Clinical Study Results

This summary reports the results of only one study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to patients. The results of this study might be different than the results of other studies that the researchers review.

Sponsor:	Seagen, Inc., a wholly owned subsidiary of Pfizer
Medicine(s) Studied:	Tucatinib
Protocol Number:	C4251004/SGNTUC-022 (MOUNTAINEER-02)
Dates of Study:	14 April 2021 to 17 April 2024
Title of this Study:	Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel Versus Paclitaxel and Ramucirumab in Previously Treated HER2+ Gastroesophageal Cancer [A Randomized, Double-Blind, Placebo Controlled, Active Comparator Phase 2/3 Study of Tucatinib in Combination With Trastuzumab, Ramucirumab, and Paclitaxel in Subjects With Previously Treated, Locally-Advanced Unresectable or Metastatic Human Epidermal Growth Receptor 2 Positive (HER2+) Gastric or Gastroesophageal Junction Adenocarcinoma (GEC)]
Date(s) of this Report:	14 November 2024

– Thank You –

If you participated in this study, Seagen Inc., a wholly owned subsidiary of Pfizer, the Sponsor, would like to thank you for your participation. This study was funded by Seagen, Inc., a wholly owned subsidiary of Pfizer, Bothell, WA, USA.

This summary will describe the study results. If you have any questions about the study or the results, please contact the doctor or staff at your study site.

Why was this study done?

What is gastric adenocarcinoma and gastroesophageal junction adenocarcinoma (GEC)?

- Gastric adenocarcinoma is stomach cancer that starts from the stomach's inner lining.
- Gastroesophageal junction adenocarcinoma is a type of cancer of the "esophagus", the tube that connects your mouth and stomach.

Both of these cancers are called "GEC" and are types of gut cancer. Participants in this study had 1 of these 2 types of cancer. The cancer had spread from where it started to other parts of the body (it was "metastatic") and could not be completely removed by surgery (it was "unresectable").

Participants in this study all had "HER2+" cancer. HER2 is a type of protein found on the surface of some cells. Cancers with high levels of HER2 are called HER2-positive (HER2+). Cancer that is HER2+ is treated differently than cancer with low levels of HER2. This is because HER2 helps tumors survive and grow quickly.

What were the study medications?

In this study, tucatinib was used with 3 other drugs called trastuzumab, ramucirumab, and paclitaxel.

- Tucatinib (too-CAT-in-ib) is a drug that is designed to target and turn off the HER2 protein inside tumor cells, which helps to stop the tumor cells from growing. Tucatinib is approved to treat breast cancer and cancer of the lower part of the gut called the colon. In this study it was an investigational medicine because it was being investigated for use in GEC. Tucatinib is taken as a pill, by mouth.

- Trastuzumab (tras-TOO-zoo-mab), also known as Herceptin®, is an antibody that is designed to attach to the HER2 protein on the surface of tumor cells. An antibody is a protein that allows the immune system to find and react to anything that the body does not recognize. This may help to stop the tumor cells from growing. Trastuzumab is given as an injection into a vein (IV infusion).
- Ramucirumab (ram-oo-SIH-roo-mab) and paclitaxel (pac-lee-TAX-ell) are anti-cancer drugs that are often used to treat gut cancer. They can stop the cancer from growing. Both are given as an IV infusion.

What was the purpose of this study?

Researchers wanted to learn about the effects of tucatinib when it was given with trastuzumab, ramucirumab, and paclitaxel. Researchers wanted to find out what the right dose of paclitaxel might be in this combination. This is called “dose optimization” and researchers were looking for the “optimized dose”.

The researchers had planned to continue to look at the study treatment with more participants. However, the Sponsor decided not to do any other parts of the study.

Researchers wanted to know:

What was the optimized dose of paclitaxel when it was given with tucatinib, trastuzumab, and ramucirumab?

How safe and well tolerated was treatment with tucatinib when it was given with trastuzumab, ramucirumab, and paclitaxel?

What medical problems did participants have during the study?

What happened during the study?

How was the study done?

First, a study doctor (researcher) checked each participant to make sure they were able to join the study. This is called “screening”.

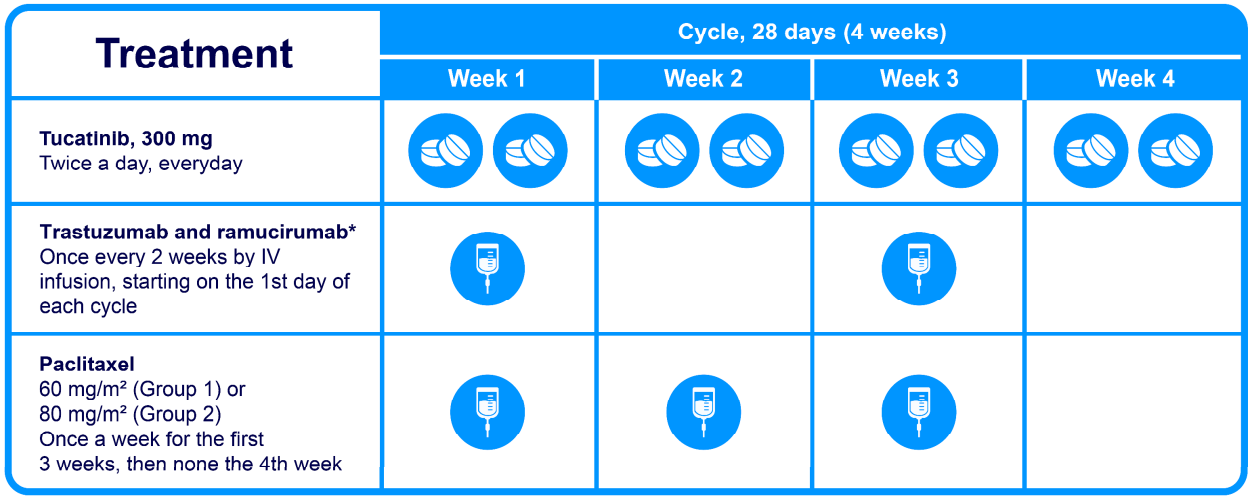
Participants who qualified for treatment after screening then entered the “treatment phase”. Treatment was divided into blocks of 28 days (4 weeks) called “cycles”. Participants were treated in the study until their cancer got worse, they experienced unacceptable medical problems, they left before the study was over by their own choice, the study doctor decided it was best for a participant to stop taking the study treatment, or the Sponsor decided to end the study, whichever occurred first.

Participants were assigned to 1 of 2 treatment groups.

Participants were assigned to Group 1 at first. They received paclitaxel at a dose of 60 mg/m^2 with tucatinib, trastuzumab, and ramucirumab, as shown in Figure 1.

Once researchers saw that Group 1 participants were able to tolerate the treatment, the next participants were assigned to Group 2. Participants in Group 2 received paclitaxel at a dose of 80 mg/m^2 with tucatinib, trastuzumab, and ramucirumab, as shown in Figure 1.

Figure 1: Study treatment



*Trastuzumab was given at a dose of 6 mg/kg on the 1st day of the 1st cycle and then 4 mg/kg for the next and any future doses. Ramucirumab was given at a dose of 8 mg/kg.

This dose optimization part of the study was “open-label”, which means that the participants and researchers knew which medicines the participants received.

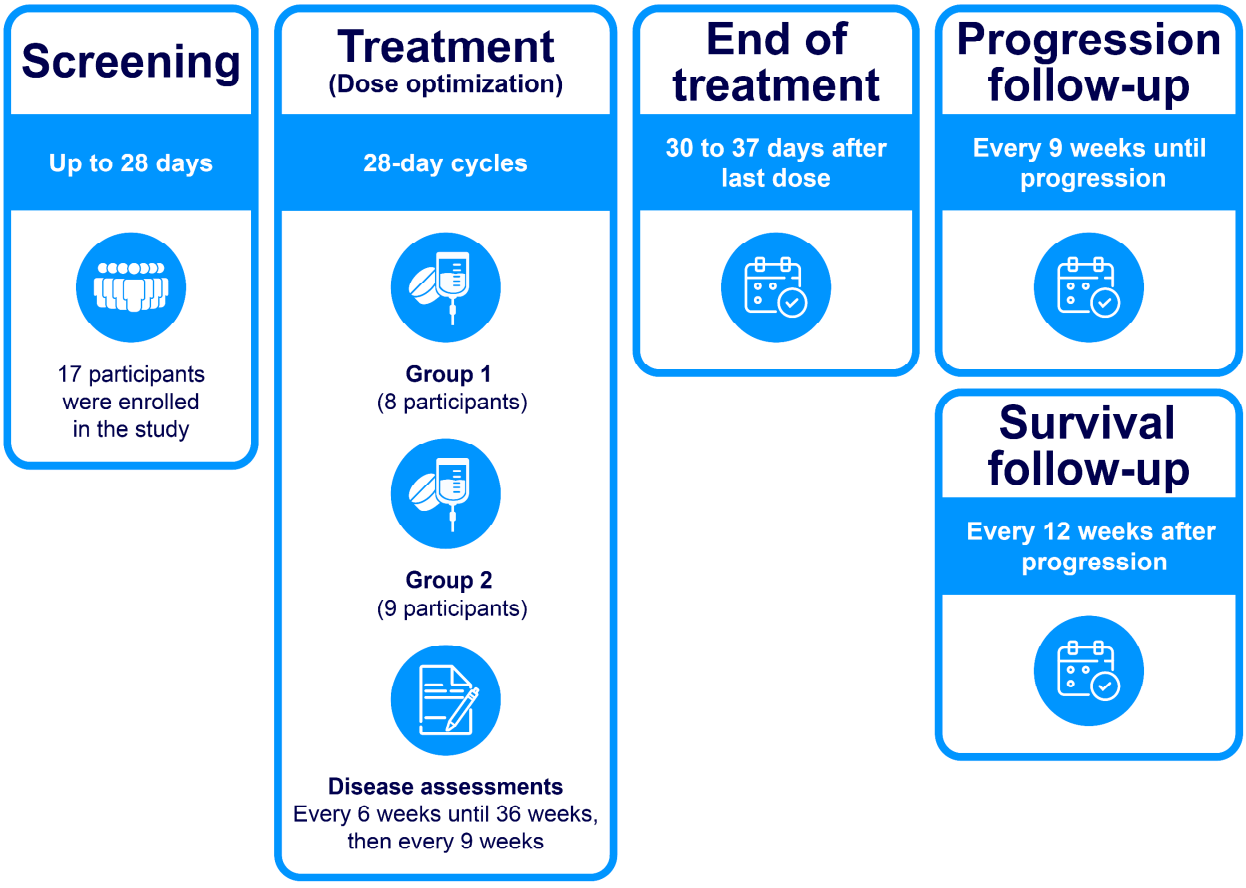
Researchers took blood and urine samples from participants during the study. They also asked participants how they were feeling. Scans were done to look at the participants’ cancer.

Participants had a follow-up visit after their treatment ended. They were then contacted about every 9 to 12 weeks to see how they were doing.

On 30 September 2022, study enrollment was ended by the Sponsor and the study sites stopped contacting participants after their end of treatment follow-up visit.

Figure 2 shows what happened during the study.

Figure 2: Study plan



Where did this study take place?

The Sponsor ran this study at 15 locations in Australia, Canada, South Korea, Taiwan, and the United States.

When did this study take place?

It began 14 April 2021 and ended 17 April 2024.

Who participated in this study?

The study included adult participants who had a diagnosis of GEC that had spread to other parts of the body, was not completely removeable by surgery, and was HER2+. Participants had been treated with other cancer treatments before this study.

- A total of 16 men participated
- A total of 1 woman participated
- All participants were between the ages of 38 and 68 years.

Participants were to be treated until their cancer got worse, they had unacceptable medical problems, they left before the study was over by their own choice, or the study doctor decided it was best for a participant to stop taking the study treatment. Of the 17 participants who started the study:

- 14 participants stopped taking the study treatment because their cancer got worse.
- 1 participant stopped taking the study treatment due to a medical problem.
- 1 participant stopped taking the study treatment because a study doctor decided that was best for the participant.
- 1 participant stopped taking the study treatment by their own choice.

How long did the study last?

Study participants were in the study for varying lengths of time depending on how they responded to treatment. The entire study took about 3 years to complete.

When the study ended in April 2024, the Sponsor began reviewing the information collected. The Sponsor then created a report of the results. This is a summary of that report.

What were the results of the study?

What was the optimized dose of paclitaxel when it was given with tucatinib, trastuzumab, and ramucirumab?

To answer this question, researchers looked at whether any participants had “dose-limiting toxicities” (DLTs) during Cycle 1 of the study treatment. These are medical problems that are severe and may be caused by taking study treatment at a dose that might be too high. DLTs may mean that a participant has to stop taking the study treatment, either completely or for a short time.

Group 1

None (0) of the 8 participants in Group 1 had a DLT during the 1st cycle of treatment.

Group 2

Two (2) out of 9 participants (22.2%) in Group 2 had at least 1 DLT during the 1st cycle of treatment.

- 1 of these participants had the DLT of swelling and irritation in the mouth.
- 1 of these participants had the DLTs of loose stools (diarrhea) and tiredness (fatigue).

From these results, researchers were not able to decide on an optimized dose of paclitaxel when it is given with tucatinib, trastuzumab, and ramucirumab.

How safe and well tolerated was treatment with tucatinib when it was given with trastuzumab, ramucirumab, and paclitaxel?

Researchers looked at all the study results to answer this question, including medical problems. Medical problems are discussed in the next section of the report.

Based on all the results, researchers believed that the participants in both groups were able to tolerate tucatinib when it was given with trastuzumab, ramucirumab, and paclitaxel.

This does not mean that everyone in this study had these results. This is a summary of just some of the main results of this study. Other studies may have different results.

What medical problems did participants have during the study?

The researchers recorded any medical problems the participants had during the study. Participants could have had medical problems for reasons not related to the study (for example, caused by an underlying disease or by chance). Or, medical problems could also have been caused by a study treatment or by another medicine the participant was taking. Sometimes the cause of a medical problem is unknown. By comparing medical problems across many treatment groups in many studies, doctors try to understand what effects a study medication might have on a participant.

All 17 participants (100%) in this study had at least 1 medical problem. A total of 1 participant left the study because of a medical problem. The most common medical problems – those reported by more than 25% of the 17 participants – are described below.

Below are instructions on how to read Table 1. Table 2 can be read in a similar way.

Instructions for Understanding Table 1.

- The **1st** column of Table 1 lists medical problems that were commonly reported during the study. All medical problems reported by more than 25% of the 17 participants are listed.
- The **2nd** column tells how many of the 8 participants in Group 1 reported each medical problem. Next to this number is the percentage of the 8 participants in Group 1 who reported the medical problem.
- The **3rd** column tells how many of the 9 participants in Group 2 reported each medical problem. Next to this number is the percentage of the 9 participants in Group 2 who reported the medical problem.
- Using these instructions, you can see that 4 out of the 8 participants (50.0%) in Group 1 reported diarrhea. A total of 8 out of the 9 participants (88.9%) in Group 2 reported diarrhea.

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group 1 (8 Participants)**	**Group 2 (9 Participants)**
Loose stools (diarrhea)	4 out of 8 participants (50.0%)	8 out of 9 participants (88.9%)
Tiredness (fatigue)	2 out of 8 participants (25.0%)	7 out of 9 participants (77.8%)
Nausea	2 out of 8 participants (25.0%)	7 out of 9 participants (77.8%)
Nosebleed	2 out of 8 participants (25.0%)	6 out of 9 participants (66.7%)
Nerve damage affecting sensation of pain, temperature, and touch	1 out of 8 participants (12.5%)	7 out of 9 participants (77.8%)
Hard or dry stools (constipation)	3 out of 8 participants (37.5%)	4 out of 9 participants (44.4%)
Inflammation of the lining of the mouth	2 out of 8 participants (25.0%)	5 out of 9 participants (55.6%)
High blood pressure	2 out of 8 participants (25.0%)	4 out of 9 participants (44.4%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group 1 (8 Participants)**	**Group 2 (9 Participants)**
Low level of white blood cells called "neutrophils"	1 out of 8 participants (12.5%)	5 out of 9 participants (55.6%)
Fever	3 out of 8 participants (37.5%)	3 out of 9 participants (33.3%)
Weight loss	2 out of 8 participants (25.0%)	4 out of 9 participants (44.4%)
Pain in the belly	3 out of 8 participants (37.5%)	2 out of 9 participants (22.2%)
Hair loss	3 out of 8 participants (37.5%)	2 out of 9 participants (22.2%)
Increased "AST" liver test result	3 out of 8 participants (37.5%)	2 out of 9 participants (22.2%)
Feeling less hungry	1 out of 8 participants (12.5%)	4 out of 9 participants (44.4%)
Shortness of breath	1 out of 8 participants (12.5%)	4 out of 9 participants (44.4%)

Table 1. Commonly reported medical problems by study participants		
Medical Problem	**Group 1 (8 Participants)**	**Group 2 (9 Participants)**
Vomiting	1 out of 8 participants (12.5%)	4 out of 9 participants (44.4%)

All participants experienced at least 1 medical problem that was considered related to at least 1 of the study treatments.

Did participants experience any medical problems that were Grade 3 or higher?

Researchers grade medical problems as follows:

- Grade 3 medical problems are those considered as severe or medically significant by the study doctors.
- Grade 4 medical problems are those considered as “life-threatening” (could harm participants’ health) and require urgent intervention by the study doctors.
- Grade 5 medical problems are those that result in death.

A total of 15 out of 17 participants (88.2%) had at least 1 medical problem that was Grade 3 or higher. The most common medical problems that were Grade 3 or higher – those reported for more than 2 out of the 17 participants – are shown in Table 2 below.

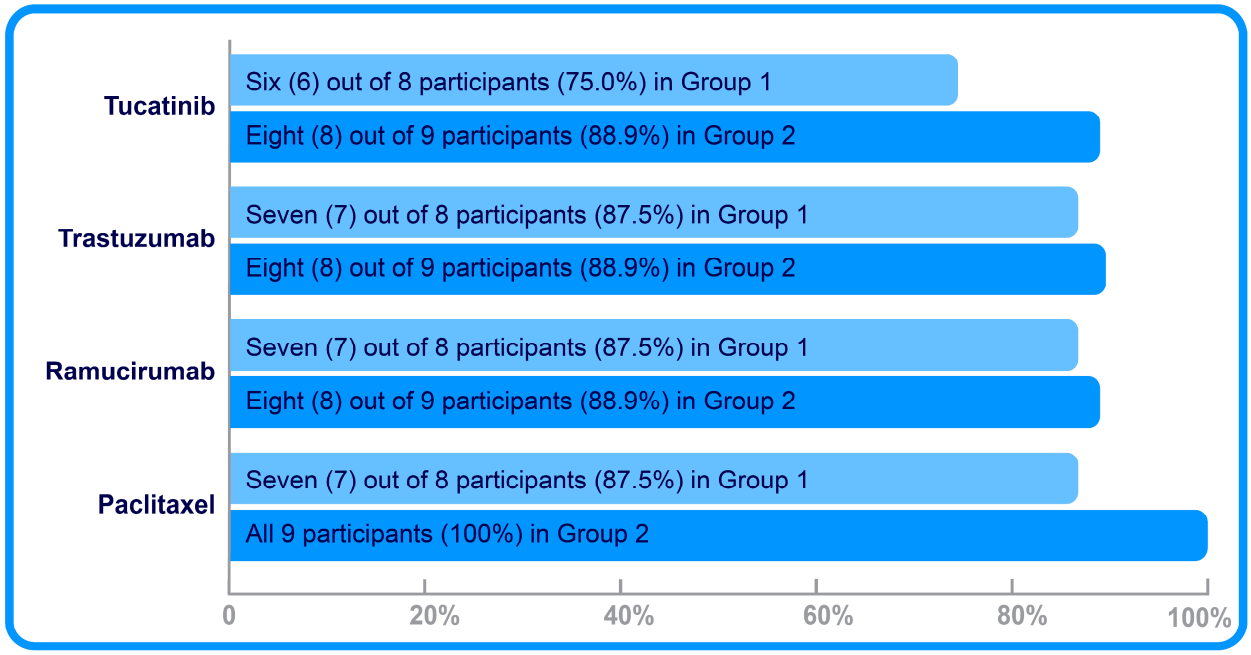
Table 2. Commonly reported Grade 3 or higher medical problems by study participants

Medical Problem	Group 1 (8 Participants)	Group 2 (9 Participants)
Low level of white blood cells called "neutrophils"	1 out of 8 participants (12.5%)	4 out of 9 participants (44.4%)
High blood pressure	1 out of 8 participants (12.5%)	3 out of 9 participants (33.3%)
Loose stools (diarrhea)	2 out of 8 participants (25.0%)	1 out of 9 participants (11.1%)
Tiredness (fatigue)	0	3 out of 9 participants (33.3%)

Did participants have any of their tucatinib, trastuzumab, ramucirumab, or paclitaxel doses delayed, not taken, or changed due to medical problems?

A total of 16 out of 17 participants (94.1%) had at least 1 medical problem that led to their study treatment being delayed, not taken, or changed. The number of these participants for each medicine is shown in Figure 3 below.

Figure 3: Percentage of participants who had doses delayed, not taken, or changed



Did study participants have any serious medical problems?

A medical problem is considered “serious” when it is life-threatening, needs hospital care, or causes lasting problems.

A total of 9 out of 17 participants (52.9%) had serious medical problems. This included 4 out of 8 participants (50.0%) in Group 1 and 5 out of 9 participants (55.6%) in Group 2. No serious medical problems were seen for more than 1 participant.

The researchers believed that the following 4 serious medical problems were related to the study treatment:

- 1 serious medical problem of **ALT liver test increased** (Group 1) and 1 serious medical problem of **fainting** (Group 2) were believed to be related to tucatinib
- 1 serious medical problem of **stroke** (Group 2) was believed to be related to ramucirumab
- 1 serious medical problem of **fever** (Group 2) was believed to be related to paclitaxel.

No serious medical problems were believed to be related to trastuzumab.

A total of 3 participants died during the study. These participants were all in Group 1. The researchers believed that these deaths were due to the participants’ cancer and were not related to the study treatments.

Where can I learn more about this study?

If you have questions about the results of your study, please speak with the doctor or staff at your study site.

For more details on your study protocol, please visit:

www.pfizer.com/research/research_clinical_trials/trial_results	Use the protocol number C4251004/SGNTUC-022

The full scientific report of this study is available online at:

www.clinicaltrials.gov	Use the study identifier **NCT04499924**
www.clinicaltrialsregister.eu	Use the study identifier 2020-003249-12

Please remember that researchers look at the results of many studies to find out which medicines can work and are safe for patients.

Again, if you participated in this study, **thank you** for volunteering. We do research to try to find the best ways to help patients, and you helped us to do that!