Clinical Trial Results

Research Sponsor:	Eisai
Drug Studied:	Lenvatinib or E7080
National Clinical Trial #:	NCT01136733
EudraCT #:	2010-019484-10
Protocol #:	E7080-G000-205
Trial Period:	March 2012 to June 2014
Short Trial Title:	A trial to see if the drugs lenvatinib and everolimus alone or combined together help reduce tumors in people with advanced kidney cancer

Thank you!

As a clinical trial participant, you belong to a large community of participants around the world who help researchers answer important health questions and discover new medical treatments.

Eisai, a Japanese pharmaceutical company and the sponsor of this trial, thanks you for your help. Eisai is committed to improving health through continuing research into areas of unmet need and sharing with you the results of the trial you participated in. Eisai prepared this summary with an independent non-profit organization called CISCRP and a medical and regulatory writing organization called Synchrogenix.

If you have questions about the results, please speak with the doctor, research nurse, or other team member at your trial site.

What has happened since my trial ended?

You were in this trial for up to 2 years, but the trial is still going on. The research sponsor reviewed the data collected up to June 2014 and created a report of the results.

This trial had a Part A and a Part B. This is a summary of the results from Part B.

Part B included 153 participants from 37 sites in Czech Republic, Poland, Spain, the United Kingdom, and the United States.

Why was the research needed?

Researchers were looking for a different way to treat people with advanced kidney cancer. Standard treatments like chemotherapy and radiation usually do not work on this type of cancer. So, researchers were interested in a drug called lenvatinib that can stop the growth of new blood vessels that help cancer grow and spread.

Researchers in this trial wanted to find out the effects of combining lenvatinib and a drug called everolimus for the treatment of advanced kidney cancer. Everolimus works in a different way to stop cancer cells from growing and spreading. It is used to treat advanced kidney cancer and other types of cancer. Researchers wanted to know how long taking lenvatinib and everolimus together kept participants' cancer from getting worse. They compared the effects of taking the drugs together to taking each drug on its own.

The main questions researchers asked in Part B were:

- How long did taking lenvatinib and everolimus together keep participants' cancer from getting worse?
- Did lenvatinib taken with everolimus help participants in other ways?
- Did lenvatinib taken with everolimus help participants live longer?
- How did lenvatinib and everolimus act in the body?
- What adverse events did participants taking both lenvatinib and everolimus have? An adverse event is a medical problem that may or may not be caused by the trial drug.

To answer these questions, researchers asked for the help of men and women like you. Participants in this trial were 37 to 79 years old. They all had advanced kidney cancer that either could not be removed by surgery or had spread outside the kidney.

What kind of trial was this?

This trial was "open-label". That means that the participants, the trial doctors, and the staff knew what drugs participants were getting. During Part B, all participants took lenvatinib, everolimus, or both.

What happened during the trial?

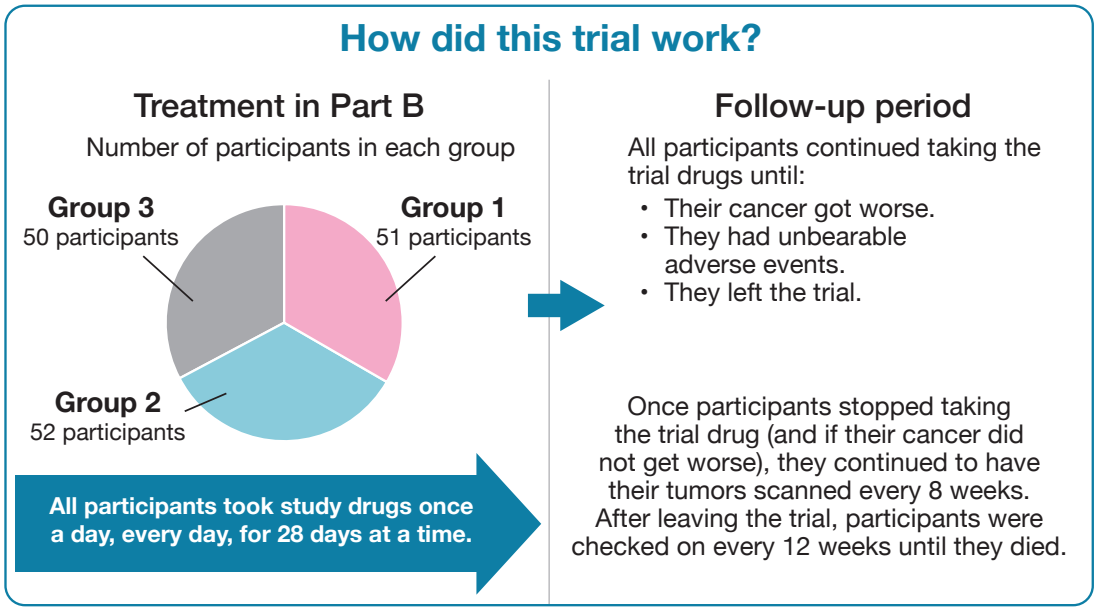
Before the trial started, trial doctors did full check-ups, including taking blood and urine samples, to make sure each participant could join the trial. Then doctors did scans to see how advanced each participant's cancer was. They also checked each participant's heart health.

During the treatment period, participants took pills containing the trial drugs by mouth once a day for 28-day cycles. Participants were randomly assigned to 1 of 3 groups:

- **Group 1:** 18 milligrams (mg) of lenvatinib and 5 mg of everolimus
- **Group 2:** 24 mg of lenvatinib
- **Group 3:** 10 mg of everolimus

The doses of both lenvatinib and everolimus were chosen based on the results of previous trials.

The figure below shows how the trial was done.



Throughout the trial, trial doctors took blood and urine samples and checked participants' weight, height, temperature, blood pressure, heart rate, and breathing rate. Trial doctors also asked how participants were feeling and kept track of any medical problems.

Every 8 weeks, trial doctors scanned participants' tumors to see if the cancer was improving. Participants could continue taking the trial drugs until their cancer got worse, they had an unbearable adverse event, or they decided to leave the trial. Their cancer was considered worse if their existing tumors got bigger or new tumors grew.

During the follow-up period, participants who stopped taking the trial drugs and whose cancer did not get worse continued to have their tumors scanned every 8 weeks. Participants who stopped taking the trial drugs because their cancer got worse were still checked on every 8 weeks but did not have their tumors scanned. After leaving the trial, participants were checked on every 12 weeks until they died.

What were the results of the trial?

This is a summary of the overall results of Part B of this trial, not just your individual results. The results for each participant may have been different. Other trials may provide new information or different results. You should not make changes to your treatment based on the results of a single trial without first talking to your doctor.

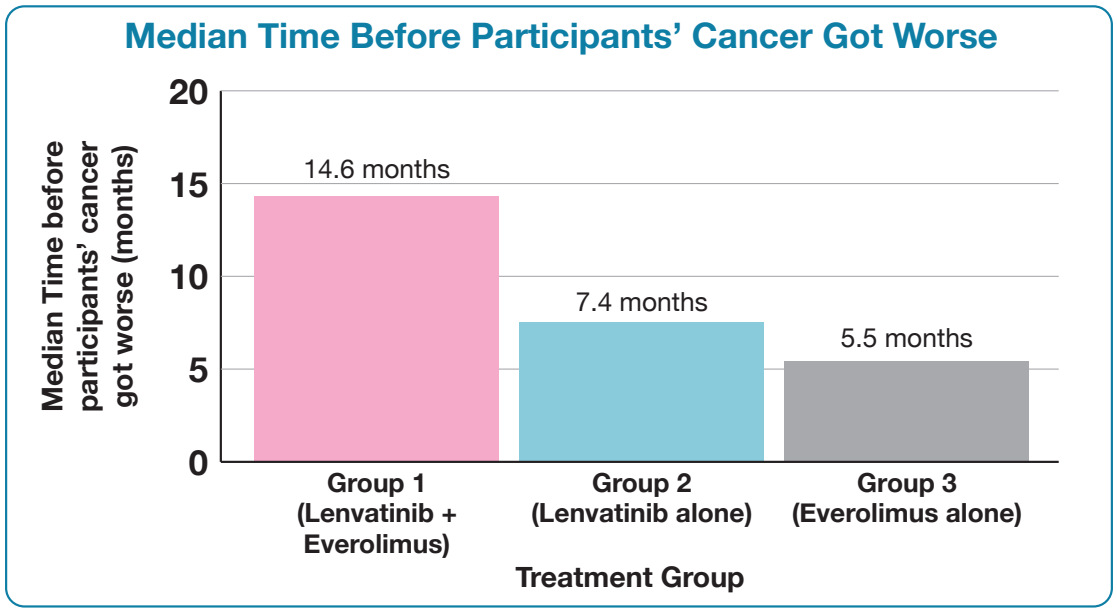
How long did taking lenvatinib and everolimus together keep participants' cancer from getting worse?

Researchers looked at the amount of time before participants' cancer got worse.

Researchers found the following:

- **Lenvatinib and everolimus together:** It took 14.6 months for participants' cancer to get worse
- **Lenvatinib alone:** It took 7.4 months for participants' cancer to get worse
- **Everolimus alone:** It took 5.5 months for participants' cancer to get worse

The chart below shows about how the median time each treatment worked before cancer got worse. The median is the amount of time about halfway between the shortest time and the longest time it took for participants' cancer to get worse. Compared to the median time, it took longer for half of the participants' cancer to get worse, and it took less time for the other half of the participants' cancer to get worse.



After the trial ended, researchers asked a separate group of doctors to look at all the tumor scans. The researchers wanted to learn if each participant's cancer was really getting worse. None of the doctors in this separate group knew what treatment the person had. These doctors agreed with researchers in your trial. They found it took longer for cancer to get worse in participants taking lenvatinib with everolimus. This was compared to participants taking either lenvatinib or everolimus alone.

Did lenvatinib taken with everolimus help participants in other ways?

Yes. Researchers looked at how many participants either had all of their cancer disappear, or their tumors got smaller and no new tumors appeared.

More participants who took lenvatinib with everolimus had their cancer disappear or their tumors get smaller or stay the same compared to participants who took lenvatinib or everolimus alone:

- **Lenvatinib and everolimus together:** Out of 51 participants in this group, 22 participants (43.1%) had their cancer disappear or their tumors get smaller or stay the same.
- **Lenvatinib alone:** Out of 52 participants in this group, 14 participants (26.9%) had their cancer disappear or their tumors get smaller or stay the same.
- **Everolimus alone:** Out of 50 participants in this group, 3 participants (6.0%) had their cancer disappear or their tumors get smaller or stay the same.

The doctors who looked at tumor scans after the trial ended agreed with this result. They found that more cancer disappeared or tumors got smaller or stayed the same in people who took lenvatinib with everolimus. This was compared to people who took only lenvatinib or everolimus.

Did lenvatinib taken with everolimus help participants live longer?

Yes. Researchers also looked at how long participants lived. They found that participants who took lenvatinib and everolimus together lived longer, compared to participants who took just 1 drug.

- **Lenvatinib and everolimus together:** Participants in this group lived for about
- 25.5 months while they were followed in the trial.
- **Lenvatinib alone:** Participants in this group lived for about 18.4 months while they were followed in the trial.
- **Everolimus alone:** Participants in this group lived for about 17.5 months while they were followed in the trial.

How did lenvatinib and everolimus act in the body?

Researchers tested participants' blood to see how much of the trial drugs were in the blood. Knowing this amount helps researchers understand better how the trial drugs act in the body. They learned the following:

- The highest amount of lenvatinib in the blood was similar for participants who took it with everolimus (Group 1) and participants who took lenvatinib alone (Group 2).
- The average amount of lenvatinib in the blood was 20% lower for participants who took it with everolimus (Group 1) compared to participants who took lenvatinib alone (Group 2).
- The highest and average amounts of everolimus in the blood was higher in participants who took it with lenvatinib (Group 1) compared to participants who took everolimus alone (Group 3).
- For participants in Group 1, taking everolimus with lenvatinib did not affect how lenvatinib acted in the body.
- How lenvatinib acted in the body did not depend on the type of tumor participants had or the level of certain kidney proteins, but depended slightly on participants' weight.

What medical problems did participants have?

A lot of research is needed to know whether a drug causes an adverse event. So when new drugs are being studied, researchers keep track of all adverse events that participants have. They may or may not be caused by the study drug.

How many participants had adverse events during the trial?

During the trial, all 153 out of the 153 participants (100.0%) who took lenvatinib and everolimus had adverse events during the treatment period, and 31 participants stopped taking the trial drug because of adverse events.

The table below shows how many participants had adverse events in this trial and how many stopped taking the trial drugs because of an adverse event by treatment group.

Adverse Events in This Trial

	Lenvatinib and everolimus (Out of 51 participants)	Lenvatinib alone (Out of 52 participants)	Everolimus alone (Out of 50 participants)
How many participants had adverse events?	51 participants (100.0%)	52 participants (100.0%)	50 participants (100.0%)
How many participants stopped taking the trial drugs because of adverse events?	12 participants (23.5%)	13 participants (25.0%)	6 participants (12.0%)

Did any participants have serious adverse events?

An adverse event is called “serious” when it is life threatening, causes lasting problems, or the participant needs to be admitted to a hospital.

Within 30 days of the end of the trial, 12 participants died:

- 4 participants (7.8%) in the group taking lenvatinib with everolimus,
- 4 participants (7.7%) in the group taking lenvatinib alone, and
- 4 participants (8.0%) who took everolimus alone.

Half of these participants died because their cancer got worse. For the other participants, the medical problems that caused death were:

- Bleeding in the brain
- Bleeding in the skull
- Complications from a general infection
- Complications from a specific type of bacterial infection
- Breathing problems
- Heart attack

In this trial, the following patients had serious medical problems.

- 28 participants (54.9%) who took lenvatinib with everolimus,
- 27 participants (51.9%) who took lenvatinib alone, and
- 21 participants (42.0%) who took everolimus alone.

The table below shows the serious adverse events that happened in at least 5% of participants.

Serious Adverse Events in This Trial

Serious Adverse Event	Lenvatinib and everolimus (Out of 51 participants)	Lenvatinib alone (Out of 52 participants)	Everolimus alone (Out of 50 participants)
Fewer red blood cells	4 participants (7.8%)	1 participants (1.9%)	4 participants (8.0%)
Dehydration	4 participants (7.8%)	0 participants (0.0%)	0 participants (0.0%)
Diarrhea	3 participants (5.9%)	0 participants (0.0%)	0 participants (0.0%)
Greater risk of bruising and bleeding	3 participants (5.9%)	0 participants (0.0%)	0 participants (0.0%)
Kidney failure	2 participants (3.9%)	4 participants (7.7%)	0 participants (0.0%)
Fluid buildup around the lungs	1 participants (2.0%)	0 participants (0.0%)	3 participants (6.0%)

What were the most common non-serious adverse events?

The table below shows the most common non-serious adverse events in this trial. A non-serious adverse event was considered "common" if it happened in at least 25% of participants.

Most Common Non-Serious Adverse Events in This Trial

Non-Serious Adverse Event	Lenvatinib and everolimus (Out of 51 participants)	Lenvatinib alone (Out of 52 participants)	Everolimus alone (Out of 50 participants)
Swelling in legs and arms	14 participants (27.5%)	8 participants (15.4%)	9 participants (18.0%)
Irregular heartbeat or changes in body temperature	12 participants (23.5%)	19 participants (36.5%)	1 participants (2.0%)
Joint pain	12 participants (23.5%)	13 participants (25.0%)	7 participants (14.0%)
Kidney disease	11 participants (21.6%)	16 participants (30.8%)	7 participants (14.0%)
Difficulty speaking	10 participants (19.6%)	19 participants (36.5%)	2 participants (4.0%)

Where can I learn more about the trial?

You can learn more about your trial online at:

- www.clinicaltrials.gov/show/results/NCT01136733
- www.clinicaltrialsregister.eu/ctr-search/search?query=2010-019484-10

Official trial title: An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

The results presented here are for a single trial. Other trials may provide new information or different results. You should not make changes to your treatment based on the results of a single trial without first talking to your doctor.

Eisai, the sponsor of this trial, has headquarters in Tokyo, Japan, and regional headquarters in Woodcliff Lake, 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 trial. 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 participants 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 http://www.eisai.com.

CISCRP

The Center for Information & Study/Trial on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical trials, nor is it involved in conducting clinical trials.

CISCRP
One Liberty Square, Suite 510
Boston, MA 02109

1-877-MED-HERO

www.ciscrp.org

synchrogenix
A CERTARA COMPANY

Synchrogenix is a worldwide medical and regulatory writing organization and is not involved in recruiting participants or in conducting clinical trials.

Synchrogenix Headquarters
2 Righter Parkway, Suite 205
Wilmington, DE 19803

1-302-892-4800

www.synchrogenix.com