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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)
Scientific

Contact name
Prof Josef Tabernero

Contact details
Vall d'Hebron University Hospital,
Institute of Oncology (VHIO)
P. Vall d'Hebron 119-129
Barcelona
Spain
08035

Type(s)
Public

Contact name
Dr Institut de Recherches Internationales Servier

Contact details
50, rue Carnot
Suresnes
France
92284
+33 1 55 72 43 66
clinical.trial.management@servier.com

Additional identifiers

ClinicalTrials.gov (NCT)
NCT02848443

Clinical Trials Information System (CTIS)
2015-004894-34

Protocol serial number
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

Primary study design
Interventional

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

Study type(s)
Treatment

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(s)
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

Key secondary outcome(s)
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

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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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

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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
United Kingdom

England

Austria

France

Germany

Hungary

Italy

Spain

Study participating centre
Vall d'Hebron University Hospital (Hospital Vall D'Hebron) [VHIO]
Passeig de la Vall d'Hebron, 119-129
Barcelona
Spain
08035

Study participating centre
University Hospital of Valencia (Hospital Clínic Universitari de València)
nº, Av. de Blasco Ibáñez, 17
Valencia
Spain
46010

Study participating centre

Institut Gustave Roussy
114 Rue Edouard Vaillant
Villejuif
France
94805

Study participating centre
Hôpital Saint Antoine
184 Rue du Faubourg Saint-Antoine
Paris
France
75012

Study participating centre
CHU Timone
264 Rue Saint-Pierre
Marseille
France
13005

Study participating centre
Centre Eugène Marquis
Avenue de la Bataille Flandres-Dunkerque
Rennes
France
35042

Study participating centre
HOSPITAL UNIV. GREGORIO MARAÑON
Planta -1 Unidad de investigación Oncológica
Edificio de Oncología
C/Maiquez nº 7
Madrid
Spain
28007

Study participating centre
Hospital Universitario Madrid Sanchinarro
Centro Integral Oncológico Clara Campal
Calle Oña, 10
Madrid

Spain
28050

Study participating centre
Hospital Universitario Ramón y Cajal de Madrid Unidad de Oncología Digestiva
Servicio de Oncología Médica (consulta 5)
Ctra. De Colmenar Viejo km 9.100
Madrid
Spain
28034

Study participating centre
Hôpital Pitié
Groupe Hospitalier La Pitié Salpêtrière
47-83 Bd de l'Hôpital
Paris
France
75013

Study participating centre
Policlinico G.B. Rossi
A.O.U.I. di Verona Piazzale L. Scuro, 10
U.O.C. di Oncologia - Centro Ricerche Cliniche di Verona s.r.l.
Verona
Italy
37134

Study participating centre
Azienda Ospedaliera Garibaldi
Nesima
S.C. di Oncologia Medica ARNAS
Via Palermo, 636
Catania
Italy
95122

Study participating centre
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.)
Oncologia Medica e Patologia Gastroenterica IRCCS -
Via Piero Maroncelli, 40
Meldola

Italy
47014

Study participating centre
Klinikum der Universität München
Campus Großhadern
Medizinische Klinik und Poliklinik III
Marchioninistr. 15
Munich
Germany
81377

Study participating centre
St. Josef-Hospital
Klinikum der Ruhr-Universität Bochum
Abt. für Hämatologie, Onkologie und Palliativmedizin
Gudrunstr. 56
Bochum
Germany
44791

Study participating centre
Universitätsklinikum Hamburg
Eppendorf II. Medizinische Klinik und Poliklinik
(Onkologie, Hämatologie, KMT mit Sektion Pneumologie)
Hubertus Wald Tumorzentrum - UCCH
Martinistr. 52, Gebäude Ost 24
Hamburg
Germany
20246

Study participating centre
Medizinische Universität Wien
Klinische Abteilung für Onkologie
Allgemeines Krankenhaus – Universitätskliniken
Währinger Gürtel 18-20
Wien
Austria
1090

Study participating centre

Orszagos Onkologiai Intezet
"B" Belgyogyaszati-Onkologiai O.
Es Klin. Farmakologiai O.
Rath Gyorgy u. 7-9.
Budapest
Hungary
1122

Study participating centre
Magyar Honvedseg Egeszsegugyi
Kozpont
Onkologiai Osztaly
Podmaniczky u. 111.
Budapest
Hungary
1062

Study participating centre
Semmelweis Egyetem
I. sz. Belgyogyaszati Klinika - Klin.
Farmakologiai Reszleg
Koranyi S. u. 2/a.
Budapest
Hungary
1083

Study participating centre
Christie Hospital NHS Foundation Trust
GI & Endocrine
550 Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
Universitätsklinikum Ulm
Zentrum für Innere Medizin
Klinik für Innere Medizin I
Albert-Einstein-Allee 23
Ulm
Germany
89081

Study participating centre
Klinikum Wolfsburg
Medizinische Klinik II
Sauerbruchstrasse 7
38440 Wolfsburg
Wolfsburg
Germany
38440

Study participating centre
ICO Badalona. H. Germans Trials y Pujol
Servicio de Oncología médica
Carretera de Canyet s/n
Badalona
Spain
08916

Study participating centre
HIA Bégin
69, avenue de Paris
Saint Mandé
Saint Mandé
France
94160

Sponsor information

Organisation
Servier (France)

ROR
https://ror.org/034e7c066

Funder(s)

Funder type
Industry

Funder Name
ADIR

Results and Publications

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