in the study were 2 to 21 years old. Of these participants, 52% were male, and 48% were female. They all had a solid tumor that had not responded to treatment or had come back since previous treatment.

The study had 2 parts:

- **Part 1**: The researchers wanted to learn about the safety of different doses of lenvatinib when taken together with everolimus. The participants in this part of the study had solid tumors, including tumors in the brain or spinal cord.
- **Part 2**: Using the selected doses of lenvatinib and everolimus from Part 1, the researchers wanted to learn how lenvatinib and everolimus work together to shrink the solid tumors of the participants. Participants in this part of the study were divided into 3 separate groups depending on what type of solid tumor they had:



All of the participants in this study had a solid tumor that had spread to another part of the body. They had a solid tumor that had not responded to treatment or had come back since previous treatment.

People could not take part in the study if they had planned to have surgery, had unhealed wounds or fractures, or infections that needed treatment.

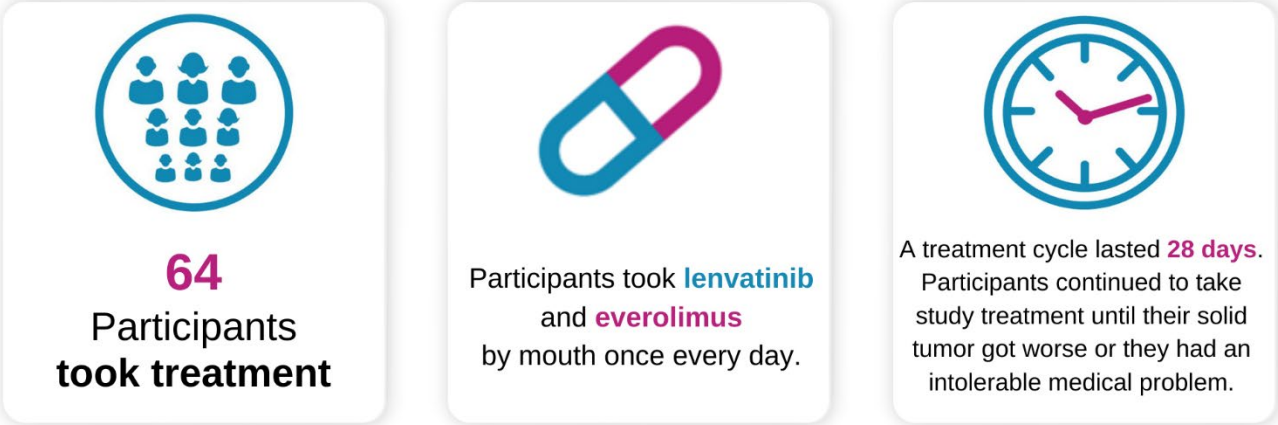
This study was "open-label". This means that the participants, the study doctors and staff, and the sponsor knew which study treatment the participants took.

Lenvatinib capsules and everolimus tablets were taken by mouth once every day. A suspension from lenvatinib capsule was prepared for children who could not swallow capsules. A suspension is a liquid with solid particles in it. Some participants took everolimus as a tablet that dissolves in the mouth. This type of tablet is called orodispersible tablet.

The study treatment was given in 28-day time periods called treatment cycles. The amount of lenvatinib and everolimus participants took was measured in milligrams per square meter (mg/m^2) based on each participant's body surface area.

- **In Part 1**, both lenvatinib and everolimus were taken once every day for 28 days. Two dose levels (8 and 11 mg/m^2) of lenvatinib and 1 dose level (3 mg/m^2) of everolimus were tested.
- **In Part 2**, the selected dose levels of lenvatinib and everolimus in Part 1 were taken once every day in repeating 28-day cycles.

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:

- Confirmed the participants had a solid tumor that was coming back or not responding to previous treatment
- Did a 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 and body to assess their tumors

During treatment in Parts 1 and 2, the participants took lenvatinib together with everolimus in 28-day cycles.

Throughout the treatment, the study doctors or staff did the following:

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

At the end of Parts 1 and 2 of the study, participants could continue to receive the same study treatment until:

- Their solid tumors got worse
- They had medical problems that made them leave the study
- They chose to leave the study
- The sponsor chose to end the study

Within 28 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

Partcipants were also asked about adverse reactions and medicines they were taking.

The figure below shows how the study was done.

How did this study work?

Before the study started

The study doctors or staff:

- Took imaging scans to assess each participant's tumor
- Checked each participant to see if they could join the study
- Took blood and urine samples

During treatment period

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

The study doctors or staff:

- Did imaging scans to assess each participant's tumor
- 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 **28 days** after taking their last dose of study treatment.

The study doctors or staff did final check-ups, collected blood and urine samples, and asked if participants had medical problems and medicines participants were taking.

What were the results of the study?

This is a summary of the main results from all participants in Parts 1 and 2 of the study. 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.

Results from Part 1 in 23 participants with a solid tumor

What was the highest dose of lenvatinib with manageable side effects that can be given together with everolimus to participants with solid tumors?

To answer this question, researchers looked at the results from all of the participants in Part 1 of the study. Participants took 1 of 2 different doses of lenvatinib and 1 dose of everolimus. Study doctors then checked if participants had DLTs.

Researchers found that 2 out of 12 participants who took the 11 mg/m^2 dose level of lenvatinib and 3 mg/m^2 dose level of everolimus had a DLT.

Based on the safety results from Part 1, the doctors and experts learned that side effects due to lenvatinib at 11 mg/m^2 dose level and everolimus at 3 mg/m^2 dose level once daily could generally be treated and managed. Doctors and experts decided to use these dose levels in Part 2 of the study.

What were the DLTs of lenvatinib, when given together with everolimus to participants with a solid tumor?

To answer this question, researchers looked at the DLTs of all participants in Part 1 of the study.

Researchers found the following DLTs happened in Part 1 of the study:

- Excess protein in the urine
- High blood levels of triglycerides (a type of fat in the body)
- High level of blood cholesterol

Results from Part 2 in 40 participants with solid tumors

How effective are the selected doses of lenvatinib and everolimus at shrinking the tumors of participants with certain solid tumors after 16 weeks of treatment?

To answer this question, the researchers looked at the results from participants with:

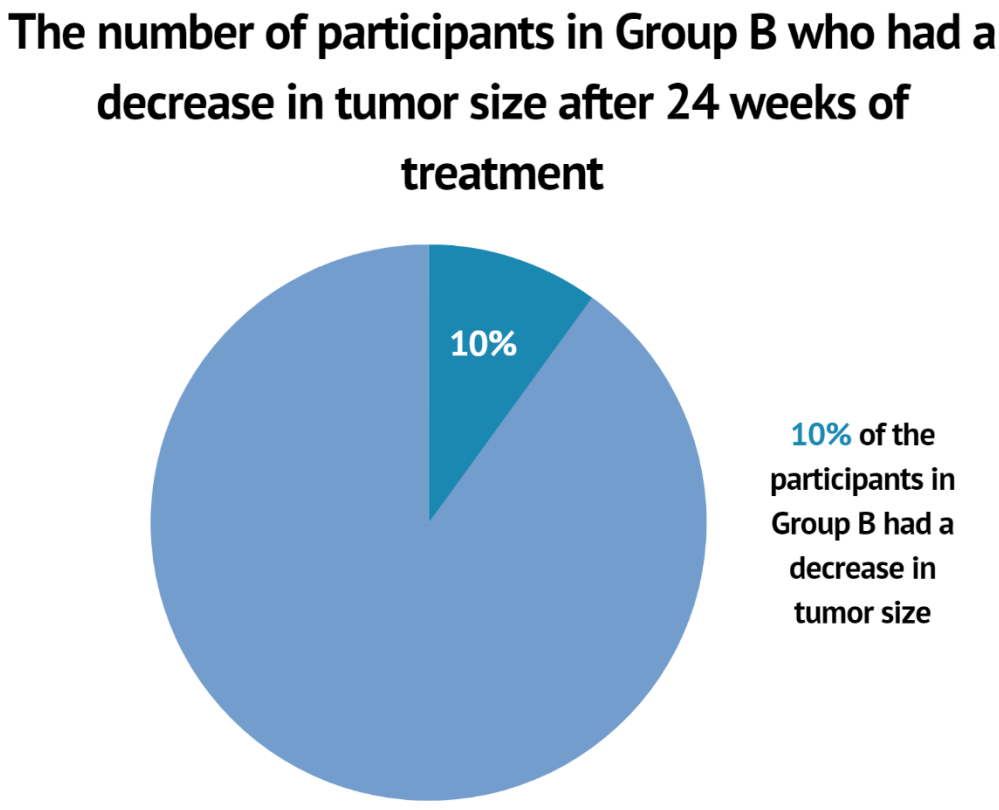
- Group A (10 participants): cancer of bone or soft tissue
- Group B (20 participants): cancer of the tissue that forms striated muscle
- Group C (10 participants): cancer of glial cells

Study doctors looked at the scan results and compared the size of each participant's tumor before they started the study treatment with the size when they had received the study treatment.

Researchers found the following:

- No participants in Groups A and C had a decrease in tumor size.
- 2 out of 20 participants in Group B had a decrease in tumor size.

The chart below shows the number of participants in Group B who had a decrease in tumor size.



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?

In this study,

- All 23 participants (100%) had adverse reactions during Part 1 of the study.
- 38 out of 41 participants (93%) had adverse reactions during Part 2 of the study.

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

Adverse Reactions in this Study

	Out of 23 participants in Part 1 of the study	Out of 41 participants in Part 2 of the study
How many participants had adverse reactions?	23 (100%)	38 (93%)
How many participants had serious adverse reactions?	4 (17%)	11 (27%)
How many participants stopped receiving either study drug because of adverse reactions?	2 (9%)	3 (7%)

What were the most common serious adverse reactions?

In this study,

- 4 participants (17%) had serious adverse reactions during Part 1 of the study.
- 11 participants (27%) had serious adverse reactions during Part 2 of the study.

No participants died due to serious adverse reactions during the study.

What were the most common adverse reactions?

In Part 1 of the study, the most common adverse reactions were:

- High blood pressure
- Underactive thyroid gland
- High blood levels of triglycerides

In Part 2 of the study, the most common adverse reactions were:

- High blood levels of triglycerides
- Excess protein in the urine
- Diarrhea

The table below shows the adverse reactions that happened in more than 40% of participants in either part of the study. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions in this Study

	Out of 23 participants in Part 1 of the study	Out of 41 participants in Part 2 of the study
High blood levels of triglycerides	11 (48%)	23 (56%)
High blood pressure	14 (61%)	14 (34%)
Diarrhea	10 (44%)	16 (39%)
Underactive thyroid gland	12 (52%)	14 (34%)
Excess protein in the urine	8 (35%)	18 (44%)
Pain in abdomen	10 (44%)	9 (22%)

How has this study helped patients and researchers?

In this study, researchers learned more about how lenvatinib, when given together with everolimus, may have helped people with certain solid tumors.

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 pediatric clinical studies with lenvatinib 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:

- http://www.clinicaltrials.gov - Once you are on the website, type **NCT03245151** into the search box and click "**Search**".

Full study title: A Phase 1/2 Study of Lenvatinib in Combination with Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors

Protocol number: E7080-A001-216

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 +1 888-274-2378.

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