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

**Submission date**
02/02/2016

**Recruitment status**
No longer recruiting

**Registration date**
02/03/2016

**Overall study status**
Completed

**Last Edited**
23/06/2021

**Condition category**
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

**Plain English summary of protocol**
Not provided at time of registration and not expected to be available in the future

## Contact information

**Type(s)**
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# Additional identifiers

### EudraCT/CTIS number
2015-004894-34

### IRAS number

### ClinicalTrials.gov number
NCT02848443

### Secondary identifying numbers
CL1-95005-001

# Study information

### Scientific Title
Phase I dose-escalation of S 95005 (TAS-102) in combination with oxaliplatin in metastatic colorectal cancer

### Study objectives
To assess the safety and tolerability and to determine the recommended phase 2 dose of S 95005 given in combination with oxaliplatin in patients with metastatic colorectal cancer.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Comité Ético de Investigación Clínica del Hospital Universitari Vall d'Hebron, 04/03/2016

### Study design
Multicentre open-label non-randomised non-comparative study

### Primary study design
Interventional

### Secondary study design
Non randomised study

### Study setting(s)
Hospital

### Study type(s)
Treatment

### Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

### Health condition(s) or problem(s) studied

Metastatic colorectal cancer

## Interventions
This is a one-arm study, which will be conducted in 2 parts:
1. A dose-escalation part to determine the maximum tolerated dose (MTD) of S 95005 in combination with oxaliplatin: a minimum of 3 patients will be enrolled at the initial dose level of 25 mg/m² of S95005 in combination with 85 mg/m² of oxalipatin. Patients will be included by groups of 3.
2. An expansion part in patients treated at the recommended dose defined in the dose escalation part of this study to evaluate the safety, PK, and preliminary efficacy of S 95005 in combination with oxaliplatin and either bevacizumab or nivolumab.
The treatments will be given until unacceptable toxicity according to the investigator, disease progression or patient withdrawal. The follow-up will last up to 6 months after the end of the participation in the study.

S95005 : film-coated tablets containing 15mg of trifluridine and 7.065mg of tipiracil hydrochloride, or 20mg of trifluridine and 9.42mg of tipiracil hydrochloride, given orally at the dose of 25 or 30 or 35 mg/m2/dose

Oxaliplatin: concentrate for solution for infusion containing 5mg/ml of oxaliplatin, administered intravenously at the dose of 65 to 85 mg/m2

Bevacizumab: concentrate for solution for infusion containing 25mg/ml of bevacizumab, administered intravenously at the dose of 5 mg/kg

Added 05/04/2017:
Nivolumab: concentrate for solution for infusion containing 10 mg/ml of nivolumab, administered intravenously at the dose of 3 mg/kg.

## Intervention Type
Drug

## Phase
Phase I

## Drug/device/biological/vaccine name(s)
1. S95005 (trifluridine/tipiracil hydrochloride) 2. Oxaliplatin 3. Bevacizumab 4. Nivolumab

## Primary outcome measure
1. Maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of S95005 when given in combination with oxaliplatin, during the first two cycles in the dose-escalation part
2. Safety tolerance profile of S 95005 given in combination with oxaliplatin, at each visit, from the informed consent signature to the withdrawal visit, assessed by: adverse events, physical examinations and ECOG performance status, laboratory examinations (haematology, biochemistry and urinalysis), vital signs, ECG and body weight

## Secondary outcome measures
Secondary outcome measures as of 05/04/2017:
1. Main pharmacokinetic parameters of S 95005 and its main metabolites, and oxaliplatin, from day 1 of cycle 1 to day 5 of cycle 2
2. Antitumor activity (objective response rate, duration of response, Progression-free survival

and Overall survival) assessed by RECIST (Response Evaluation Criteria in Solid Tumors) and CEA (Carcinoembryonic Antigen), from the informed consent signature to the withdrawal visit
3. Safety tolerance profile of S 95005 in combination with oxaliplatin and either bevacizumab or nivolumab assessed by: adverse events, physical examinations and performance status, laboratory examinations (haematology, biochemistry and urinalysis), vital signs and body weight, from the informed consent signature to the withdrawal visit
4. PDL-1 expression, tumour-infiltrating CD8 T cell density: tumor biopsy at baseline and at the end of cycle 4
5. Exploratory endpoints: Proteomic and genomic biomarkers using blood samples, after consent signature from day 1 of cycle 1 to the withdrawal visit (all patients), and tumour biopsies (for patients receiving nivolumab, at baseline and at the end of cycle 4)

Original secondary outcome measures:
1. Main pharmacokinetic parameters of S 95005 and its main metabolites, and oxaliplatin, from day 1 of cycle 1 to day 5 of cycle 2
2. Antitumor activity (objective response rate, duration of response, Progression-free survival and Overall survival) assessed by RECIST (Response Evaluation Criteria in Solid Tumors), from the informed consent signature to the withdrawal visit
3. Exploratory endpoints: Proteomic and genomic biomarkers using blood samples, after consent signature from day 1 of cycle 1 to the withdrawal visit

### Overall study start date
14/12/2015

### Completion date
09/04/2020

## Eligibility

### Key inclusion criteria
Inclusion criteria as of 24/11/2016:
1. Age 18 years or older
2. Histologically confirmed metastatic colorectal cancer pretreated by at least one line of standard chemotherapy
3. Restaging scan within 28 days before the first study drug intake
4. During the dose-escalation part, patient must have at least one evaluable or measurable metastatic lesion; and during the expansion part, patient must have at least one measurable metastatic lesion
5. Life expectancy of more than 3 months
6. Performance status Eastern Cooperative Oncology Group (ECOG): 0-1
7. Adequate bone marrow, liver, and kidney function
8. For patient who will receive bevacizumab: coagulation parameters in normal limit or in therapeutic limit for patients treated with anticoagulant
9. Women of childbearing potential must have a negative pregnancy test. Female participants of childbearing potential and male participants with partners of childbearing potential must agree to use highly effective birth control method. Women and female partners using hormonal contraceptive must also use a barrier method.
10. Capacity to take oral tablet(s) without difficulty
11. Has provided written informed consent
12. Is willing and able to comply with scheduled visits and study procedures

Added 06/04/2017: For patients who will receive nivolumab: patients eligible for tumour biopsy and who agree to have two sequential biopsies during the study

Original inclusion criteria:
1. Age 18 years or older
2. Histologically confirmed metastatic colorectal cancer pretreated by at least one line of standard chemotherapy and naïve to oxaliplatin in the metastatic setting
3. Restaging scan within 28 days before the first study drug intake
4. During the dose-escalation part, patient must have at least one evaluable or measurable metastatic lesion; and during the expansion part, patient must have at least one measurable metastatic lesion
5. Life expectancy of more than 3 months
6. Performance status Eastern Cooperative Oncology Group (ECOG): 0-1
7. Adequate bone marrow, liver, and kidney function
8. For patient who will receive bevacizumab: coagulation parameters in normal limit and adequate proteinuria
9. Women of childbearing potential must have a negative pregnancy test
Both males and females must agree to use effective birth control method
10. Capacity to take oral tablet(s) without difficulty
11. Has provided written informed consent
12. Is willing and able to comply with scheduled visits and study procedures

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Sex
Both

## Target number of participants
94

## Total final enrolment
78

## Key exclusion criteria
Exclusion criteria as of 05/04/2017:
1. Grade 2 or higher peripheral neuropathy
2. During expansion part, patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy with oxaliplatin
3. Patients with brain metastases or leptomeningeal metastasis
4. Other active malignancy within the last 3 years (except for basal cell carcinoma or a non-invasive/in situ cervical cancer)
5. Has had certain other recent treatment e.g. major surgery, field radiation, participation in another interventional study within the specified time frames prior to study drug administration
6. For patient who will receive bevacizumab: history of allergic reactions/hypersensitivity to

bevacizumab to any components used in the formulation, to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
7. Grade 3 or higher hypersensitivity reaction to oxaliplatin, or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with premedication
8. Patient previously treated by S 95005 or history of allergic reactions attributed to compounds of similar or biologic composition to S 95005 or any of its excipient, or has rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Certain serious illnesses or serious medical conditions
10. Any condition that, in the judgment of the Investigator, may affect the patient's ability to understand and sign the informed consent and fully comply with all study procedure
11. Pregnancy or breast feeding
12. For patients planned to receive nivolumab:
12.1. Patients with active autoimmune disease or history of clinically severe autoimmune disease.
12.2. Patients with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone equivalent) or other immunosuppressive medications within the specified time frames prior to first study drugs intake.
12.3. Prior treatment with anti-PD-1, anti-PD-L1, anti-programmed cell death ligand-2, anti-CD137, anti-OX-40, anti-CD40, anti-cytotoxic T lymphocyte-associated antigen-4 antibodies (CTLA-4), or any other immune checkpoint inhibitors.
12.4. Prior events of immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated rash, immune-mediated encephalitis.
12.5. Allergic reactions/hypersensitivity to nivolumab or any components used in its formulation or previous severe hypersensitivity reaction to treatment with another monoclonal antibody.
12.6. Has a known history of active tuberculosis (Bacillus Tuberculosis).

Exclusion criteria as of 24/11/2016:
1. Grade 2 or higher peripheral neuropathy
2. During expansion part, patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy with oxaliplatin
3. Patients with brain metastases or leptomeningeal metastasis
4. Other active malignancy within the last 3 years (except for basal cell carcinoma or a non-invasive/in situ cervical cancer)
5. Has had certain other recent treatment e.g. major surgery, field radiation, received investigational agent, within the specified time frames prior to study drug administration
6. History of allergic reactions/hypersensitivity to bevacizumab (for patient who will receive bevacizumab) or any components used in the formulation
7. Grade 3 or higher hypersensitivity reaction to oxaliplatin, or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with premedication
8. Patient previously treated by S 95005 or history of allergic reactions attributed to compounds of similar or biologic composition to S 95005 or any of its excipient, or has rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Certain serious illnesses or serious medical conditions
10. Any condition that, in the judgment of the Investigator, may affect the patient's ability to understand and sign the informed consent and fully comply with all study procedure
11. Pregnancy or breast feeding

Original exclusion criteria:
1. Grade 2 or higher peripheral neuropathy
2. Patients who had recurrence during or within 6 months of completion of the adjuvant

chemotherapy with oxaliplatin
3. Patients with brain metastases or leptomeningeal metastasis
4. Other active malignancy within the last 3 years (except for basal cell carcinoma or a non-invasive/in situ cervical cancer)
5. Has had certain other recent treatment e.g. major surgery, field radiation, received investigational agent, within the specified time frames prior to study drug administration
6. History of allergic reactions/hypersensitivity to bevacizumab (for patient who will receive bevacizumab) or any components used in the formulation
7. Grade 3 or higher hypersensitivity reaction to oxaliplatin, or grade 1-2 hypersensitivity reaction to oxaliplatin not controlled with premedication
8. Patient previously treated by S 95005 or history of allergic reactions attributed to compounds of similar or biologic composition to S 95005
9. Certain serious illnesses or serious medical conditions
10. Any condition that, in the judgment of the Investigator, may affect the patient's ability to understand and sign the informed consent and fully comply with all study procedure
11. Pregnancy or breast feeding

### Date of first enrolment
09/05/2016

### Date of final enrolment
24/01/2019

## Locations

### Countries of recruitment
Austria

England

France

Germany

Hungary

Italy

Spain

United Kingdom

### Study participating centre
**Vall d'Hebron University Hospital (Hospital Vall D'Hebron) [VHIO]**
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**Study participating centre**
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**Study participating centre**
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# Sponsor information

**Organisation**
Servier (France)

**Sponsor details**

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### Sponsor type
Industry

### Website
https://clinicaltrials.servier.com/

### ROR
https://ror.org/034e7c066

## Funder(s)

### Funder type
Industry

### Funder Name
ADIR

## Results and Publications

### Publication and dissemination plan
Summary results and a lay summary will be published on https://clinicaltrials.servier.com/ within 12 months after the end of the study.

### Intention to publish date
09/04/2021

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from https://clinicaltrials.servier.com/ after the Marketing Authorisation has been granted.

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Basic results | | | 17/05/2021 | No | No |
| Plain English results | | | 23/06/2021 | No | Yes |