Clinical trial SUMMARY

Short study title

Phase I study of S 95005 in combination with oxaliplatin in metastatic colorectal cancer.

Full scientific title:

Phase I dose-escalation of S95005 (TAS-102) in combination with oxaliplatin in metastatic colorectal cancer.

Therapeutic area:
Oncology

Indication:
Colorectal cancer

Study phase:
Phase 1

17 June 2021
Final version

In this summary:

CLINICAL TRIAL SUMMARY

Phase I study of S 95005 in combination with oxaliplatin in metastatic colorectal cancer.

We would like to thank all the patients who participated in the study. As clinical study participants, they help researchers to discover new medicines for the benefit of all 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 the patients. For medical science to progress, a lot of people in many studies are involved all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results.

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.

1 Why was this study done?

S95005, also named trifluridine/tipiracil, is a drug already marketed in some countries. It is used to treat patients with gastric, colon or rectal cancer that has spread to other parts of the body when standard treatments are no longer effective.

The purpose of this study was to test whether S95005 combined with other anticancer drugs would help people with colon and rectal cancer that has spread after previously receiving chemotherapy. The anticancer medicines combined with S95005 were oxaliplatin, and then either bevacizumab or nivolumab:

- S95005 and oxaliplatin are drugs that block the growth of cancer cells.
- Bevacizumab is a drug that blocks the blood vessels which provide blood to the tumour. It slows the growth of the tumour.
- Nivolumab helps the immune system fight tumour cells.

This study was done in 2 parts. In part 1, S95005 was combined with another marketed drug called oxaliplatin. In part 2, a third marketed drug, either bevacizumab or nivolumab, was added.

The main objectives of this study were:

- To look at the safety of S95005 given in combination with oxaliplatin.
- To find out the highest tolerated dose of S95005 when taken together with oxaliplatin.

One objective of part 2 of the study was to evaluate how S95005 given in combination with oxaliplatin + bevacizumab or nivolumab works on colon and rectal cancer.

2 When and where did this study take place?

When was it performed?

- This study started in May 2016.
- It ended in April 2020.

Where did the study take place?

The study took place in the following countries:

Country	Number of patients
France	25
Spain	21
Italy	12
Hungary	7
Germany	6
United Kingdom	4
Austria	3

3 Who participated in the study?

Which patients were included in the study?

Patients in the study had to meet specific criteria, including:

- At least 18 years of age or older.
- Diagnosed with a colorectal cancer.
- Cancer had spread to other parts of the body.
- Previously treated with at least one cancer therapy.

How many patients participated in the study?

78 patients joined the study (31 women and 47 men):

- 24 patients participated in part 1 of the study.
- 54 patients participated in part 2 of the study.

All patients stopped the treatment, most of them because of the progression of the cancer.

How old were the patients?

The average age of the patients was 59 years in part 1 and 62 years in part 2. In this study, the youngest patient was 32 years old and the oldest patient was 83 years old.

4 Which treatments did patients receive?

All patients received S95005 tablets orally and oxaliplatin by an infusion into a vein.
Those participating in part 2 also received bevacizumab or nivolumab given by an infusion into a vein.

Patients took the drugs over time periods called "cycles". A cycle lasted 14 days:

- During the first 5 days, patients took the S95005 tablets, twice daily, then no treatment for 9 days.
- On the first day, patients also received one infusion of oxaliplatin.

During part 2, on the first day of the cycle, patients also received:

- One infusion of bevacizumab (group A) or
- One infusion of nivolumab (group B).

These 14-day cycles were maintained as long as the cancer did not get worse and if the patient did not have too severe side effects.

5 How was the study done?

The study is called an "open-label, dose escalation" study:

- "Open label" means that patients and doctors knew which treatment was given to the patient.
- "Dose escalation" means that different increasing doses of the study drug were tested.

During part 1 (dose-escalation part), 3 different doses of S95005 (twice daily) were tested: 25 mg or 30 mg or 35 mg per square meter (m^2) of body surface area. Oxaliplatin was given at the dose of 85 mg/m^2. This means that the dose depended on the size of the patient's body.

To find the highest tolerated dose, the 3 different doses of S95005 combined with oxaliplatin were tested one after the other in small groups of patients (3 to 6 patients).

For each dose of S95005, doctors checked the safety of the combination, especially certain severe medical events. These events, called DLT (Dose Limiting Toxicity), could be caused by the S95005 or oxaliplatin or both, during cycle 1 or cycle 2. Doctors were allowed to increase the dose of S95005 for the next group of patients only if few of these severe medical events occurred. These events allowed the doctors to define the highest tolerated dose. It is the dose at which less than a third of patients had some of these severe medical events.

Then, new patients joined the study for part 2. They received the combination of S95005 (at the highest tolerated dose) and oxaliplatin + bevacizumab or nivolumab.

During part 2 of the study, early results showed a low efficacy of nivolumab added to S95005 + oxaliplatin (group B). Therefore, researchers decided to stop patient enrolment in this group.

During the study, patients visited the doctors regularly. During the visits, the doctors collected information about the patients' health.

6 What were the side effects?

What about side effects?

Like all medicines, S95005 can cause side effects although not everybody gets them.
Side effects are unwanted events thought to be related to S95005, or to oxaliplatin. In this summary, we described side effects thought to be related to S95005.

The tables below show the number of patients who experienced side effects during part 1 and part 2 of the study.

Part 1: Patients received S95005 in combination with oxaliplatin

	Part 1 (24 patients)
Patients who had side-effect(s)	22 patients (92%)
Patients who had serious* side effect(s)	4 patients (17%)
Patients who stopped the treatment because of side effect(s)	1 patient (4%)

**See definition below*

Part 2 – group A: Patients received S95005 in combination with oxaliplatin and bevacizumab
Part 2 – group B: Patients received S95005 in combination with oxaliplatin and nivolumab

	Part 2 group A (37 patients)	Part 2 group B (17 patients)
Patients who had side effect(s)	36 patients (97%)	17 patients (100%)
Patients who had serious* side effect(s)	5 patients (14%)	3 patients (18%)
Patients who stopped the treatment because of side effect(s)	6 patients (16%)	0 patient (0%)

**See definition below*

How many patients had serious side effects?

A side effect is considered serious when:

- The patient needs to be hospitalized.
- The patient's life is in danger.
- It causes permanent damage or death.
- Or it may put the patient at risk and requires a medical intervention to prevent the situations listed above.

During part 1 of the study, 4 patients out of 24 (17%) had serious side effects: feeling sick, vomiting, decrease in the number of red blood cells, fever with lack of white blood cells called neutrophils, and lack of platelets cells that help the blood to clot.

During part 2 of the study, 5 patients out of 37 (14%) had serious side effects in group A: lack of white blood cells called lymphocytes, decrease in the number of white blood cells called neutrophils, severe reduction in blood cells, diarrhoea, vomiting, heart attack and bleeding at the site of the stoma (a stoma is an opening on the abdomen that can be connected to the digestive or urinary system).

In group B, 3 patients out of 17 (14%) had serious side effects: decrease in the number of red blood cells, fever with lack of white blood cells called neutrophils, lack of white blood cells called neutrophils, inflammation of the lungs, blood clot(s) in the lungs, and lack of platelets cells that help the blood to clot.

In part 1 of the study, 1 patient (4%) stopped treatment because of serious side effects. In part 2, 6 patients (16%) in group A and none in group B stopped treatment because of serious side effects.

No patient died because of an unwanted event thought to be related to the S95005.

What were the other side effects?

The tables below show the other side effects reported during part 1 and part 2 of the study. Only the most common side effects (occurring in at least 10 patients) are presented.

Part 1: Patients received S95005 in combination with oxaliplatin

	Part 1 (24 patients)
Unusual weakness	15 patients (63%)
Feeling sick	11 patients (46%)
Diarrhoea	10 patients (42%)

Part 2 – group A: Patients received S95005 in combination with oxaliplatin and bevacizumab
Part 2 – group B: Patients received S95005 in combination with oxaliplatin and nivolumab

	Part 2 group A (37 patients)	Part 2 group B (17 patients)
Lack of white blood cells called neutrophils	18 patients (49%)	11 patients (65%)
Feeling sick	19 patients (51%)	7 patients (41%)
Diarrhoea	12 patients (32%)	7 patients (41%)
Vomiting	12 patients (32%)	6 patients (35%)
Tiredness	10 patients (27%)	7 patients (41%)
Unusual weakness	10 patients (27%)	6 patients (35%)
Decrease in the number of white blood cells called neutrophils	11 patients (30%)	0 patient (0%)

7 What were the study results?

During the dose-escalation (part 1), one patient had a dose limiting toxicity (DLT, severe medical events that doctors checked in order to decide if they could increase the dose or not). The DLT was a fever with lack of white blood cells called neutrophils. It occurred at the maximum planned dose of the study drug S95005 (35 mg/m^2) + oxaliplatin 85 mg/m^2. This dose was the highest tolerated dose.

8 How has this study helped patients and researchers?

This study helped researchers find the recommended dose (dose that could be both safe and effective for patients) to be used for the combination of S95005 + oxaliplatin.

This study also helped researchers in their understanding of S95005 in combination with other anticancer drugs, in that type of cancer.

By participating in this study, patients benefited from medical follow-up with experts in cancer.

9 Are there plans for further studies?

Because the results of this study were not promising enough, no other studies with the combination S95005 + oxaliplatin are foreseen to date.
Other studies with the combination S95005 + bevacizumab are ongoing in patients with colon or rectal cancer.

10 Further information

What is the clinical study identification number?

- Protocol Number: CL1-95005-001
- EudraCT Number: 2015-004894-34

Who did the study?

The company organizing and funding the research (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 (www.servier.com).

Where can you learn more about this study?

- The scientific summary is also available on the Servier Clinical Trial Data website. (https://clinicaltrials.servier.com/)
- In this document, we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary on the Servier Clinical Trial Data website.

  In accordance with the recommendations of the Cancer Plan III (Measure 5.4), this document was submitted for review and guidance to the Clinical Cancer Research Patients Committee of La Ligue Nationale contre le Cancer.