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 people with certain solid tumors

Thank you!

You took part in this clinical study for the study drug lenvatinib, also called E7080, 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 certain cancers called solid tumors. All of the participants in this study had cancer that had spread to another part of the body.

This study was done in 2 Parts, participants who had solid tumors took part in Part 1. In Part 2, participants with 1 of 6 types of solid tumor were divided into different groups, depending on the type of solid tumors they had.

This report summarizes the results from all participants in Part 1, and from participants in Part 2 who had melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell cancer (HNSCC), or urothelial cancer (UC). The Part 2 results for the participants with other solid tumors are summarized in different reports.

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

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 July 2015 and ended in July 2022.

The study included 357 participants from 46 study sites in the United States, Spain, and Norway. All participants took at least 1 dose of study treatment.

The sponsor of the study reviewed the data collected during the study and created a report of the results.

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 solid tumors 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. Pembrolizumab helps to shrink tumors by helping the immune system to identify and target cancer cells.

The researchers in this study wanted to find out if lenvatinib and pembrolizumab work when given together to people 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 is the highest dose of lenvatinib with manageable side effects, when given together with pembrolizumab to participants with solid tumors?
- How effective is lenvatinib, when given together with pembrolizumab, at shrinking the tumors of participants with melanoma, NSCLC, HNSCC, or UC after 24 weeks of treatment?
- For those that responded to study treatment, how long did their response last?
- What adverse reactions did participants receiving lenvatinib and pembrolizumab have? An adverse reaction is a medical problem that may be caused by the study treatment.

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 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 included in Part 1 and Part 2 of the study were 31 to 87 years old. Of these participants, 49% were male, and 51% were female.

The study had 2 parts:

- **In Part 1**, the researchers wanted to learn about the safety of different doses of lenvatinib when taken with pembrolizumab. The participants in this part of the study had 1 of 6 different solid tumors.
- **In Part 2**, using the selected dose of lenvatinib from Part 1, the researchers wanted to learn how lenvatinib and pembrolizumab work together to shrink the tumors of participants with melanoma, NSCLC, HNSCC, or UC. They also wanted to learn how long the participants continued to respond to the study treatment.

All of the participants had cancer that had spread to another part of the body. They had cancer that had got worse after being treated with standard treatments for their cancer, or cancer for which no effective standard treatment was available.

People could not take part in the study if they had certain heart conditions within 6 months of starting the study, a condition where the lung tissue became swollen and required steroid treatment, history of an organ transplant, or an active infection.

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.

The study treatment was given in 21-day time periods called treatment cycles. The amount of lenvatinib and pembrolizumab received was measured in milligrams (mg).

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

- **In Part 1**, lenvatinib was taken once every day for 21 days, 2 doses of lenvatinib were tested, 20 mg and 24 mg. All participants received a single 200 mg dose of pembrolizumab.
- **In Part 2**, a 20 mg dose of lenvatinib was taken once every day in repeating 21-day cycles. A 200 mg dose of pembrolizumab was given once during each 21-day cycle.

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 did the following:

- Performed 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 Part 1 and Part 2, 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 medical problems each participant was experiencing

Each participant could continue receiving the study treatment until any of the following occurred:

- Their cancer got worse
- They had medical problems that made it difficult to continue
- They became pregnant
- They chose to leave the study
- The sponsor chose to end the study

Participants could continue to receive the same study treatment until they had received pembrolizumab a maximum of 35 times. After receiving pembrolizumab 35 times, participants could continue to receive lenvatinib only.

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
- Underwent a scan of the brain and the body to assess their tumors

The chart 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 solid tumors that had spread to other parts of the body
- Checked each participant to see if they could join the study
- 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.

In Part 1, 13 participants with solid tumors were included to help find the highest dose of lenvatinib with manageable side effects, when given together with pembrolizumab.

In Part 2, 344 participants were divided into separate groups depending on the type of cancer they had.

The results from all participants in Part 1, and the participants with melanoma, NSCLC, HNSCC, or UC in Part 2 are summarized in this report.

What were the results of the study?

This is a summary of the main results from all participants in Part 1 combined, and from the participants with melanoma, NSCLC, HNSCC, or UC in Part 2 combined. The results from each person are not individually shown in this summary. But the results each person had are part of the summary of combined 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 13 participants with solid tumors

What is the highest dose of lenvatinib with manageable side effects, when given together with pembrolizumab to participants with solid tumors?

To answer this question, the researchers looked at the results from all of the participants in Part 1 of the study. Participants received 1 of 2 different doses of lenvatinib during Part 1, either 20 mg or 24 mg. They all received the same 200 mg dose of pembrolizumab.

Study doctors checked if the participants had medical problems that would make them take a lower dose. These medical problems are called dose-limiting toxicities or DLTs.

Researchers found that 2 out of 3 participants who received a 24 mg dose of lenvatinib had a DLT. None of the participants who received the 20 mg dose of lenvatinib had a DLT.

Based on the safety results from Part 1, the 20 mg dose of lenvatinib, combined with a 200 mg dose of pembrolizumab, was used during Part 2.

Results from Part 2 in 84 participants with melanoma, NSCLC, HNSCC, or UC

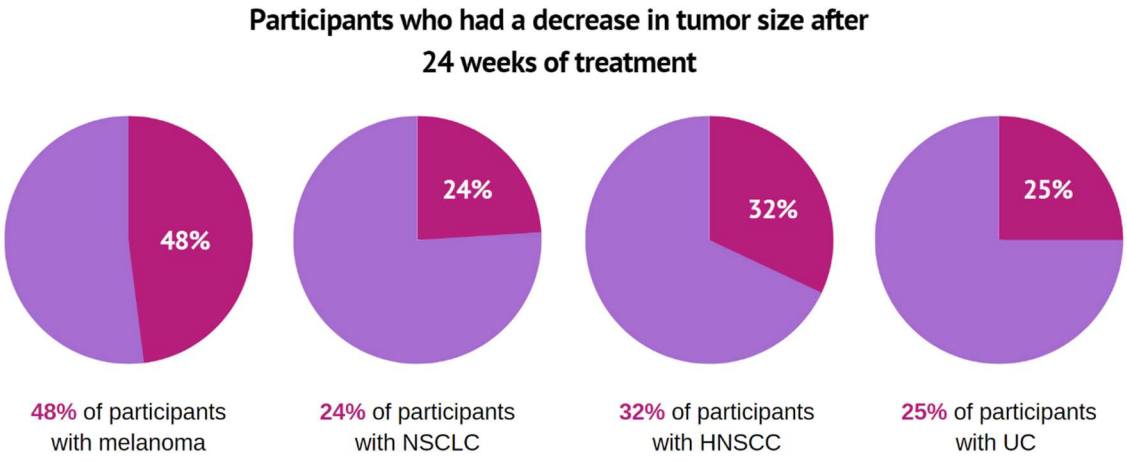
How effective is lenvatinib, when given together with pembrolizumab, at shrinking the tumors of participants with melanoma, NSCLC, HNSCC, or UC after 24 weeks of treatment?

To answer this question, the researchers looked at the results from participants with melanoma, NSCLC, HNSCC, or UC. Study doctors looked at the scan results and compared the size of each participant's tumor before they started the study treatment, and after receiving study treatment for 24 weeks.

Overall, the following participants had a decrease in tumor size after 24 weeks of treatment:

- 10 out of 21 participants (48%) with melanoma
- 5 out of 21 participants (24%) with NSCLC
- 7 out of 22 participants (32%) with HNSCC
- 5 out of 20 participants (25%) with UC

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



For those that responded to study treatment, how long did the response last in participants with melanoma, NSCLC, HNSCC, or UC?

To answer this question, the researchers looked at the results from participants with melanoma, NSCLC, HNSCC, or UC who had responded to study treatment.

The table below shows how long the participants who responded to treatment, continued to respond.

The midpoint is shown in months for each type of cancer, half of those who responded to treatment responded for longer, and half responded for a shorter time.

Midpoint Times of Response for Participants who Responded to Study Treatment

	Melanoma	NSCLC	HNSCC	UC
Midpoint time participants continued to respond to study treatment	13 months	15 months	7 months	41 months

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 treatment 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?

During Parts 1 and 2 of the study, in total 80 out of 84 participants (95%) with melanoma, NSCLC, HNSCC or UC had adverse reactions.

Participants who had adverse reactions during Parts 1 and 2 of the study:

- All participants (100%) with melanoma
- 20 out of 21 participants (95%) with NSCLC
- 21 out of 22 participants (96%) with HNSCC
- 18 out of 20 participants (90%) with UC

The table on the next page shows how many participants had adverse reactions.

Adverse Reactions in This Study

	Out of 21 participants with melanoma who received study treatment	Out of 21 participants with NSCLC who received study treatment	Out of 22 participants with HNSCC who received study treatment	Out of 20 participants with UC who received study treatment
How many participants had adverse reactions?	21 (100%)	20 (95%)	21 (96%)	18 (90%)
How many participants had serious adverse reactions?	6 (29%)	6 (29%)	5 23%)	6 (30%)
How many participants stopped receiving either study drug because of adverse reactions?	0 (0%)	4 (19%)	4 (18%)	5 (25%)

What were the most common serious adverse reactions?

In this study, 23 out of 84 participants (27%) with melanoma, NSCLC, HNSCC, or UC had a serious adverse reaction. The only serious adverse reactions that happened in 2% or more of the participants were:

- Dehydration in 3 out of 84 participants (4%)
- Swollen gallbladder in 2 out of 84 participants (2%)
- High blood pressure in 2 out of 84 participants (2%)
- Inflammation of the lungs in 2 out of 84 participants (2%)
- Diarrhea in 2 out of 84 participants (2%)

There were other serious adverse reactions, but these happened in fewer participants.

There were 2 participants (2%) who died due to an adverse reaction:

- 1 participant with NSCLC died due to a bleed into a lung
- 1 participant with UC died due to a bleed in the intestines

What were the most common adverse reactions?

In this study, 80 out of 84 participants (95%) with melanoma, NSCLC, HNSCC, or UC had an adverse reaction. The most common adverse reactions were:

- Tiredness in 40 out of 84 participants (48%)
- Diarrhea in 36 out of 84 participants (43%)
- Decreased appetite 36 out of 84 participants (43%)

The table below shows the adverse reactions that happened in 30% or more of participants with melanoma, NSCLC, HNSCC, or UC. There were other adverse reactions, but these happened in fewer participants.

Most Common Adverse Reactions in This Study

	Out of 21 participants with melanoma who received study treatment	Out of 21 participants with NSCLC who received study treatment	Out of 22 participants with HNSCC who received study treatment	Out of 20 participants with UC who received study treatment
Tiredness	11 (52%)	12 (57%)	11 (50%)	6 (30%)
Diarrhea	10 (47%)	9 (43%)	8 (36%)	9 (45%)
Decreased appetite	10 (48%)	13 (62%)	7 (32%)	6 (30%)
High blood pressure	9 (43%)	6 (29%)	9 (41%)	7 (35%)
High level of protein in the urine	7 (33%)	8 (38%)	5 (23%)	11 (55%)
Underactive thyroid gland	6 (29%)	8 (38%)	6 (27%)	6 (30%)
Feeling sick	9 (43%)	5 (24%)	5 (23%)	5 (25%)
Problem with the voice	9 (43%)	5 (24%)	6 (27%)	2 (10%)
Pain or stiffness in joints	7 (33%)	6 (29%)	3 (14%)	2 (10%)
Swelling inside the mouth	1 (5%)	5 (24%)	7 (32%)	1 (5%)

How has this study helped patients and researchers?

In this study, researchers learned about the safety of lenvatinib when given together with pembrolizumab to people with solid tumors. They also learned how lenvatinib and pembrolizumab may help people with certain solid tumors that have spread to another part of the body.

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 2017-000300-26 in the search box and click "**Search**".
- http://www.clinicaltrials.gov - Once you are on the website, type NCT02501096 into the search box and click "**Search**".

Full study title: A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors

Protocol number: E7080-A001-111

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 numbers for general information are 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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