SERVIER

Clinical Trial Summary

Study of AG-270 in Participants With Advanced Solid Tumors or Lymphoma With MTAP* Loss

methylthioadenosine phosphorylase

Full scientific title: A Phase 1 Study of AG-270 in the Treatment of Subjects with Advanced Solid Tumors or Lymphoma with Homozygous Deletion of MTAP

We thank all the participants who took part in the study. Clinical study participants are very important for making progress in science, for the benefit of patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for patients. For medical science to progress, many studies involving patients are running all around the world. This summary only shows the results from this one study. You should not change your current treatment based on the results of this single study. If you have any questions about this study, please talk to your doctor.

Therapeutic area:
Oncology

Disease:
Advanced Solid Tumors or Lymphoma

Study phase:
Phase 1

Final version
20/12/2023

In this summary:

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1 Why was this study done?

The study was done to test a new cancer drug called AG-270 (also called S95033) in participants with advanced solid tumors or lymphomas.

Cancers fall into two categories: solid tumor cancers and blood cancers.

Solid tumor cancers are abnormal growths of cells in organ(s) of the body such as the lung, breast, or pancreas. In advanced stages of disease, solid tumors may spread in the body.

Blood cancers affects blood cells in the body. Lymphoma is a type of blood cancer.

AG-270 was tested in patients whose cancer had lost a protein called methylthioadenosine phosphorylase (MTAP). In this type of cancer, it is believed that AG-270 will be potentially helpful for alternative treatment. Indeed, AG-270 works by decreasing levels of a substance called S-adenosylmethionine (SAM). In laboratory experiments, reducing the levels of SAM in cancer cells with MTAP loss slows their growth.

In this study, AG-270 was combined with other drugs that block the growth of cancer cells. The drugs are called docetaxel, nab-paclitaxel, and gemcitabine. These drugs are marketed and used in several countries for cancer treatment.

The main goal of this study was to find the highest dose of AG-270 that participants could take without too much risk (highest tolerated dose) when given:

- alone (treatment 1).
- in combination with docetaxel (treatment 2).
- in combination with nab-paclitaxel and gemcitabine (treatment 3).

2 When and where did this study take place?

When did the study take place?

- This study started in February 2018.
- It ended in April 2023.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
United States	64
Spain	11
France	10

3 Who participated in the study?

Which participants were included in the study?

To take part, participants had to:

- Be at least 18 years of age.
- Have advanced cancer with MTAP loss.
- For treatment 1:
  - Have solid tumor or lymphoma that worsened despite treatment, and with no other standard treatment available.
- For treatment 2:
  - Have a specific type of lung cancer called non-small cell lung cancer, or.
  - Have another type of solid tumor cancer if doctor considers docetaxel a standard option for its treatment.
- For treatment 3:
  - Have cancer in the pancreas (the organ lying behind the lower part of the stomach).

How many participants took part in the study?

In all, 85 participants took part in the study. Among them, 83 received the treatment (38 women and 45 men) and 2 stopped the study before receiving the treatment.

How old were the participants?

The average age of the participants was 63 years in treatment 1, 59 years in treatment 2, and 62 years in treatment 3. The youngest participant was 24 years old and the oldest was 87 years old.

4 Which treatments did the participants receive?

In **treatment 1,** participants received:

- AG-270 tablets taken orally at doses from 50 milligrams (mg) to 400 mg once daily or 200 mg twice daily, every day of each cycle.

In **treatment 2,** participants received:

- AG-270 tablets taken orally at doses of 100 mg, 150 mg, or 200 mg once daily for the first week.
- From the second week, along with AG-270 daily tablets they also received docetaxel through an infusion (an injection given slowly into a vein), every 21 days, at a dose of 75 mg per square meter (m^2) of body surface area (75 mg/m^2) or 55 mg/m^2 depending on the tolerability.

In **treatment 3,** participants received:

- AG-270 tablets taken orally at doses of 100 mg, 150 mg, or 200 mg once daily for the first week.
- From the second week, along with AG-270 daily tablets they also received nab-paclitaxel at a dose of 100 mg/m^2 or 125 mg/m^2 and gemcitabine at a dose of 800 mg/m^2 or 1000 mg/m^2, depending on the tolerability, given through infusions. Infusions were given on Days 1, 8, and 15 of each cycle.

The participants took the drugs during time periods called “cycles”. One cycle lasted 28 days in treatment 1, 21 days in treatment 2, and 28 days in treatment 3. These cycles were repeated for as long as the cancer did not progress and if the participant did not have too severe side effects. The participant could also decide to stop the treatment at any time.

5 How was the study carried out?

The study is called an “open-label” study. This means that both the participants and the research doctors knew which treatment was taken.

Among the 85 participants included in the study; 2 participants stopped the study before receiving the treatment. A total of 83 participants took part in a treatment arm, as follows:

- Treatment 1: 40 participants.
- Treatment 2: 25 participants.
- Treatment 3: 18 participants.

To find the highest tolerated dose, the doctors tested different doses of AG-270 alone or in combination with docetaxel or with nab-paclitaxel and gemcitabine, in small groups of participants. The first group received the lowest dose, then each new group received a higher dose, as appropriate, until the highest tolerated dose was found. For each dose to be tested, the doctors checked the safety of the study drugs. Then, the researchers decided whether to increase the dose in the next group of participants.

On average, the participants in treatment 1 and treatment 2, were treated for about 3 months. In treatment 3, the participants were treated for about 4 to 5 months.

The participants visited the doctors regularly. During the visits, the doctors collected information about the participants’ health.

6 What were the side effects?

Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.

In this summary, we describe unwanted medical events thought to be caused by AG-270, and/or docetaxel, and/or nab-paclitaxel, and/or gemcitabine.

The results may be presented differently in other documents related to the study.

The tables below show the number of participants who had side effects in each group of treatment.

	Treatment 1 (out of 40 participants)
Participants who had side effect(s)	28 (70%)
Participants who had serious* side effect(s)	4 (10%)
Participants who stopped the treatment because of side effect(s)	1 (3%)

**See definition of serious side effects below*

	Treatment 2 (out of 25 participants)
Participants who had side effect(s)	24 (96%)
Participants who had serious* side effect(s)	10 (40%)
Participants who stopped the treatment because of side effect(s)	3 (12%)

**See definition of serious side effects below*

	Treatment 3 (out of 18 participants)
Participants who had side effect(s)	17 (94%)
Participants who had serious* side effect(s)	2 (11%)
Participants who stopped the treatment because of side effect(s)	4 (22%)

**See definition of serious side effects below*

What were the types of side effects?

The table below shows the most common side effects reported in treatment 1 (reported by more than 10% of participants).

	Treatment 1 (out of 40 participants)
Tiredness	10 (25%)
Increase in blood levels of bilirubin, indicating liver problems	6 (15%)
High blood levels of bilirubin, indicating liver problems	5 (13%)

= participants

The table below shows the most common side effects reported in treatment 2 (reported by more than 20% of participants).

	Treatment 2 (out of 25 participants)
Decrease in the number of red blood cells	11 (44%)
Decrease in the number of white blood cells called neutrophils	11 (44%)
Diarrhoea	10 (40%)
Hair loss	7 (28%)
Tiredness	7 (28%)
Low level of platelets (needed for blood clotting)	6 (24%)

= participants

The table below shows the most common side effects reported in treatment 3 (reported by more than 30% of participants).

	Treatment 3 (out of 18 participants)
Hair loss	7 (39%)
Decrease in the number of red blood cells	7 (39%)
Decrease in the number of white blood cells called neutrophils	7 (39%)
Decrease in number of platelets, cells that help the blood to clot	7 (39%)
Vomiting	7 (39%)
Increase in liver enzyme called ALT	6 (33%)
Diarrhoea	6 (33%)
Low level of neutrophils, a type of white blood cells	6 (33%)
Low level of platelets (needed for blood clotting)	6 (33%)

= participants

What were the serious side effects?

A side effect is considered serious when:
- the participant needs to be hospitalised,
- it causes lasting damage or death,
- the participant's life is in danger, or
- it is medically important in the doctor's opinion.

In **treatment 1**, serious side effects were:
- allergic reaction (1 participant)
- red raised skin rash and high blood levels of bilirubin, indicating liver problems (1 participant)
- liver injury (2 participants)

In **treatment 2**, serious side effects were:
- uncommon lung infection (1 participant)
- lung infection (1 participant)
- diarrhoea (2 participants)
- low level of neutrophils with fever (1 participant)
- vomiting (1 participant)
- decrease in the number of red blood cells (1 participant)
- inflammation of the moist body surfaces (1 participant)
- decrease in the number of white blood cells called neutrophils, rectal bleeding, and low level of platelets (needed for blood clotting) (1 participant)
- increase in blood levels of bilirubin, indicating liver problems (1 participant)

In **treatment 3**, serious side effects were:
- dangerous drop in blood pressure caused by severe infection (1 participant)
- low level of platelets (needed for blood clotting) (1 participant)

In the study, no participants died because of an unwanted medical event thought to be caused by the treatments in the study.

7 What were the study results?

The study was stopped earlier than planned. The sponsor reassessed the clinical development of the study drug and decided to stop including participants into the study and to not pursue the development with AG-270. This decision was not due to the safety of the study drug AG-270.

This document presents only the results for the main goal of the study. Other results are available in other documents listed in section 10.

The highest tolerated dose of AG-270 found was 200 mg once daily in the treatment 1 and 150 mg once daily in the treatment 2.

Due to the premature stop of the study, the highest tolerated dose of AG-270 in combination with nab-paclitaxel and gemcitabine in the treatment 3 was not possible to determine.

8 How has this study helped research?

The study helped researchers gather more information on the safety of the AG-270 when given alone or in combination with other drugs. This study also helped researchers in their understanding of the study drugs for the treatment of cancer.

This summary shows only the main results from this one study.

9 Are there plans for further studies?

No other studies with AG-270 are planned.

10 Further information

What are the identification numbers of the study?

- Protocol code: AG270-C-001
- EudraCT number: 2017-004384-13
- US NCT number: NCT03435250

Who did the study?

The company that organised and funded the research, called the "sponsor", is the Institut de Recherches Internationales Servier based in Suresnes, France.

How can you contact the sponsor?

Contact us on the Servier website
https://servier.com/en/

Where can you learn more about this study?

You can find more information about this study on these websites:

- https://clinicaltrials.servier.com/find-clinical-trials
- http://www.clinicaltrials.gov/

In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary at https://clinicaltrials.servier.com/glossary/

You can find general information about clinical trials on https://clinicaltrials.servier.com/